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Use of Adjuvant Chemotherapy Following Cystectomy in Patients with Deep Muscle-Invasive Transitional Cell Carcinoma of the Bladder

Practice Guideline Report #3-2-1

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SUMMARY

Guideline Question

What is the role of adjuvant chemotherapy in the treatment of patients with deep muscle-invasive transitional cell carcinoma of the bladder (pT2b or pT3 or pT4 and pN0-pN2)* who have undergone cystectomy? Overall survival, disease-free survival, adverse effects, and quality of life are the outcomes of interest.

Target Population

These recommendations apply to adult patients with deep muscle-invasive transitional cell carcinoma of the bladder (defined as pT2b or pT3 or pT4 and pN0-pN2* only) who have undergone cystectomy. They do not apply to adult patients with superficial muscle invasion (pT2a).

Recommendations

- Post-surgical adjuvant chemotherapy should not be routinely offered to this group of patients.
- It is reasonable to consider the use of adjuvant chemotherapy in high-risk patients for improvement of disease-free survival, provided there is full discussion of the lack of overall survival benefit and the associated risks and toxicities.

Qualifying Statements

- The Genitourinary Cancer Disease Site Group (GU DSG) did not identify any trials that directly compared different chemotherapy regimens in this patient population. If chemotherapy is opted for, the GU DSG recommends the use of a cisplatin-based combination chemotherapy regimen such as methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) or cisplatin-methotrexate-vinblastine (CMV).

* Sobin LH, Wittekind CH, editors. TNM Classification of Malignant Tumors, 5th ed. Toronto: J. Wiley; 1997. p.187-90.

- Randomized controlled trials of gemcitabine-cisplatin and dose-intensive MVAC plus granulocyte-colony stimulating factor in the setting of metastatic transitional cell bladder cancer provide indirect evidence that these regimens could offer equivalent benefit to MVAC or CMV, but with less toxicity, in patients with muscle-invasive disease. The effectiveness of these regimens in the adjuvant setting after cystectomy is currently being evaluated in a randomized trial.

Methods

Entries to MEDLINE (1985 through October 2002), CANCELIT (1985 through October 2002), and the Cochrane Library (2002, Issue 4) databases were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative's GU DSG and methodologists. This practice guideline report has been reviewed and approved by the GU DSG, which comprises medical and radiation oncologists, urologists, and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Results from four small, randomized studies do not provide conclusive evidence of a survival advantage for adjuvant chemotherapy compared with observation. Three of the four trials provide evidence of significantly longer disease-free survival in patients treated with adjuvant chemotherapy, compared with observation.

Future Research

These recommendations do not preclude the use of adjuvant chemotherapy in the context of clinical trials. The GU DSG encourages patient enrolment in clinical trials.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #3-2-2: *Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder.*

For further information about this practice guideline report, please contact: Dr. Himu Lukka, Chair, Genitourinary Cancer Disease Site Group, Hamilton Regional Cancer Centre, 699 Concession Street, Hamilton ON, L8V 5C2; TEL (905) 387-9711 ext. 67699; FAX (905) 575-6326.

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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FULL REPORT

I. QUESTION

What is the role of adjuvant chemotherapy in the treatment of patients with deep muscle-invasive transitional cell carcinoma (TCC) of the bladder (pT2b or pT3 or pT4 and pN0-pN2) (1) who have undergone cystectomy? Overall survival, disease-free survival, adverse effects, and quality of life are the outcomes of interest.

II. CHOICE OF TOPIC AND RATIONALE

In recent years, effective combination chemotherapy regimens have been developed and tested in patients with advanced or metastatic TCC of the urothelium. Although toxic and causing significant morbidity and, in some cases, early mortality, these regimens have yielded moderate response rates. Unfortunately, responses are rarely sustained, with only a very small proportion of patients achieving durable remission (2).

The use of chemotherapy in the treatment of earlier stages of TCC of the bladder has attracted interest, mainly because approximately 50% of patients with high-grade bladder cancer and deep muscle invasion will ultimately die of disseminated disease despite adequate local control (3). These systemic relapses are due to occult micrometastasis, which might be favourably modulated through the use of effective chemotherapy delivered in the adjuvant setting.

Using chemotherapy to improve either overall or disease-free survival, first in metastatic and then earlier stage disease, has proven to be effective in other disease sites such as adenocarcinoma of the breast. With breast cancer, chemotherapy was initially used in locally advanced or metastatic breast cancer, later as adjuvant treatment in node-positive disease, and more recently in selected patients with node-negative disease. In all stages of the disease, favourable results have been documented (4).

Adjuvantive chemotherapy for bladder cancer has been studied in a number of randomized trials, primarily in the neoadjuvant setting. Post-operative adjuvant chemotherapy has the advantages of not delaying time to definitive local therapy and not exposing patients to unnecessary cytotoxic therapy due to clinical overstaging. In a number of centres, adjuvant chemotherapy for TCC of the bladder is routinely employed as part of standard practice, particularly for patients who are node positive (pN1, pN2), for histologically high-grade tumours, and for deeply invasive or locally advanced tumours (pT2b or pT3 or pT4 and pN0-pN2). Other centres do not employ this form of therapy outside of clinical trials.

