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Use of Chemotherapy in Advanced Unresectable or Metastatic Transitional Cell Carcinoma of the Bladder or Urothelium

Practice Guideline Report #3-12

Members of the Genitourinary Disease Site Group

Report Date: June 19, 2002

SUMMARY

Guideline Question

What is the optimal chemotherapeutic regimen for patients with advanced unresectable or metastatic cancer of the bladder or urothelium? Overall and progression-free survival, toxicity, quality of life, and clinical improvement are the outcomes of interest.

Target Population

These recommendations apply to adult patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium.

Recommendations*

- Chemotherapy with gemcitabine-cisplatin (GC) or dose-intense methotrexate, vinblastine, doxorubicin, and cisplatin given with granulocyte-colony stimulating factor (DI-MVAC + G-CSF) should be offered to patients with advanced unresectable or metastatic cancer of the bladder or urothelium for the purpose of improving survival.
- Standard MVAC without G-CSF (S-MVAC) remains a chemotherapeutic option and provides similar survival benefits to GC or DI-MVAC + G-CSF but with higher risks of toxicity, including toxic death. In a recent large randomized trial comparing GC with S-MVAC, statistically and clinically significant differences in toxicity favouring GC over S-MVAC were seen; rates of neutropenic sepsis, mucositis, and unfavourable effects on weight were significantly less with GC. Similar significant differences in toxicity were observed in another large randomized trial that compared DI-MVAC + G-CSF with S-MVAC; in this trial, rates of severe leukopenia, neutropenic fever, and mucositis were significantly less with DI-MVAC + G-CSF compared with S-MVAC.
- Chemotherapy with cisplatin-methotrexate-vinblastine (CMV) is a reasonable alternative for patients who cannot receive doxorubicin or gemcitabine therapy, but has toxicities similar to those of S-MVAC.

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* Details of dose and schedules for recommended treatment regimens are provided in Appendix 1 of the full Practice Guideline Report.

Qualifying Statements

- This guideline does not apply to patients with superficial or locally advanced transitional cell carcinoma of the bladder or bladder cancer of non-transitional histology.

Methods

Entries to MEDLINE (1996 through November 2000), CANCERLIT (1983 through October 2000), and Cochrane Library (2000, Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2000) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected by one member and reviewed by three members of the Practice Guidelines Initiative's Genitourinary Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Genitourinary Cancer Disease Site Group, 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 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 consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- S-MVAC and CMV have demonstrated improved response, progression-free survival, and overall survival rates when compared with control chemotherapy regimens in randomized trials. Toxicity associated with S-MVAC and CMV is not inconsequential and toxic death rates up to five percent have been reported.
- Combination chemotherapy with S-MVAC, GC, and DI-MVAC + G-CSF provides similar overall and progression-free survival outcomes. One large trial comparing GC with S-MVAC detected an equivalent response rate and no statistically significant difference in overall survival (median survival, 13.8 months versus 14.8 respectively; hazard ratio [HR], 1.04; 95% CI, 0.82-1.32; p=0.75). Another trial, published in abstract form, detected a superior response rate and no statistically significant difference in two-year survival with DI-MVAC + G-CSF when compared with S-MVAC (35% versus 25%, respectively; HR, 0.80; 95% CI, 0.60-1.06; logrank p=0.1218)
    - Toxicity risks differ among chemotherapy regimens with reported toxic death rates of up to five percent with S-MVAC, one percent with GC, and three percent with DI-MVAC + G-CSF.
    - GC was associated with significantly less neutropenic sepsis (1% versus 12%, p<0.001), grade 3 or 4 mucositis (1% versus 22%, p=0.001), and unfavourable effects on weight (weight gain ≥5% from baseline, 12% versus 3%; p=0.002 and weight loss ≥5% from baseline, 8% versus 16%; p=0.02) compared to S-MVAC. Clinically important differences favouring GC were observed in rates of grade 4 neutropenia (30% versus 65%), neutropenic fever (2% versus 14%), and grade 3 or 4 alopecia (11% versus 55%). GC was associated with more grade 3 or 4 anemia (27% versus 18%) and asymptomatic thrombocytopenia (57% versus 21%) than S-MVAC.
    - DI-MVAC + G-CSF was associated with significantly less grade 2 to 4 leukopenia (41% versus 84%, p<0.001), neutropenic fever (10% versus 26%, p<0.001), and grade 3 or 4 mucositis (10% versus 17%, p=0.034), but more asymptomatic grade 2 to 4 thrombocytopenia (38% versus 29%, p<0.033) compared to S-MVAC.

Future Research

As most patients with advanced unresectable or metastatic cancer of the bladder or urothelium die of the disease within two years of diagnosis despite the use of cisplatin-based combination chemotherapy, these patients should continue to be encouraged to participate in controlled clinical trials studying novel agents and drug combinations.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #3-2-1: *Use of Adjuvant Chemotherapy Following Cystectomy in Patients with Deep Muscle-Invasive 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. 54703; FAX (905) 575-6326.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit http://www.cancercare.on.ca/access_PEBC.htm for all additional Practice Guidelines Initiative reports.

