Adjuvant chemotherapy for deep muscle-invasive transitional cell bladder carcinoma – a practice guideline

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Background and purpose: *To examine the role of adjuvant chemotherapy in the treatment of patients with deep muscle-invasive transitional cell carcinoma (TCC) of the bladder who have undergone cystectomy.*

Materials and methods: *A systematic review of the published literature was combined with a consensus process, involving the interpretation of evidence within the context of conventional practice, to develop an evidence-based practice guideline for use in Ontario.*

Results: *Five randomized controlled trials (RCTs) comparing adjuvant chemotherapy with observation were found that reported data on survival. Sample sizes of the trials were small, and each of the trials evaluated a cisplatin-based chemotherapy regimen; however, none studied less toxic combination chemotherapy regimens such as gemcitabine-cisplatin or dose-intensive methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) with granulocyte-colony stimulating factor (G-CSF). One trial was excluded due to inadequate reporting of outcomes. The remaining four studies failed to demonstrate an overall survival benefit in favor of adjuvant chemotherapy, although three of the four trials showed statistically significant benefits for adjuvant chemotherapy with respect to disease-free survival.*

Conclusions: *As randomized trials have not proven a benefit in overall survival, adult patients with deep muscle-invasive TCC of the bladder should not be routinely offered adjuvant chemotherapy following cystectomy. Disease-free survival may be improved by adjuvant chemotherapy, but it is unclear whether this improvement compensates for the detrimental effects of chemotherapy. If a patient chooses adjuvant chemotherapy to improve disease-free survival they should be made aware of the lack of proven overall survival benefit, and a cisplatin-based combination chemotherapy regimen such as MVAC or CMV is recommended. RCTs of gemcitabine-cisplatin and dose-intensive MVAC plus G-CSF in the setting of metastatic TCC of the bladder provide indirect evidence that these regimens could offer equivalent benefit to MVAC and CMV but with less toxicity in patients with muscle-invasive disease. The use of these regimens in the adjuvant setting after cystectomy is currently being evaluated in a randomized trial (EORTC trial 30994).*

Key Words: bladder neoplasm, chemotherapy, adjuvant, practice guideline

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Introduction

In recent years, several 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, these

responses are rarely sustained, with only a very small proportion of patients achieving durable remission.[1]

The use of chemotherapy in the treatment of earlier stages of TCC of the urothelium 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.[2] These systemic relapses are due to occult micrometastasis, which might be favorably 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 breast cancer, favorable results with adjuvant chemotherapy have been documented.[3] Adjunctive chemotherapy for urothelial cancer has been studied in a number of randomized trials, primarily in the neoadjuvant setting. Postoperative adjuvant chemotherapy has the advantages of not delaying time to definitive local therapy or 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 tumors, and for deeply invasive or locally advanced tumors (pT2b or pT3 or pT4 and pN0-pN2). Other centres do not use this form of therapy outside of clinical trials.

A clinical practice guideline was developed to answer the question "What is the role of adjuvant chemotherapy in the treatment of patients with deep muscle-invasive TCC of the bladder who have undergone cystectomy?"

Methods

Guideline development

This guideline was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle.[4] Evidence was selected and reviewed by three members of the CCOPGI's Genitourinary Cancer Disease Site Group (GU DSG) and methodologists. The GU DSG comprises urologists, medical and radiation oncologists, and two community representatives. This guideline 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. It is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Feedback from practitioners was obtained through a mailed survey. Practitioners whose practices were relevant to the guideline topic were identified through lists obtained from regional cancer centres. Surveys were sent to a random sample of Ontario practitioners (n=123) comprising of urologists, medical oncologists, and radiation oncologists with expertise in treating genitourinary cancers. The survey consisted of nine questions asking for ratings on the quality of the draft guideline and whether it should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at 2 weeks (post card) and 4 weeks (second mailing of survey). The GU DSG reviewed results of the survey and considered practitioner written comments when finalizing the practice guideline.

Literature search strategy

The MEDLINE (1985 through April 2001) and CANCERLIT (1985 through March 2001) databases were searched using the medical subject heading (MeSH) "bladder neoplasms" 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", "adjuvant chemotherapy". These terms were then combined with the following methodological search terms: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. A search of the Cochrane Library (2001, Issue 2) and personal reprint files was also conducted. Relevant articles identified by the search, or cited in papers and review articles, were retrieved and reviewed.

Study selection

All RCTs that compared adjuvant chemotherapy with observation in the treatment of patients who had undergone cystectomy for the treatment of deep muscle-invasive TCC of the bladder were reviewed. To be eligible for inclusion into this systematic review, it was necessary that each study report provide comparisons of overall survival data and/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. Phase I and II study reports were excluded from this review due to the availability of RCTs. Study reports published in a language other than English or in abstract form were also excluded.