The purpose of this practice guideline report is to review the available evidence concerning adjuvant chemotherapy for deep muscle-invasive bladder cancer after cystectomy in order to make recommendations for appropriate treatment.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC) using methods of the Practice Guidelines Development Cycle (5). Evidence was selected and reviewed by three members of the PGI's Genitourinary Cancer Disease Site Group (GU DSG) and methodologists. Members of the GU DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on adjuvant chemotherapy for patients with deep muscle-invasive TCC of the bladder, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended

to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

A systematic search of MEDLINE (Ovid) (1985 through October 2002), CANCELIT (Ovid) (1985 through October 2002), and the Cochrane Library (2002, Issue 4) databases was carried out. "Bladder neoplasms" (Medical subject heading (MeSH)) was combined with "carcinoma, transitional cell" (MeSH) and "chemotherapy, adjuvant" (MeSH) and each of the following phrases used as text words: "bladder neoplasm", "bladder cancer", "transitional cell carcinoma", and "adjuvant chemotherapy". These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. A search of personal reprint files was also conducted. The Physician Data Query (PDQ) clinical trials database on the Internet (http://cancer.gov/search/clinical_trials/) was searched for reports of new or on-going trials. Relevant articles were selected and reviewed by three reviewers and the reference lists from these sources, as well as recently published review papers, were searched for additional trials.

Inclusion Criteria

All randomized controlled trials (RCTs) that compared adjuvant chemotherapy with observation in patients who had undergone cystectomy for the treatment of deep muscle-invasive TCC of the bladder were reviewed. To be eligible for inclusion in the systematic review, it was necessary that each trial provide comparisons of overall survival or disease-specific survival data. Quality of life was also considered an important outcome of interest. RCTs that compared different chemotherapy regimens were also considered.

Exclusion Criteria

1. Phase I or II trials were excluded due to the availability of RCTs.
2. Papers published in a language other than English, abstracts, letters, and editorials were also excluded.

Synthesizing the Evidence

The GU DSG undertook a critical assessment of the RCTs, including an evaluation of trial quality, to inform their decision concerning whether data pooling should be performed (see Section IV. RESULTS, Synthesizing the Evidence).

IV. RESULTS

Literature Search Results

Five RCTs that compared adjuvant chemotherapy with observation in patients who had undergone cystectomy for the treatment of muscle-invasive TCC of the bladder were eligible for inclusion in this systematic review of the evidence (6-10). On review, one of the five trials was found to be incomplete due to inadequate reporting of survival outcomes (10). The published paper of this trial provided very little information regarding statistical analyses; no p-values,

confidence intervals, or survival curves were reported. Attempts to obtain this missing data, including attempts to contact the primary author, were unsuccessful. A description of this incomplete trial is included in Table 1. Since data from this trial were not available there is no entry for this trial in Table 2. The remaining four RCTs (6-9) form the basis of this review.

No RCTs that compared two different chemotherapy regimens or reported quality of life data were identified.

Synthesizing the Evidence

The relatively small sample size of the randomized trials and their corresponding limited statistical power to detect clinically significant differences in overall survival raised the issue of whether the trials should be pooled in a meta-analysis. With this potential pooling in mind, the trials were assessed as to their quality using the methods of Detsky et al (11), Chalmers et al (12), and O'Rourke et al (13) (see Appendix 1). None of the four trials was found to have serious flaws in their quality. All were published in peer-reviewed journals and involved randomized comparisons of adjuvant chemotherapy treatment versus control. All reported the eligibility criteria and clinical interventions for both study arms. While only one trial stated the randomization methods, all trials provided evidence that prognostic factors were balanced between study arms. All studies reported an intent-to-treat analysis using appropriate statistical methods, and all patients were accounted for in all studies. Three trials reported the number of patients that were not enrolled but seen concurrently in the study institutions. One trial was stopped appropriately at the time of interim analysis, and another was stopped due to slow accrual.

Although the quality of the trials was deemed adequate, they were judged to be clinically heterogeneous as they enrolled patients with different baseline risks of clinical disease progression, and therefore, different potential efficacy of the interventions. For example, nine percent of patients enrolled in the Studer et al trial had involved lymph nodes and 55% had stage T3A disease or less (7), whereas 70% of patients enrolled in the Freiha et al trial had involved lymph nodes and no patient had less than T3B disease (9) (see Appendix 1). In light of the clinical heterogeneity of enrolled patients and the substantial clinical heterogeneity in relevant aspects of the treatment protocols studied in the trials, the consensus of the GU DSG was that the clinical heterogeneity of the studies precluded their combination in a meta-analysis (14).

Outcomes

Five RCTs of adjuvant chemotherapy compared with observation for the treatment of patients who had undergone cystectomy for muscle-invasive TCC of the bladder are described in Table 1; data from the four trials for which results were available are presented in Table 2.