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 enable 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.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:
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FULL REPORT

I. QUESTION

What is the optimal chemotherapeutic regimen for patients with advanced unresectable or metastatic cancer of the bladder or urothelium? Overall and progression-free survival, toxicity, quality of life, and clinical improvement are the outcomes of interest.

II. CHOICE OF TOPIC AND RATIONALE

Transitional cell carcinoma of the urothelial tract is considered chemosensitive and at least a dozen different cytotoxic agents have demonstrated activity in phase II trials (1,2). Despite definitive local therapy with cystectomy and/or radical radiotherapy, approximately 50% of patients with stage II or III transitional cell carcinoma of the bladder ultimately die of their cancer, usually due to complications of metastatic disease (3). Since the mid-1980s, combination chemotherapy including methotrexate, vinblastine, and cisplatin with (MVAC) or without doxorubicin (CMV) have been considered standard combination chemotherapy regimens for treatment of patients with metastatic bladder or urothelial cancer (standard MVAC is referred to as S-MVAC in succeeding text). Recent randomized trials have compared other drug combinations with S-MVAC. The purpose of this practice guideline report is to review chemotherapy regimens which might improve the overall and/or progression-free survival of patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium and to identify those likely to provide optimal benefits to this patient population.

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 (4). Evidence was selected by one member and reviewed by three members of the CCOPGI's Genitourinary Cancer Disease Site Group (GU DSG) and methodologists.

The practice guideline report is a convenient and up-to-date source of the best available evidence on chemotherapy for patients with advanced unresectable or metastatic cancer of the bladder or urothelium, 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 enable 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) (1966 through November 2000) and CANCERLIT (Ovid) (1983 through October 2000) databases was carried out. "Bladder neoplasms" (medical subject heading (MeSH)), "carcinoma, transitional cell" (MeSH), "bladder cancer" (text word), bladder carcinoma" (text word), "carcinoma of the bladder" (text word), "cancer of the bladder" (text word), "transitional cell cancer" (text word), "transitional cell

carcinoma" (text word), were combined with "drug therapy" (MeSH and text word), "drug therapy, combination" (MeSH), "antineoplastic agents" (MeSH), "chemotherapy" (text word), "gemcitabine" (text word), and "gemzar" (text word). These terms were then combined with the search terms for the following study designs: practice guidelines, meta-analyses, systematic reviews, randomized controlled trials, and controlled clinical trials. A search of the Cochrane Library database (Issue 4, 2000) and personal reprint files was also conducted. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) for 1997 through 2000 were searched for reports of new or on-going trials. Relevant articles and abstracts were selected by one GU DSG member and reviewed by three GU DSG members and a methodologist. Reference lists from these sources, as well as from review articles on advanced unresectable or metastatic cancer of the bladder or urothelium were also searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or abstracts of:

1. Randomized controlled trials that assessed chemotherapy in patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium and that provided comparisons of overall survival and/or progression-free survival data.
2. Evidence-based practice guidelines concerning chemotherapy for advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium that were based on current evidence.

Exclusion criteria

1. Phase I and phase II trials were not considered for inclusion in this report due to the availability of randomized controlled trials.
2. Trials that contained fewer than 30 patients were excluded, based on a preliminary review of the available evidence.
3. Letters and editorials were not considered.

Synthesizing the Evidence

Statistical pooling was considered. The trials employed different chemotherapy regimens in control and experimental arms, and one regimen (S-MVAC) was used on the experimental arm of some trials and on the control arm of other trials. In light of the clinically important differences in chemotherapy protocols studied in the trials and the stated focus of the practice guideline report to identify (an) optimal chemotherapeutic regimen(s) for patients with advanced unresectable or metastatic cancer of the bladder or urothelium, the GU DSG decided that statistical pooling would not provide clinically useful data and that such pooling could be misleading.

IV. RESULTS

Literature Search Results

The literature search identified two practice guidelines (5,6), both published in 1998, one published in French (5). Since both were based on expert consensus rather than a systematic review of evidence and did not consider the most recent available evidence, they were not considered further. Ten randomized controlled trials (one published in abstract form) that compared cisplatin-based combination chemotherapy with control chemotherapy regimens in patients with advanced unresectable or metastatic transitional cell cancer of the bladder or urothelium were eligible for inclusion in the systematic review of the evidence (7-17). One trial was reported in two publications (13,14).

Outcomes

The ten randomized controlled trials which compared cisplatin-based combination chemotherapy with control chemotherapy regimens in patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium are summarized in Table 1 (trial design), Table 2 (results), and Table 3 (toxicity) (7-17). One trial was reported in two papers (13,14).

Overall survival

All ten randomized controlled trials reported overall survival data (Table 2) (7-17).

Trials published prior to 1990

Four of five trials that were reported prior to 1990 compared single-agent cisplatin (experimental arm) to cisplatin in combination regimens with cyclophosphamide (8), doxorubicin and cyclophosphamide (9,10), or methotrexate (11). The fifth trial reported prior to 1990 compared single-agent doxorubicin with doxorubicin plus cisplatin (7). Each of the five trials reported no statistically significant difference in survival between the two study arms (7-11).