Assessment of trial quality and data pooling

A critical appraisal and interpretative summary of available RCT data was planned. If appropriate, statistical pooling of published overall and disease-free survival data was also planned to facilitate this interpretation using methods described by Parmar et al.[5]

Results

Summary of randomized controlled trials

Five RCTs that compared adjuvant chemotherapy with observation for the treatment of patients who had undergone cystectomy for deep muscle-invasive TCC of the bladder were identified as eligible for inclusion in this systematic review of the evidence.[6-10] A description of these studies is presented in Table 1. No RCTs that compared two different chemotherapy regimens were identified. 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. Therefore, this RCT was excluded and the remaining four RCTs formed the basis of this systematic review of the evidence.[6-9] Data from these four trials are presented in Table 2. None of the identified RCTs reported quality of life data.

In each of the trials, patients were randomly assigned to a control arm (observation only) or a treatment arm (adjuvant chemotherapy), after radical cystectomy and/or lymph node dissection.[6-10] Chemotherapy was started at or within 6 weeks after radical cystectomy and pelvic lymph node dissection in three of the trials,[6,9,10] 8 weeks post-surgery in one trial,[7] and timing of chemotherapy relative to cystectomy was unspecified in one trial.[8] 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 studies were small, with patient accruals ranging from 49 to 91 Table 2. The chemotherapy regimens also differed between studies, although all contained cisplatin Table 1. One RCT used single-agent cisplatin;[7] the others studied combination chemotherapy regimens including MVAC,[8] CMV,[9] or cisplatin-doxorubicin-cyclophosphamide (CAP).[6] A substantial number of patients (ranging from 12% to 52%) who had been randomized to receive chemotherapy either received no chemotherapy, 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 deep muscle-invasive bladder cancer.[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 observation versus chemotherapy groups to be 2.4 years (29 months) versus 4.25 years (51 months), respectively. The 2- and 3-year survival probabilities for observation versus chemotherapy (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 observation and chemotherapy curves cross just prior to 5 years after cystectomy. This finding explains why the 5-year survival data are in the opposite direction (i.e., worse survival with chemotherapy) from median survival times, which are less than 5 years. Updated survival curves for the Skinner et al trial have recently been published in a report by Stein et al.[14] At a median follow-up of 14 years, there was a trend toward improved overall survival favoring adjuvant chemotherapy that was not statistically significant (p=0.062 logrank test stratified by nodal status).

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 the two 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 trial.[14] The updated data on disease-free survival from the Skinner trial[14] showed a trend toward improved disease-free survival favoring adjuvant chemotherapy that did not prove statistically significant (p=0.052 logrank test stratified by nodal status). Stöckle and colleagues[8] have also provided

TABLE 1. **Randomized controlled trials of adjuvant chemotherapy versus observation in patients with muscle-invasive transitional cell bladder cancer: trial descriptions**

First author, year	Ref.	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 day 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 and/or pN1 or pN2 *	NR (range, 58-96 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+/-, MO‖	62 (range, 29-94 mos)	P: 100 mg/m^2 MTX: 30 mg/m^2 V: 4 mg/m^2 4 cycles, 21 d each	22/25 (88%)	2/25 (8%)	1/25 (4%)
Bono 1997	10	T2-T4a, pN+/-‖	mean follow up: 69.2 (range, 7-132 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 TNM staging system.[11,12] Corresponding diagnoses using the fifth edition of the tumor staging system[13] would be T2b, T3 or T4.

† This trial was stopped after 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 tumor 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 seven (10.6%) of the 66 patients who received chemotherapy (four patients with pN+ disease, three patients with pN0 disease).

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

updated data since their preliminary study in 1992;[15] however, the median follow-up time was not explicitly reported. Attempts to obtain this information by contacting the authors were unsuccessful. Additionally, since only one patient was re-treated with chemotherapy at relapse and all patients who relapsed died of their disease, disease-free survival may be similar to overall survival.

TABLE 2. **Randomized controlled trials of adjuvant chemotherapy versus observation in patients with muscle-invasive transitional cell bladder cancer: trial results**

First author, year	Ref.	Trial arms	No. patients enrolled/ evaluated	No. (%) patients node positive	Disease-free survival Median (mos)	5-yr rate	Overall DFS	Survival Median (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%-69%)	p=0.65 logrank
		Chemo	40/37	3 (8%)	NR	NR		NR	57% (40%-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, mos – months, NR – not reported, No. – number, Obs – observation following cystectomy group, yr - year

Assessment of trial quality and data pooling

The GU DSG undertook an assessment of the four RCTs, including an evaluation of trial quality, to inform their decision concerning whether data pooling should be performed.