In each of the trials, patients were randomly assigned to a treatment arm (adjuvant chemotherapy) or a control arm (observation only) after radical cystectomy and/or lymph node dissection (6-10). Chemotherapy was started at or within six weeks after radical cystectomy and pelvic lymph node dissection in three of the trials (6,9,10), at eight weeks post-surgery in one trial (7), and the timing of chemotherapy relative to cystectomy was unspecified in one trial (8). The diagnoses of these patients are outlined in Table 1. All patients had deep muscle-invasive TCC with or without lymph node metastases. Studer et al (7) excluded patients who had N2 or N3 nodal disease as revealed by preoperative axial computerized tomography.

The sample sizes in all of these trials were small, ranging from patient accruals of 49 to 91 (Table 2). The chemotherapy regimens also differed among trials, although all contained cisplatin (Table 1). One trial evaluated single-agent cisplatin (7); the others studied combination chemotherapy regimens including methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) (8), cisplatin-methotrexate-vinblastine (CMV) (9), and cisplatin-doxorubicin-cyclophosphamide (CAP) (6). A substantial number of patients who had been randomized to receive

chemotherapy received no chemotherapy (range, 4% to 31%), less than two courses of chemotherapy, or had their regimens modified on an individual basis (Table 1).

Overall Survival

In the three trials that reported statistical comparisons of chemotherapy versus observation, adjuvant chemotherapy did not significantly prolong overall survival of patients with muscle-invasive TCC of the bladder (6,7,9). The trial by Skinner et al (6) warrants some clarification since the median survival values and five-year survival rates appear contradictory (Table 2). In their paper, Skinner et al report median survival for chemotherapy versus observation groups to be 4.25 years (51 months) versus 2.4 years (29 months), respectively. The two- and three-year survival probabilities for chemotherapy versus observation (data not shown) are in the same direction as median survival (i.e., better survival associated with chemotherapy). However, it appears from examination of the survival curves (Skinner et al, 1991, p. 462, Figure 2A) that the chemotherapy and observation curves cross just prior to five years after cystectomy. This finding explains why the five-year survival data are in the opposite direction (i.e., worse survival with chemotherapy) from the median survival times, which are less than five years.

Table 1. Randomized controlled trials comparing adjuvant chemotherapy with observation in patients with deep muscle-invasive transitional cell carcinoma of the bladder: trial descriptions.

First author, year (reference)	Diagnoses of bladder cancer included in trial	Median follow-up (mos)	Chemotherapy regimen	No. (%) of patients in chemotherapy arm who received:		
				Planned chemotherapy	Reduced chemotherapy	No chemotherapy
Skinner, 1991 (6)	pT3, pT4, or N+/- M0*	32	P: 100 mg/m ² A: 60 mg/m ² C: 600 mg/m ² 4 cycles, 28 d intervals	21/44 (48%) cisplatin dose average, 83%; dose intensity, 79%	12/44 (27%) cisplatin dose average, 85%; dose rate, 81%	11/44 (25%)
Studer, 1994 (7) †	T1, T2-T4a, N0-N2, M0*	69	P: 90 mg/m ² 3 cycles, 4 wk intervals	24/37 (65%)‡	6/37 (16%)	7/37 (19%)
Stöckle, 1996 (8)	pT3b, pT4a, or pN1 or pN2*	NR (range, 58 to 96 mos)	MTX: 30 mg/m ² V: 6 mg/m ² P: 70 mg/m ² A or E: 30 mg/m ² 3 cycles	16/26 (62%)	2/26 (8%)	8/26 (31%)§
Freiha 1996 (9)	PT3b, pT4, N+/-, M0	62 (range, 29 to 94 mos)	P: 100 mg/m ² MTX: 30 mg/m ² V: 4 mg/m ² 4 cycles, 21d each	22/25 (88%)	2/25 (8%)	1/25 (4%)
Bono 1997 (10)	T2-T4a, pN+/-	Mean follow-up: 69.2 (range, 7 to 132 mos)	P: 70 mg/m ² MTX: 40 mg/m ² 4 cycles, 21 d each	59/66 (89%)¶	7/66 (11%)¶	0

* The diagnoses listed in this entry of the table are based on the third edition of the Tumour Nodes Metastases (TNM) staging system (15,16). Corresponding diagnoses using the fifth edition of the tumour staging system (1) would be T2b, T3, or T4, respectively.

† This trial was stopped after a planned interim analysis. Differences between the groups were smaller than expected and the accrual rate was too low to detect smaller differences.

‡ Three patients received reduced doses because of toxicity.

§ One of these patients received chemotherapy without cisplatin; the remaining seven refused chemotherapy before or during cycle 1.

|| The report of this trial does not specify the tumour staging system used.

¶ All patients with N+ disease received chemotherapy (n=31). Patients with N0 disease were randomized to chemotherapy (n=35) or observation (n=48). Discontinuations of chemotherapy cycles were necessary in 7 (10.6%) of the 66 patients who received chemotherapy (4 patients with pN+ disease and 3 patients with pN0 disease).

NOTE: A – doxorubicin (adriamycin), C – cyclophosphamide, d – day, E – epirubicin, m – metre, mg – milligram, MTX – methotrexate, mos – months, No. – number, NR – not reported, P – cisplatin, V – vinblastine, wk – week(s).

Table 2. Randomized controlled trials comparing adjuvant chemotherapy with observation in patients with deep muscle-invasive transitional cell carcinoma of the bladder: trial results.