Trials published during the 1990s

Two randomized controlled trials published during the 1990s compared S-MVAC combination chemotherapy (experimental arm) with cisplatin-based chemotherapy (12,13,14). One study compared S-MVAC with cyclophosphamide-doxorubicin-cisplatin combination chemotherapy (12). Results from this study indicated statistically significant improvements in response rate (65% versus 46%, p=0.05) and overall survival (median survival, 11.1 months versus 8.3 months; logrank p=0.000315) with S-MVAC. A North American Intergroup study compared S-MVAC with single-agent cisplatin (13,14). This study also detected significant improvements in response rate (39% versus 12%, p=0.0001) and overall survival (median survival, 12.5 months versus 8.2 months; logrank p=0.00015) with S-MVAC.

A Medical Research Council trial published in 1998 compared CMV combination chemotherapy with methotrexate plus vinblastine (15). Risk of death was reduced by 32% favouring CMV (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.51-0.90; logrank p=0.0065). Median survival was 8.5 months and seven months for CMV and methotrexate plus vinblastine, respectively. Evidence from a post hoc analysis of this trial indicated that CMV chemotherapy was more effective for patients with poor World Health Organization (WHO) performance status than for patients with good performance status.

Trials published after the 1990s

Two recent randomized controlled trials published in 2000 have used S-MVAC as the control arm for comparison with newer combination chemotherapy regimens (16,17). The EORTC-30924 study, reported in abstract form, randomized 263 patients to S-MVAC or a regimen of dose-intense MVAC plus granulocyte colony stimulating factor (DI-MVAC + G-CSF) (16). Median follow-up was 38 months. Ninety percent of patients had WHO performance status scores of 0 or 1. There was a slight imbalance in the number of patients with visceral metastases, with more patients in the S-MVAC arm than in the DI-MVAC + G-CSF arm presenting with visceral metastases (40% versus 31% respectively; p=0.100). An unadjusted analysis showed no statistically significant difference in overall survival at two years between the two trial arms (25% versus 35% for S-MVAC versus DI-MVAC + G-CSF, respectively; HR, 0.80; 95% CI, 0.60-1.06; logrank p=0.1218).

The second recent trial, carried out by an international consortium of investigators, compared a combination of GC with S-MVAC control in 405 patients (17). After randomization, there were small imbalances that favoured the control (S-MVAC) arm in the following pre-

treatment variables: alkaline phosphatase level, M1 status, presence of visceral metastases (S-MVAC, 46% versus GC, 49%), and number of disease sites. Eighty-two percent of patients had a Karnofsky score of 80 or better. Unadjusted analyses indicated no statistically significant difference in overall survival between the two trial arms (median survival, 14.8 months versus 13.8 months for S-MVAC and GC, respectively; HR, 1.04; 95% CI, 0.82-1.32; p=0.75). The analysis of overall survival adjusted for performance status, the presence of visceral metastases at presentation, and alkaline phosphatase levels confirmed the findings of no statistically significant difference in overall survival (HR, 0.95; 95% CI, 0.74-1.22; p-value not reported, but stated to be non-significant).

Table 1. Trial descriptions of randomized controlled trials comparing chemotherapy regimens for the treatment of advanced unresectable or metastatic transitional cell cancer of the bladder or urothelium.