The relatively small sample size of the RCTs 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,[16] Chalmers et al,[17] and O'Rourke et al.[18] 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 two trials stated randomization methods,[6,8] all trials provided evidence of balance in prognostic factors 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 seen concurrently in participating institutions that were not enrolled in the clinical trials.[6,8,9] One trial was stopped appropriately at the time of interim analysis[8] and another was discontinued due to slow accrual.[7]

Although the quality of the trials was deemed adequate, the trials were judged to be clinically heterogeneous as they enrolled patients with different base-line risks of clinical disease progression, and therefore, different potential efficacy of chemotherapy interventions. For example, 9% of patients enrolled in the Studer trial[7] had involved lymph nodes and 55% had stage T3A disease or less, whereas 70% of patients enrolled in the Freiha study[9] had involved lymph nodes and no patient had less than T3B disease. In light of the clinical heterogeneity of enrolled patients, and the substantial clinical heterogeneity in relevant aspects of the treatment protocols studied in these trials, the consensus of the GU DSG was that the clinical heterogeneity of the studies precluded their combination in a meta-analysis.[19]

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, mucositis), and death from neutropenic sepsis.[9]

Lymph node involvement

Skinner and colleagues[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 adjuvant chemotherapy for patients

TABLE 3. **Adverse effects of chemotherapy in randomized controlled trials of adjuvant chemotherapy versus observation in muscle-invasive transitional cell bladder cancer**

First author, year	Ref.	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	Not reported
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 ≥ 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

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 there were no statistically significant differences 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 and colleagues[15] performed a multivariate analysis using a Cox proportional hazard model in which treatment assignment at randomization and basic prognostic factors (patient sex, age at diagnosis, tumor stage, 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 and 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 and colleagues[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 trial[7] were node-negative; only four patients (10%) on the control arm and three patients (8%) on the chemotherapy arm were lymph node positive, making subgroup analysis or multivariate analysis unfeasible.

Results of the practitioner feedback survey

Sixty percent of practitioners returned surveys and 81% of practitioners agreed with the draft of the guideline. The main points raised by the 22% of practitioners who provided written comments were: 1) that it would be important to compare outcomes in patients who received less or no chemotherapy, as a result of toxicity or study design, to those who received maximal therapy in order to evaluate whether submaximal chemotherapy is a better treatment regimen; 2) that it would be useful to examine outcomes by either obtaining primary patient data or pooling studies for which disease-free survival data are available; and 3) a number of practitioners commented on the poor quality of available evidence. The GU DSG deliberated all comments provided by practitioners, but no substantive modifications were made to the practice guideline. More detailed survey results and the GU DSG's responses to comments are available in the full guideline report which can be found at www.ccopebc.ca.

Discussion

The four small RCTs evaluating the role of adjuvant chemotherapy for the treatment of deep 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-intensified MVAC plus G-CSF were identified. All four trials failed to detect a survival benefit with adjuvant chemotherapy. However, due to the small sample sizes involved, moderate sized treatment effects could not be excluded. Three of the four studies did demonstrate a statistically significant improvement in disease-free survival with adjuvant chemotherapy over observation, which also appeared to be clinically significant. In these studies, a large percentage of patients either did not receive the planned full course of chemotherapy or received no chemotherapy at all. Substantial toxicity was noted in patients who received chemotherapy.

Two of the four RCTs reported data examining the relationship between lymph node involvement and survival[6] or disease-free survival.[6,15] Results from these studies 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 the subgroup analysis in this trial 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.

In developing this practice guideline, the GU DSG's primary focus was to evaluate the empirical evidence. Presently, available evidence does not support the routine use of adjuvant cisplatin-based chemotherapy in patients with deep muscle-invasive TCC of the bladder; and limited data preclude the formulation of treatment recommendations for subgroups of patients defined by nodal status. Disease-free survival appears to be improved with adjuvant chemotherapy; however, it is unclear whether this improvement out weighs 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 RCTs 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 chemotherapy from one of the RCTs is recommended. As MVAC has been shown 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[20] and dose-intensive MVAC chemotherapy administered with G-CSF[21] have similar activity to standard MVAC in terms of survival outcomes, but with less toxicity. There are presently no completed trials demonstrating the effectiveness of either of these treatment regimens in the adjuvant setting; however, the EORTC has recently initiated a randomized phase III trial (EORTC Protocol 30994) that is specifically designed to evaluate the role of these regimens in the adjuvant setting after cystectomy.[22] Other large RCTs of adjuvant chemotherapy that are currently underway include an evaluation of MVAC versus paclitaxel and carboplatin in patients with muscle-invasive disease at high risk of relapse,[23] and MVAC versus observation in patients defined by p53 gene status.[24] Whenever possible, patients should be encouraged to participate in these trials. An alternative treatment strategy for patients with muscle-invasive TCC of the bladder includes the use of neoadjuvant chemotherapy prior to cystectomy. A discussion of the role of neoadjuvant chemotherapy is considered in a separate guideline prepared by the GU DSG that is currently being prepared for publication.

Practice guideline

These recommendations apply to adult patients with deep muscle-invasive TCC 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).

- 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.
- 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 TCC of the bladder 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.
- Participation in clinical trials of adjuvant chemotherapy in this setting should be encouraged.

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Please see the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) web site (http://www.ccopebc.ca) for a complete list of current Disease Site Group members. □

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