First author, year (ref)	Trial arms	No. pts enrolled/evaluable	No. (%) pts node positive	Disease-free survival			Survival		
				Med (mos)	5-yr rate	Overall DFS	Med (mos)	5-yr rate (95% CI)	Overall survival
Skinner, 1991 (6) *	Obs	47/47	16 (34%)	23	34%	p=0.011 (unstratified Wilcoxon)	29	44%	p=0.099 (unstratified Wilcoxon)
	Chemo	44/44	17 (39%)	79	51%		51	39%	
Studer, 1994 (7) *	Obs	40/40	4 (10%)	NR	NR	NR	NR	54% (39 to 69%)	p=0.65 logrank
	Chemo	40/37	3 (8%)	NR	NR		NR	57% (40 to 74%)	
Stöckle, 1996 (8) †	Obs	NR/23	13 (57%)	NR	14%‡	p=0.006 logrank	NR	NR	NR
	Chemo	NR/26	16 (62%)	NR	42%‡		NR	NR	
Freiha, 1996 (9) ‡	Obs	28/25	17 (68%)	12	23%‡	p=0.01 logrank	36	34% §	p=0.32 logrank
	Chemo	27/25	18 (72%)	37	53%‡		63	54% §	

* The report of this trial is not explicit about whether patients who relapsed were treated.

† Personal communication with first author revealed that only one patient was re-treated with chemotherapy at relapse, and all patients who relapsed died of their disease. The author suggested that under these circumstances, overall survival may be similar to disease-free survival.

‡ Patients who relapsed were treated with cisplatin-methotrexate-vinblastine chemotherapy.

§ These values were obtained from disease-free survival curves or overall survival curves.

NOTE: Chemo – adjuvant chemotherapy group, CI – confidence interval, DFS – disease-free survival, Med – median, mos – months, NR – not reported, No. – number, Obs – observation following cystectomy group, pts – patients, ref – reference, yr – year.

Disease-free Survival

Disease-free survival, defined as the time from cystectomy until evidence of disease recurrence, was significantly prolonged in the adjuvant chemotherapy groups compared with controls in all three trials that reported statistical comparisons between trial arms (6,8,9). Median follow-up times ranged from 62 months in one study (9) to 14 years in a recent update of the Skinner et al trial.¹ Stöckle et al (8) have provided updated data since their preliminary report in 1992 (17); however, the median follow-up time was not explicitly reported. In personal communication with the corresponding author, clarification of the median follow-up time could not be provided as he has since left the institution of note. Additionally, since only one patient was re-treated with chemotherapy at relapse and all patients who relapsed died of their disease, the author suggested that disease-free survival may be similar to overall survival.

Adverse Effects

Adverse effects associated with the adjuvant chemotherapy regimens used in the trials are outlined in Table 3. Symptomatic toxicities included nausea and vomiting (7), dehydration (6), peripheral neuropathy and impaired renal function (7), gastrointestinal toxicities (bleeding and mucositis), and death from neutropenic sepsis (9).

¹ After the guideline-in-progress report had been circulated for practitioner feedback, a GU DSG member found updated survival curves for the Skinner et al trial (6) at a median follow-up of 14 years reported in Stein JP, Lieskovsky G, Cote R, Groshen S, Feng A-C, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666-75. The differences between the two arms were not statistically significant for overall survival (p=0.062 stratified logrank test) or recurrence-free survival (p=0.052 stratified logrank).

Table 3. Reports of adverse effects of chemotherapy in randomized controlled trials of adjuvant chemotherapy versus no adjuvant chemotherapy in muscle-invasive transitional cell carcinoma.

First author, year (reference)	No. of patients evaluated in chemotherapy arm	Adverse effects
Skinner, 1991 (6)	44	10 hospitalizations/108 courses of chemotherapy 5 cases neutropenia and fever 1 case dehydration 4 cases dehydration, neutropenia, and fever
Studer, 1994 (7)	37	30 patients treated 12 cases (40%) nausea 7 cases (23%) vomiting Peripheral neuropathy: reversible - 4 cases (13%) permanent - 3 cases (10%) Impaired renal function: reversible - 3 cases(10%) permanent - 5 cases (17%)
Stöckle, 1996 (8)	26	NR
Freiha, 1996 (9)	25	1 death due to neutropenia and sepsis after 1 cycle 2 cases required hospitalization for neutropenia and fever 6 cases neutropenia leading to delay in chemotherapy 1 case heart failure (nonfatal) 3 cases renal function necessitating reduction in cisplatin dose 8 cases gastrointestinal toxicity 2 cases deep venous thrombosis 1 case deep venous thrombosis and nonfatal pulmonary embolus
Bono, 1997 (10)	66	Grade \geq grade 3 9 cases neutropenia 13 cases mucositis 11 cases renal adverse effects 1 case hematological adverse effects 2 cases "other" adverse effects Note that some patients experienced more than one adverse effect.

Note: No. – number, NR – not reported.