First author, year (reference no.)	Disease site and stage	No. of patients Control v experimental randomized (eligible)	Control therapy	Experimental therapy
Gagliano 1983 (7) [SWOG-7624]	Bladder T3, T4, M1	NR (48) v NR (44) Total: 107 (102) *	Doxorubicin 50 mg/m^2 iv q 21 days	AC q 21 days: Doxorubicin 50 mg/m^2 iv Cisplatin 50 mg/m^2 iv
Soloway 1983 (8) [NBCCGA]	Regionally advanced or metastatic urothelial	62 (50) v 63 (59)	Cisplatin 70 mg/m^2 iv q 21 days	CP q 21 days: Cisplatin 70 mg/m^2 iv Cyclophosphamide 750 mg/m^2 iv
Khandekar 1985 (9) [ECOG]	Disseminated TCC of the urinary tract	NR (67) v NR (63) Total: 135 (130)	Cisplatin 60 mg/m^2 iv q 21 days †	CAD q 21 days: Cyclophosphamide 400 mg/m^2 iv Doxorubicin 40 mg/m^2 iv Cisplatin 60 mg/m^2 iv
Troner 1987 (10) [SECSG]	Inoperable or metastatic cancer of the bladder, ureter or renal pelvis	NR (57) v NR (52) Total: 116 (109) ‡	Cisplatin 60 mg/m^2 iv q 21 days	CAD q 21 days: Cyclophosphamide 400 mg/m^2 iv Doxorubicin 40 mg/m^2 iv Cisplatin 60 mg/m^2 iv
Hillcoat 1989 (11) [ABCSG]	Recurrent or metastatic TCC of the urothelial tract	55 (55) v 53 (53)	Cisplatin 80 mg/m^2 iv q 28 days §	CM q 28 days: Methotrexate 50 mg/m^2 iv d1,15 Cisplatin 80 mg/m^2 iv d2
Logothetis 1990 (12)	Metastatic urothelial tumours	Total: 110 ‖	CISCA (repeated q 21 days): cyclophosphamide 650 mg/m^2 iv d1 doxorubicin 50 mg/m^2 iv d2 cisplatin 100 mg/m^2 iv d2	MVAC q 28 days: Methotrexate 30 mg/m^2 iv d1,15,22 Vinblastine 3 mg/m^2 iv d2,15,22 Doxorubicin 30 mg/m^2 iv d2 Cisplatin 70 mg/m^2 iv d2
Loehrer 1992 (13) Saxman 1997 (14) [Intergroup]	Advanced urothelial carcinoma not curable by surgery or RT	NR (122) v NR (133) Total: 269 (255)	Cisplatin 70 mg/m^2 iv q 28 days	MVAC q 28 days: Methotrexate 30 mg/m^2 iv d1,15,22 Vinblastine 3 mg/m^2 iv d2,15,22 Doxorubicin 30 mg/m^2 iv d2 Cisplatin 70 mg/m^2 iv d2
Mead 1998 (15) [MRC ABCWP]	TCC of the urothelial tract incurable by surgery or radiotherapy	106 (106) v 108 (108) ¶	MV q 21 days: Methotrexate 30 mg/m^2 iv d1,8 Vinblastine 4 mg/m^2 iv d1,8 Folinic acid 15 mg po q 6 hours x 4 d2,9	CMV q 21 days: Methotrexate 30 mg/m^2 iv d1,8 Vinblastine 4 mg/m^2 iv d1,8 Cisplatin 70 mg/m^2 iv d2 Folinic acid 15 mg po q 6 hours x 4 d2,9
Sternberg 2000 (16) [abstract/poster presentation] [EORTC-30924]	Metastatic or inoperable TCC	129 (129) v 134 (134)	MVAC q 28 days: Methotrexate 30 mg/m^2 iv d1,15,22 Vinblastine 3 mg/m^2 iv d2,15,22 Doxorubicin 30 mg/m^2 iv d2 Cisplatin 70 mg/m^2 iv d2	Dose-intense MVAC with G-CSF q 14 days: Methotrexate 30 mg/m^2 iv d1 Vinblastine 3 mg/m^2 iv d2 Doxorubicin 30 mg/m^2 iv d2 Cisplatin 70 mg/m^2 iv d2 G-CSF 300 μg sc d3-11
von der Maase 2000 (17)	T4b, N2, N3 or M1 TCC of the urothelium	202 (202) v 203 (203) #	MVAC q 28 days: Methotrexate 30 mg/m^2 iv d1,15,22 Vinblastine 3 mg/m^2 iv d2,15,22 Doxorubicin 30 mg/m^2 iv d2 Cisplatin 70 mg/m^2 iv d2	GC q 28 days: Gemcitabine 1000 mg/m^2 iv d1,8,15 Cisplatin 70 mg/m^2 iv d2

Notes: ABCSG – Australian Bladder Cancer Study Group, d – day, ECOG – Eastern Co-operative Oncology Group, EORTC – European Organization for Research and Treatment of Cancer, G-CSF – granulocyte-colony stimulating factor, iv – intravenous, MRC ABCWP – Medical

Research Council Advanced Bladder Cancer Working Party, NR – not reported, NBCCGA – National Bladder Cancer Collaborative Group A, po – orally, q – every, SECSG – Southeastern Cancer Study Group, TCC – transitional cell carcinoma, v – versus

* Seventy-eight patients were fully evaluable, 12 patients were partially evaluable, and two patients were not evaluable because of protocol violations.

† Patients who showed disease progression or no change on the control regimen were treated with doxorubicin 40 mg/m^2 plus cyclophosphamide 4000 mg/m^2.

‡ Eight patients were evaluable only for survival and another 10 patients were evaluable for toxicity only; 91 patients were evaluable for response.

§ Patients who showed disease progression on the control regimen were treated with methotrexate 40 mg/m^2

|| One hundred and two patients were assessable for response. Anticipated accrual for the trial was 148 patients. When data from 110 patients were analyzed, they indicated a statistically significant benefit to MVAC over CISCA, and the trial was terminated.

¶ All patients were evaluable for the main endpoint of survival. One hundred and eighty-one patients had evaluable disease and those patients were evaluated for response.

\# All randomized patients were included in survival and toxicity analyses. There were 363 patients with measurable disease. Three hundred and fifteen patients with measurable disease who had received at least one cycle of chemotherapy and had at least one follow-up assessment of tumour were assessed for response.

Table 2. Results of randomized controlled trials comparing chemotherapy regimens for advanced unresectable or metastatic transitional cell cancer of the bladder or urothelium.