Lymph Node Involvement

Skinner et al (6) assessed the effects of stratification variables (i.e., variables on which patients had been prospectively stratified) on outcomes, both as independent predictors of outcome and as factors that might interact with treatment in their study. Nodal status (no positive nodes, one positive node, or two or more positive nodes) strongly predicted survival ($p=0.0001$ Wilcoxon) and time-to-progression ($p=0.0005$ Wilcoxon). After stratifying for nodal subgroup, treatment effects were statistically significant for both overall survival ($p=0.0062$ stratified Wilcoxon) and time-to-progression ($p=0.0010$ stratified Wilcoxon). Subgroup analyses indicated a statistically significant advantage with chemotherapy for patients with no nodal involvement with respect to time-to-progression ($p=0.043$ Wilcoxon), but not survival ($p=0.14$ Wilcoxon). Patients with one involved node showed statistically significant benefits with chemotherapy for both time-to-progression ($p=0.017$ Wilcoxon) and survival ($p=0.027$ Wilcoxon), whereas no statistically significant differences existed between chemotherapy and observation for patients with two or more involved nodes for either outcome (time-to-progression, $p=0.17$ Wilcoxon; survival, $p=0.23$ Wilcoxon).

Stöckle et al (17) performed a multivariate analysis using a Cox proportional hazards model in which treatment assignment at randomization and basic prognostic factors (patient sex, age at diagnosis, tumour stage, and number of positive lymph nodes) were used as

predictors of relapse-free survival. Results indicated that treatment regimen ($p=0.0007$, two-sided) and number of positive lymph nodes ($p=0.0028$, one-sided) were significant predictors of relapse-free survival: patients in the observation arm or those with more lymph node involvement were at greater risk for recurrence. No data were provided concerning the interaction of chemotherapy with lymph node status, i.e., there were no data concerning the differential effectiveness of chemotherapy on disease-free survival in subgroups of patients defined by nodal status.

Freiha et al (9) provided data on number of survivors by nodal status for chemotherapy versus observation arms, but no statistical comparisons were reported.

Most of the patients enrolled in the Studer et al trial (7) were node-negative; only four patients (10%) in the control arm and three patients (8%) in the chemotherapy arm were lymph node positive, making subgroup analysis or multivariate analysis unfeasible.

V. INTERPRETIVE SUMMARY

The four small RCTs evaluating the role of adjuvant chemotherapy for the treatment of muscle-invasive TCC used a variety of chemotherapy regimens, but all were cisplatin-based. No completed trials studying less toxic combination regimens such as gemcitabine-cisplatin or dose-intense MVAC plus granulocyte-colony stimulating factor (G-CSF) were identified. All four trials failed to detect a survival benefit with adjuvant chemotherapy. Three of the four studies did detect a statistically significant benefit for adjuvant chemotherapy over observation with respect to disease-free survival. In these trials, a large percentage of patients did not receive the planned full course of chemotherapy or did not receive any chemotherapy. Substantial toxicity was noted in patients who received chemotherapy.

Two of the RCTs reported data examining the relationship between lymph node involvement and survival (6) or disease-free survival (6,17). Results indicated that patients with more involved nodes were at higher risk of recurrence or death. Only one small trial addressed the issue of differential effectiveness of chemotherapy in subgroups of patients defined by nodal status (6). Data from this subgroup analysis showed a chemotherapy benefit in all three subgroups defined by nodal status. The magnitude and duration of the benefit appeared to vary with the degree of lymph node involvement. The GU DSG felt that these data should be interpreted cautiously, given the poor quality of the evidence and the small numbers of patients enrolled in the trial.

The available evidence does not support the routine use of adjuvant chemotherapy for treatment of deep muscle-invasive TCC of the bladder. However, given the findings concerning a statistically significant benefit for adjuvant chemotherapy over observation with respect to disease-free survival, chemotherapy could reasonably be offered to patients for whom an improvement in disease-free survival is important. With high-risk patients for whom adjuvant chemotherapy is being considered, a full discussion of the possible benefits and associated risks and toxicities is recommended.

VI. ONGOING TRIALS

Four ongoing randomized trials (EORTC-30994, MSKCC-00138, AUO trial 22/00, and a trial by the Spanish Oncology Genito-Urinary Group (SOGUG)) of adjuvant chemotherapy following cystectomy for muscle-invasive bladder cancer have been located and are summarized below. One of these trials (MSKCC-00138) does not contain an observation control arm (as is standard in the Canadian setting); rather, it compares two chemotherapy regimens. Three other randomized trials of adjuvant chemotherapy have recently been closed or completed (E-1897, AUO trial AB05/95, and LAC-USC-4B951, NCI-G00-1715, NYU-9852). The GU DSG will monitor the progress of these trials and review reported results when they become available.

Protocol ID	Title and details of trial
EORTC-30994	Phase III randomized trial of immediate versus deferred adjuvant chemotherapy after radical cystectomy in patients with stage III or IV transitional cell carcinoma of the urothelium. After cystectomy, patients are randomized to either four cycles of immediate adjuvant chemotherapy or six cycles of chemotherapy deferred until time of clinical relapse. Choice of chemotherapy regimen is determined by centre, but will consist of one of the following chemotherapy combinations: standard MVAC, high-dose MVAC plus G-CSF, or gemcitabine-cisplatin. Outcomes of interest: overall and progression-free survival. Projected accrual: 1344 patients within 5.4 years. Status: active, as of November 2002. Summary last modified: July 2002.
MSKCC-00138	Phase III randomized trial of adjuvant doxorubicin and gemcitabine followed by paclitaxel and cisplatin versus adjuvant cisplatin and gemcitabine in patients with completely resected locally advanced transitional cell carcinoma of the bladder. Outcomes of interest: survival and toxicity; trial will also assess whether p53 and bcl-2 gene expression are predictive factors for survival. Projected accrual: 276 patients within four years. Status: active, as of November 2002. Summary last modified: July 2001.
AUO trial 22/00	Phase III randomized trial of adjuvant gemcitabine monotherapy versus deferred treatment after radical cystectomy in patients with locally advanced bladder cancer unfit for cisplatin-based chemotherapy. Within three months after cystectomy patients are randomized to either six cycles of gemcitabine monotherapy or deferred gemcitabine chemotherapy at time of relapse. Outcomes of interest: progression-free survival. Projected accrual: 178 patients. Status: active, as of February 2002.
SOGUG trial	Phase III randomized trial of adjuvant paclitaxel-cisplatin-gemcitabine versus observation in patients with locally advanced bladder cancer. After cystectomy, patients are randomized to either four cycles of paclitaxel-cisplatin-gemcitabine chemotherapy or observation. Projected accrual: 380 patients. Status: active, as of February 2002.
E-1897	Phase III randomized trial of MVAC versus paclitaxel and carboplatin as postoperative adjuvant therapy in patients with muscle-invasive transitional cell carcinoma of the bladder at high risk of relapse. Outcomes of interest: overall survival, recurrence rates, toxicity, and quality of life. Projected accrual: 490 patients within 2.6 years. Status: closed. Summary last modified: July 2001.

LAC-USC-4B951, NCI-G00-1715, NYU-9852	Phase III randomized study of MVAC versus observation alone based on p53 gene status in patients with organ confined transitional cell carcinoma of the bladder who have undergone radical cystectomy and bilateral pelvic lymphadenectomy. Outcomes of interest: overall and recurrence-free survival. Projected accrual: 760 patients within three years. Status: completed. Summary last modified: January 2001.
AUO trial AB05/95	Phase III randomized study of cisplatin-methotrexate versus MVEC after radical cystectomy in patients with locally advanced as well as node-positive bladder cancer. Projected accrual is 320 patients. Status: completed.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

In developing this practice guideline report, the GU DSG's primary focus was to evaluate the empirical evidence. Currently, available evidence does not support the routine use of adjuvant cisplatin-based chemotherapy in patients with deep muscle-invasive TCC of the bladder. Only one trial addressed the issue of differential effectiveness of chemotherapy in subgroups of patients defined by nodal status. The GU DSG felt that the quality of this evidence and the small numbers of patients included in the subgroup analysis precluded recommendations for treatment.

Disease-free survival appears to be improved with adjuvant chemotherapy; however, it is unclear whether this improvement outweighs the adverse effects of chemotherapy. In light of this apparent benefit, the GU DSG agreed that adjuvant chemotherapy might be a reasonable option to consider for high-risk patients for improvement in disease-free survival. Given this scenario, adjuvant treatment should be discussed with the patient with full disclosure of the lack of overall survival benefit and all associated risks and toxicities.

This review of the evidence did not identify any completed randomized trials that directly compared different chemotherapy regimens. Therefore, for individual patients who opt for adjuvant chemotherapy for the purpose of improving disease-free survival, a cisplatin-based combination from one of the randomized trials is recommended. As MVAC has been shown to be superior to both single-agent cisplatin and CAP in RCTs in metastatic bladder cancer, it is unlikely most oncologists would use the latter regimens as adjuvant treatment. MVAC and CMV have never been directly compared. Recently, results from randomized trials of chemotherapy in the setting of metastatic bladder cancer have shown that gemcitabine-cisplatin combination chemotherapy (18) and dose-intensive MVAC chemotherapy administered with G-CSF (20) have similar activity to standard MVAC in terms of survival outcomes, but with less toxicity. The effectiveness of both these treatment regimens in the adjuvant setting after cystectomy is currently being evaluated in a randomized trial (EORTC Protocol 30994).

The GU DSG reviewed and discussed all comments provided by physicians on the practitioner feedback questionnaire and decided that no changes to the guideline were necessary.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the GU DSG drafted the following recommendations:

Target Population

These draft recommendations apply to adult patients with deep muscle-invasive transitional cell carcinoma of the bladder (defined as pT2b or pT3 or pT4 and pN0-pN2 only) (1)

who have undergone cystectomy. They do not apply to adult patients with superficial muscle invasion (pT2a) (1).

Draft Recommendations

- Post-surgical adjuvant chemotherapy should not be routinely offered to this group of patients.
- If improvement in disease-free survival is important to an individual patient, it is reasonable to consider the use of adjuvant chemotherapy in high-risk patients, with a full discussion of the potential benefits and the associated risks and toxicities.

Qualifying Statement

- The GU DSG did not identify any trials that directly compared different chemotherapy regimens in this patient population. If chemotherapy is opted for, the GU DSG recommends the use of a cisplatin-based combination chemotherapy regimen from one of the RCTs comparing chemotherapy with observation.