First author, year (reference number)	Follow-up duration	Median survival (months): control v experimental	Overall survival comparisons	Median progression-free survival (months): control v experimental	Progression-free survival comparisons	Response rate CR + PR: control v experimental
Gagliano 1983 (7) [SWOG-7624]	NR	*Doxorubicin v AC* 6.5 v 7.2	p=0.82 (statistical test not specified)	NR	NR	*Doxorubicin v AC* 19% (8/41) v 43% (16/37) p=0.02
Soloway 1983 (8) [NBCCGA]	NR	NR	p=NS (no p-value reported)	NR	NR	*Cisplatin v CP* 20% v 11.9% * p=NS
Khandekar 1985 (9) [ECOG]	NR	*Cisplatin v CAD* 6.0 v 7.3	p=0.17 log rank; corrected p=0.15 †	NR	NR	*Cisplatin v CAD* 17% (8/48) v 33% (15/45) p=0.09
Troner 1987 (10) [SECSG]	NR	*Cisplatin v CAD* 4.8 v 6.7	p=NS (no p-value reported)	NR	NR	*Cisplatin v CAD* 15% (7/48) v 21% (9/43) p=NS
Hillcoat 1989 (11) [ABCSG]	Range, 2-5 years	*Cisplatin v CM* 7.2 v 8.7	p=0.70 logrank	*Cisplatin v CM* 2.8 v 5.0	p=0.13 logrank p=0.02 Wilcoxon	*Cisplatin v CM* 31% (17/55) v 45% (24/53) p=0.18
Logothetis 1990 (12)	NR	*CISCA v MVAC* 8.3 v 11.1	p=0.000315 logrank	NR	NR	*CISCA v MVAC* 46% v 65% p<0.05
Loehrer 1992 (13), Saxman 1997 (14) [Intergroup]	Minimum, 6 years	*Cisplatin v MVAC* 8.2 v 12.5 ‡	p=0.00015 logrank	*Cisplatin v MVAC* 2.4 v 6.6 ‡	NR	*Cisplatin v MVAC* 11.6% v 39% p=0.0001
Mead 1998 (15) [MRC ABCWP]	NR	*MV v CMV* 4.5 v 7	HR, 0.68 (95% CI, 0.51-0.90) p=0.0065 logrank	*MV v CMV* 3 v 5.5	HR, 0.55 (95% CI, 0.41-0.73) p=0.0001 logrank	*MV v CMV* 19% v 46% § p=NR
Sternberg 2000 (16) [abstract/poster presentation] [EORTC-30924]	Median, 38 months	*MVAC v DI MVAC + G-CSF* 2 year survival, 25% v 35%	HR, 0.80 || (95% CI, 0.6-1.06) p=0.1218 logrank	*MVAC v DI MVAC + G-CSF* 8.1 v 9.1	HR, 0.75 || (95% CI, 0.58-0.96) p=0.0373 logrank	*MVAC v DI MVAC + G-CSF* 58% v 72% p=0.016 2-sided chi-square
von der Maase 2000 (17)	Median, 19 months	*MVAC v GC* 14.8 v 13.8	HR, 1.04 (95% CI, 0.82-1.32) p=0.75 logrank adjusted HR, 0.95¶ (95% CI, 0.74-1.22) p=NS	*MVAC v GC* 7.4 v 7.4	HR, 1.05 (95% CI, 0.85-1.30) p=0.66 logrank adjusted HR, 0.99¶ (95% CI, 0.79-1.24) p=NS	*MVAC v GC* 45.7% v 49.4% p=0.51 chi-square

Notes: ABCSG – Australian Bladder Cancer Study Group, AC – doxorubicin-cisplatin chemotherapy, CAD – cyclophosphamide-doxorubicin-cisplatin chemotherapy, CI – confidence interval, CISCA – cyclophosphamide-doxorubicin-cisplatin chemotherapy, CM – methotrexate-cisplatin chemotherapy, CMV – methotrexate-vinblastine-cisplatin chemotherapy, CP – cisplatin-cyclophosphamide chemotherapy, CR – complete response(s), DI MVAC + G-CSF – dose intense MVAC plus granulocyte colony-stimulating factor, ECOG – Eastern Co-operative Oncology Group, EORTC – European Organization for Research and Treatment of Cancer, GC – gemcitabine-cisplatin chemotherapy, HR – hazard ratio, MRC ABCWP – Medical Research Council Advanced Bladder Cancer Working Party, MV – methotrexate-vinblastine chemotherapy, MVAC – methotrexate-vinblastine-doxorubicin-cisplatin chemotherapy, NBCCGA – National Bladder Cancer Collaborative Group A, NR – not reported, NS – not significant, PR – partial response(s), SECSG – Southeastern Cancer Study Group, SWOG – Southwest Oncology Group, v – versus.

* Ninety-three patients had measurable disease. Only those patients were evaluated for response.

† The p-value was corrected for the following factors which predicted survival, identified by Cox regression analysis: initial performance status, prior radiotherapy, and presence of lung metastases. Analyses were based on 130 patients.

‡ These data were obtained at median follow-up of 19.7 months. Survival rates for cisplatin versus MVAC at 3 years were 3.2% versus 12.3% respectively, and at 6 years were 1.6% versus 6.8% respectively. Note that data for progression-free survival were reported in a published erratum in *J Clin Oncol* 1993;11:384.

§ the response rate data were based on 88 evaluable patients who received CMV and 93 evaluable patients who received MV.

|| Hazard ratios unadjusted for chance imbalance in prognostic factors favouring the experimental arm.

¶ Hazard ratios adjusted for chance imbalance in prognostic factors favouring the control arm.

Progression-free survival

Five of the ten trials reported time-to-progression or progression-free survival data.

Trial published prior to 1990

The Hillcoat et al trial demonstrated that patients treated with cisplatin plus methotrexate chemotherapy showed a statistically significant improvement in time to progression compared with cisplatin alone early in the follow-up period (Wilcoxon p=0.02), but the two arms were not significantly different when tested with the logrank test (logrank p=0.13)(11). These data suggest an early advantage for the combined chemotherapy arm. However, by the end of two years post-randomization, the early advantage was lost and both trial arms showed 10% of patients to be progression-free.

Trials published during the 1990s

In one study published during the 1990s, progression-free survival was greater with S-MVAC (experimental arm) than with cisplatin (6.6 versus 2.4 months, statistical comparison not provided) (13). Data from a second trial published during the 1990s detected a statistically significant advantage for CMV chemotherapy (experimental arm) compared with methotrexate plus vinblastine (logrank p=0.0001; HR, 0.55; 95% CI, 0.41-0.73); the risk of death or progressive disease was reduced by 45% with CMV chemotherapy (15).

Trials published after the 1990s

The Sternberg et al trial, which involved a comparison of DI-MVAC + G-CSF (experimental arm) versus standard S-MVAC, detected a statistically significant benefit for the dose-intense regimen on unadjusted progression-free survival (logrank p=0.0373; HR, 0.75; 95% CI, 0.58-0.96) (16). The von der Maase et al trial, which reported time to progression data, detected no statistically significant difference between S-MVAC and GC chemotherapy (p=0.66) (HR, 1.05; 95% CI, 0.85-1.30; HR adjusted for pre-treatment prognostic factors, 0.99; 95% CI, 0.79-1.24) (17).

Health-related quality of life and clinical improvement

Only one study collected and reported data on quality of life and clinical improvement. Von der Maase and colleagues assessed quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30, administered at baseline and before each treatment cycle (17). Patients were included in the quality of life analysis if they had completed a baseline questionnaire and at least one additional questionnaire. Results reflect changes in median scores from baseline after each cycle. The quality of life profile was similar in both arms, with small observed differences in the measurement of fatigue. A higher proportion of patients treated with GC showed improvement in fatigue scores (33% versus 28%) and fewer GC-treated patients than S-MVAC-treated patients showed worsening of fatigue (44% versus 49% of patients). The differences were not statistically significant. Quality of life was maintained throughout treatment in both arms, and the data indicated that both arms showed improvement on measures of emotional functioning and pain.

With respect to clinical improvement, more patients on the GC arm than on the S-MVAC arm showed improved performance status (increase of 10 points or more over a period of at least four weeks, 37% versus 31% of patients, difference not statistically significant, no p-value provided) and weight (weight gain from baseline $\geq$5%, 12% versus 3% of patients, p=0.002) (weight loss from baseline $\geq$5%, 8% versus 16% of patients; p=0.02).

Toxicity

Toxicity data for the ten controlled randomized trials are summarized in Table 3.

The comparison of toxicities associated with CMV versus a methotrexate-vinblastine control indicated that rates of treatment-related death, grade 3 leucopenia or thrombocytopenia, neutropenic fever requiring hospital admission and antibiotic treatment, and grade 1 or 2 nephrotoxicity were all higher with CMV (no statistical comparisons provided) (15).

Toxicities associated with S-MVAC have been assessed relative to cyclophosphamide-doxorubicin-cisplatin (12), to single-agent cisplatin (13), to DI-MVAC + G-CSF (16), and to GC (17). When compared with cyclophosphamide-doxorubicin-cisplatin, S-MVAC was associated with lower rates of leukopenic fever and treatment-related deaths (12). In a comparison with single-agent cisplatin, S-MVAC was associated with more toxic deaths, and statistically significant increases in neutropenic fever, sepsis, grades 3 and 4 leukopenia, mucositis, and nausea and vomiting (13).

Comparisons of S-MVAC with DI-MVAC + G-CSF or GC indicated that toxicity risks differ, with reported toxic death rates of up to five percent with S-MVAC, one percent with GC, and three percent with DI-MVAC + G-CSF.[1] Significantly less grade 2 to 4 leukopenia (41% versus 84%; $p<0.001$), neutropenic fever (10% versus 26%; $p<0.001$), and grade 3 or 4 mucositis (10% versus 17%; $p=0.034$), but more asymptomatic grade 2 to 4 thrombocytopenia (38% versus 29%; $p<0.033$) were seen with DI-MVAC + G-CSF than S-MVAC (16). Similarly, GC was associated with significantly less neutropenic sepsis (1% versus 12%, $p<0.001$), grade 3 or 4 mucositis (1% versus 22%; $p=0.001$), and unfavourable effects on weight (weight gain $\geq$5% from baseline, 12% versus 3%; $p=0.002$; weight loss $\geq$5% from baseline, 8% versus 16%; $p=0.02$) than S-MVAC. Clinically significant differences favouring GC in rates of grade 4 neutropenia (30% versus 65%), neutropenic fever (2% versus 14%), and grade 3 or 4 alopecia (11% versus 55%) were also seen. GC was associated with more grade 3 or 4 anemia (27% versus 18%) and asymptomatic thrombocytopenia (57% versus 21%) than S-MVAC, but these were associated with similar transfusion rates and no excess in bleeding (17).