Future Research

These recommendations do not preclude the use of adjuvant chemotherapy in the context of clinical trials. The GU DSG encourages patient enrolment in clinical trials.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #3-2-2: *Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder*.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 123 practitioners in Ontario (86 urologists, 17 medical oncologists, and 20 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GU DSG reviewed the results of the survey.

Results

Key results of the practitioner feedback survey are summarized in Table 4. Seventy-two surveys (59.5%) were returned. Responses include returned completed surveys as well as phone, fax, and email responses. Of the 72 returns, 52 respondents (72.2%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and seven respondents (9.7%) left that question unanswered. Fifty-nine of the 72 physicians who had returned the questionnaires (81.9%) completed the survey.

Table 4. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the “ <i>Choice of Topic</i> ” section of the report, is clear.	56 (94.9)	1 (1.7)	2 (3.4)
There is a need for a clinical practice guideline on this topic.	48 (81.4)	10 (16.9)	1 (1.7)
The literature search is relevant and complete.	51 (87.9)	7 (12.1)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	54 (91.5)	3 (5.1)	2 (3.4)
The draft recommendations in this report are clear.	52 (88.1)	6 (10.2)	1 (1.7)
I agree with the draft recommendations as stated.	48 (81.4)	8 (13.6)	3 (5.1)
This report should be approved as a practice guideline.	44 (74.6)	11 (18.6)	4 (6.8)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	47 (84.0)	6 (10.7)	3 (5.4)

Summary of Written Comments

Of the 59 practitioners who completed the questionnaire, 13 practitioners (22%) provided written comments. The main points contained in the written comments were:

1. One practitioner raised a series of specific issues related to the data and its analysis.
 - (a) With reference to Table 2, the Skinner et al trial, the practitioner asked how the five-year disease-free survival rate could be 51% if overall survival was only 39%?
 - (b) The Interpretive Summary contained the following statement: “In these studies, a large percentage of patients did not receive the planned full course of chemotherapy or did not receive any chemotherapy.” The practitioner commented that the idea that maximal (potentially lethal) therapy is necessary to achieve a benefit is questionable and that it would be important to know outcomes in those who had lesser therapy due to toxicity versus by design versus those who received maximal therapy, to evaluate whether submaximal therapy might be better.
 - (c) The practitioner suggested pooling the studies for which disease-free survival data were available.
 - (d) The practitioner suggested that the GU DSG obtain primary patient data.

2. Three practitioners commented on the poor quality of the available evidence. One of the three made the additional comment that, given the poor quality of the evidence, the guideline was the best that could be done.
3. Two practitioners commented that they agreed with the draft recommendations
4. Two practitioners commented about the general difficulty of implementation of practice guidelines.

Modifications/Actions

1. The DSG responded to the questions relating to the data and its analysis as follows:
 - (a) The GU DSG agreed that it is unusual to obtain higher disease-free survival rates than overall survival rates. DSG members reviewed the original Skinner et al report (4) and concluded that these data reflected the authors' decisions about the definition of disease-free survival and about data censoring.
 - (b) Although a potential beneficial effect could be seen with a suboptimal chemotherapy regimen the GU DSG could not judge the effect of suboptimal chemotherapy from the evidence published. The GU DSG noted that substantial toxicity was noted in this patient group, which likely compromised the ability to give a full planned course of chemotherapy. The results of adjuvant chemotherapy in this setting need to be considered with these limitations, and the GU DSG felt that this would not change the conclusions.
 - (c) The GU DSG considered the possibility of pooling of data, but for reasons cited under "Synthesizing the Evidence" decided not to proceed to a meta-analysis.
 - (d) Although an attempt was made to obtain further information about the studies, the GU DSG felt that it would be difficult to obtain individual patient data. The GU DSG felt that it was reasonable to draw the conclusions highlighted in the guidelines. The limitations of the available evidence have been highlighted in the "Key Evidence" section of the practice guideline.
2. Several comments highlighted the difficulties in drawing reasonable conclusions given the limited number of studies that also had small sample sizes, and their drawbacks. The GU DSG considered these comments but felt that the question addressed in the guideline presented a significant clinical problem, and there was merit in summarizing the evidence. They felt that it was important to draw some conclusions with clear documentation of the limitations of the available evidence.

No modifications were made to the practice guideline.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Nine PGCC members approved the practice guideline report as written, and two members approved the guideline conditional on the GU DSG addressing specific concerns. The two members requested that the GU DSG critically comment on the survival data (Table 2) from the Skinner et al report (6) since the median survival times and the five-year survival rates appeared incongruent. Other suggestions put forward by the PGCC for the GU DSG's consideration were to include a more thorough description of why the GU DSG felt the trial by Bono et al (10) was an incomplete report, include quality of life as an important outcome of interest, and include minor editorial changes to improve clarity.

Modifications/Actions

The GU DSG agreed with the issues raised by members of the PGCC and made the following changes to the guideline report to address the issues: inserted a paragraph in the Outcomes section of the guideline report to clarify the discrepancy surrounding the survival data

from the Skinner et al trial; incorporated a more detailed description of the limitations of the Bono et al trial into the Literature Search Results section of the guideline report; and included quality of life as an outcome of interest, although no quality of life data were actually located by the literature search.