V. INTERPRETIVE SUMMARY

All five of the trials reported prior to 1990 reported comparisons of overall survival data between the experimental and control arms. Four of the trials compared cisplatin alone versus cisplatin in combination with cyclophosphamide (8), doxorubicin and cyclophosphamide (9,10), or with methotrexate (11). One trial compared single-agent doxorubicin with cisplatin-doxorubicin (7). All five of the trials showed no statistically significant differences between the two trial arms for overall survival benefit (7-11). Only one of the trials reported prior to 1990 provided data on progression-free survival (11). In that trial, which compared cisplatin alone with methotrexate plus cisplatin, there was a statistically significant difference in time-to-progression early in the follow-up period in favour of methotrexate-cisplatin when differences were assessed using the Wilcoxon test, but the two arms were not significantly different when tested with the logrank test. The lack of survival benefit seen in these trials could be due to lack of efficacy of the chemotherapy combinations or lack of power to detect small survival differences.

Two trials of S-MVAC compared with cisplatin alone or cisplatin-containing control arms showed significantly improved response, progression-free survival, and overall survival rates for S-MVAC, albeit at the price of increased risk and severity of toxicity (13) and a small risk of toxic death due to treatment (12,13). One study showed similar benefits and risks for CMV compared with methotrexate plus vinblastine (15).

Results from two recent, relatively large studies have shown similar response, progression-free, and overall survival rates with DI-MVAC + G-CSF or GC compared with S-

[1] The data concerning treatment-related death rates in the Sternberg et al trial (16) (S-MVAC, 5% of patients; DI-MVAC + G-CSF, 3%) were obtained through personal communication with Dr. Cora N. Sternberg.

MVAC (16,17). Toxicity is less with each of these regimens compared with S-MVAC. In the case of DI-MVAC + G-CSF, the decrease in toxicity is likely due largely to the addition of G-CSF. It is not known whether adding G-CSF to the S-MVAC regimen would produce similar results.

Table 3. Toxicity data from randomized controlled trials comparing chemotherapy regimens for advanced unresectable or metastatic transitional cell cancer of the bladder or urothelium.

First author, year (reference number)	Toxicity data
Gagliano 1983 (7)	Comparisons of toxicity, doxorubicin v doxorubicin-cisplatin (% of patients) WBC 2000-3000/mm^3, 25% v 51%; p=0.01 Thrombocytopenia (platelet count 50,000-75,000/mm^2), 2% v 8%; p=0.26 SWOG grade 2 gastrointestinal toxicity, 25% v 59%; p=0.003 Toxicity associated with doxorubicin-cisplatin (% of patients) Nephrotoxicity >50cc/min, 54%; 40-50 cc/min, 21%; 30-40 cc/min, 18%; 20-30 cc/min, 5%, <20 cc/min, 3% 1 case of fatal nephrotoxicity
Soloway 1983 (8) [NBCCGA]	% of all patients considered together Nausea and vomiting – severe, 8%; -moderate, 25% Serum creatinine rise to >1.5mg/dl, 27.5% Leukocyte count <2000/mm^3, 6.8% of 59 patients who received cyclophosphamide v 0% of patients on cisplatin-alone arm
Khandekar 1985 (9) [ECOG]	Comparisons of cisplatin v cyclophosphamide-doxorubicin-cisplatin (% of patients) Nausea and vomiting – mild/moderate, 70% v 63%; – severe, 21% v 24% Infection – mild/moderate, 0% v 3%; – life-threatening or lethal, 0% v 2% Genitourinary – mild/moderate, 16% v 18%; – life-threatening or lethal, 0% v 2% Hematologic – mild/moderate, 30% v 43%; – life-threatening or lethal, 0% v 5%
Troner 1987 (10)	Granulocytopenia <500, 27% of patients on cyclophosphamide-doxorubicin-cisplatin arm, v 0% on cisplatin-alone arm Cardiac toxicity, 2 patients on the combination chemotherapy arm Gastrointestinal toxicity was reported to be similar on the two arms.
Hillcoat 1989 (11)	Grade 3 or 4 toxicities, cisplatin v cisplatin-methotrexate (% of patients) Hematological, 8% v 27%; p=0.01 Renal, 0% v 2%; p=0.5 Mucositis, 0% v 20%; p=0.0005 Infection, 0% v 6%; p=0.12 Nausea and vomiting, 25% v 44%; p=0.06 Diarrhea, 0% v 4%; p=0.2 Other (includes electrolyte imbalance, hematuria, bleeding per rectum, phlebitis), 0% v 8%; p=0.06 Two treatment-related deaths on cisplatin-methotrexate arm, one on cisplatin arm after methotrexate therapy given.
Logothetis 1990 (12)	Comparisons of toxicity, cyclophosphamide-doxorubicin-cisplatin v MVAC (% of courses) Leukopenic fever, 14% v 5% Platinum neuropathy, including tinnitus and vertigo, 10% v 7% Renal, serum creatinine level to >0.4 mg/dL, 41% v 17% Hepatic, 10% v 10% Gastrointestinal bleeding, 1% v 1% One treatment-related death on the cyclophosphamide-doxorubicin-cisplatin arm, 0 on the MVAC arm.