Peer Review Feedback

The practice guideline report was submitted to the Canadian Journal of Urology for publication and was subsequently accepted with minor revisions to the guideline recommendations. Reviewers suggested that the GU DSG address the use of gemcitabine-cisplatin and dose-intensive MVAC plus G-CSF combination chemotherapy as adjuvant treatment in muscle-invasive TCC since both of these regimens have shown equivalent survival outcomes to standard MVAC, but with less toxicity, in metastatic bladder cancer.

Modifications/Actions

Gemcitabine-cisplatin and dose-intensive MVAC plus G-CSF are currently being evaluated in a randomized trial as adjuvant treatment in patients with muscle-invasive TCC who have undergone cystectomy; however, there are currently no completed trials demonstrating their effectiveness in the adjuvant setting. In the absence of direct evidence, the GU DSG believes it is premature to recommend these regimens as treatment for this population of patients with bladder cancer. Nonetheless, the GU DSG did feel it was important to address this issue in their recommendations. The GU DSG qualified their recommendations with a statement to indicate that results from randomized trials of gemcitabine-cisplatin and dose-intensive MVAC plus G-CSF in the setting of metastatic bladder cancer provide indirect evidence that these chemotherapy regimens could offer equivalent benefit to MVAC or CMV, but with less toxicity, in patients with muscle-invasive disease. The Interpretive Summary and DSG Consensus sections of the practice guideline report were modified to reflect this change to the guideline recommendations.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the GU DSG and the Practice Guidelines Coordinating Committee.

Target Population

These recommendations apply to adult patients with deep muscle-invasive transitional cell carcinoma of the bladder (defined as pT2b or pT3 or pT4 and pN0-pN2 (1) only) who have undergone cystectomy. They do not apply to adult patients with superficial muscle invasion (pT2a) (1).

Recommendations

- Post-surgical adjuvant chemotherapy should not be routinely offered to this group of patients.
- It is reasonable to consider the use of adjuvant chemotherapy in high-risk patients for improvement of disease-free survival, provided there is full discussion of the lack of overall survival benefit and the associated risks and toxicities.

Qualifying Statements

- The GU DSG did not identify any trials that directly compared different chemotherapy regimens in this patient population. If chemotherapy is opted for, the GU DSG recommends the use of a cisplatin-based combination chemotherapy regimen such as MVAC or CMV.

- RCTs of gemcitabine-cisplatin and dose-intensive MVAC plus G-CSF in the setting of metastatic transitional cell bladder cancer provide indirect evidence that these regimens could offer equivalent benefit to MVAC or CMV, but with less toxicity, in patients with muscle-invasive disease. The effectiveness of these regimens in the adjuvant setting after cystectomy is currently being evaluated in a randomized trial.

Future Research

These recommendations do not preclude the use of adjuvant chemotherapy in the context of clinical trials. The GU DSG encourages patient enrolment in clinical trials.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #3-2-2: *Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder*.

X. JOURNAL REFERENCE

Segal R, Winquist E, Lukka H, Chin J, Brundage M, Markman BR, and the Cancer Care Ontario Practice Guidelines Initiative Genitourinary Cancer Disease Site Group. Adjuvant chemotherapy for deep muscle-invasive transitional cell bladder carcinoma – a practice guideline. *Can J Urol* 2002; 9 (5): 1625-33.

XI. ACKNOWLEDGEMENTS

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For a complete list of the Genitourinary Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1. Assessment of quality of randomized controlled trials.

Trial first author, year (ref)	Disease stage distribution		Quality Indicators*						
	< T3B / T3B or T4	% N+	Randomization method stated?	Intent-to-treat analysis?	Pts all accounted for?	Med follow-up	No. of pts not enrolled	Evidence of balancing of prognostic factors	Other
Skinner, 1991 (6)	27%/73%	36	Yes	Yes	Yes	32 mos; min 12 mos	59	age, sex, T factor, N factor, grade, CIS, histology	Single institution; extensive node sampling protocol
Studer, 1994 (7)	55%/45%	9	No	Yes	Yes	Min 36 mos	NS	age, sex, T factor, N factor, grade, CIS, histology	Early termination due to poor accrual; 65% of pts received planned chemo cycles
Stockle, 1992 (17) 1996 (8)	Unclear; most pts with T3 or T4	59	Yes	Yes	Yes	Min 58 mos	7 in same time frame	age, sex, T factor, N factor	7 pts refused chemo; 1 pt ineligible; early termination due to stopping rule
Freiha, 1996 (9)	0%/100%	70	No	Yes	5 pts "still on follow-up"	57 mos; min 2 yrs for those reported	1	N factor, age, grade	Salvage CMV offered routinely

* For details of quality indicators, please see references 11-13.

Notes: chemo – chemotherapy, CIS – carcinoma in situ, CMV – cisplatin-methotrexate-vinblastine chemotherapy, med – median, min – minimum, mos – months, N – nodal, No. – number, pts – patients, ref – reference, T – tumour.