Loehrer 1992 (13)	<u>Grade 3 or 4 toxicity, cisplatin v MVAC (% of patients)</u> Anemia, 1% v 1%; p=0.99 Platelet nadir <25,000/mm^3, 2% v 6%; p=0.10 Leukocyte nadir <1,000/ mm^3, 1% v 24%; p<0.0001 Granulocytopenic fever, 0% v 10%; p=0.0002 Sepsis, 1% v 6%; p=0.04 Renal, 3% v 7%; p=0.22 Mucositis, 0% v 17%; p<0.0001 Nausea and vomiting, 1% v 12%; p=0.0004 Neurologic, 3% v 5%; p=0.50 Hepatic, 3% v 1%; p=0.20 Treatment-related deaths, 0 v 4%; p=0.21
Mead 1998 (15)	<u>Comparisons of toxicity, cisplatin-methotrexate-vinblastine v methotrexate-vinblastine (% of patients)</u> Patient unable to complete treatment because of toxicity, 15% v 0% Patient refused to continue treatment because of toxicity, 3% v 0% Grade 3 leucopenia or thrombocytopenia, 5 cases v 0 cases Neutropenic fever requiring hospital admission and IV antibiotics, 11 patients v 2 patients Long-term neurological toxicity, 9 patients v 1 patient Renal, Grade 1 or 2, 19 patients v 4 patients Treatment-related deaths, 4% v 0% of patients
Sternberg 2000 (16) [abstract/poster presentation]	<u>Comparisons of toxicity, Dose-intense MVAC with G-CSF v MVAC (% of patients)</u> WBC, WHO grades 2-4, 41% v 84%; p<0.001 Platelets, WHO grades 2-4, 38% v 29%; p<0.033 Neutropenic fever, 10% v 26%; p<0.001 Mucositis, WHO grades 3 and 4, 10% v 17%; trend over WHO grades p=0.034 Renal toxicity, WHO grade 3, 4% v 3%; trend over WHO grades p=0.851 Treatment-related deaths, 3% v 5%*
von der Maase 2000 (17)	<u>WHO grades 3 or 4 toxicities with incidence >2% of patients, gemcitabine-cisplatin v MVAC (% of patients)</u> Anemia, 27% v 18% Thrombocytopenia, 57% v 21% Neutropenia, 71% v 82% Mucositis, 1% v 22%; p=0.001 Nausea and vomiting, 22% v 21% Alopecia, 11% v 55% Infection, 3% v 15% Diarrhea, 3% v 8% Pulmonary, 3% v 6% Hematuria, 5% v 2% Constipation, 2%v 3% Hemorrhage, 2% v 2% State of consciousness, 1% v 4% Fever, 0% v 3% Neutropenic fever (absolute neutrophil count <500/mm^3 and fever >37°C), 2% v 14% Neutropenic sepsis 1% v 12%; p<0.001 Treatment-related deaths, 1% v 3%, p=NS

Notes: SWOG – Southwest Oncology Group, v – versus, WBC – white blood cell count, WHO – World Health Organization

* These data on toxic death rates were obtained through personal communication with Dr. Cora N. Sternberg.

In summary, the results of clinical trials indicate that S-MVAC confers a survival benefit to patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium, when compared with either single-agent cisplatin or cyclophosphamide-doxorubicin-cisplatin combination chemotherapy. DI-MVAC + G-CSF and GC appear to have similar benefits to S-MVAC in this regard, but provide the survival benefit with less toxicity. It should be noted that there have been no direct comparisons of DI-MVAC + G-CSF versus GC or of either regimen with single-agent cisplatin. Cisplatin-methotrexate-vinblastine has shown a survival benefit when compared with methotrexate-vinblastine but has not been compared with any of the regimens discussed above.

VI. ONGOING TRIALS

Protocol ID(s)	Title and details of trial
EORTC-30987	Phase III randomized study of gemcitabine-cisplatin with or without paclitaxel in patients with stage IV transitional cell carcinoma of the urothelium. As of June 2002: Status, active. Projected accrual, 610 patients within 3.04 years.
EORTC-GU-30986	Phase III randomized study of gemcitabine and carboplatin versus methotrexate, carboplatin, and vinblastine in patients with advanced cancer of the urothelium. As of June 2002: Status, active. Projected accrual, 225 patients within 5 years.
E-4897 GUMC-01011	Phase III randomized study of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. As of December 2001: Status, closed. Projected accrual, 330 patients within 3.3 years.
MDA-DM-92025 NCI-T92-0107D	Phase III randomized trial of FAP (F-FU/IFN-A/CDDP) vs MVAC (MTX/VBL/DOX/CDDP) in patients with advanced urothelial cancers. As of January 2000: Status, closed. Projected accrual, 186 patients over 4 years.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The two relatively large studies which compared either DI-MVAC + G-CSF versus S-MVAC or GC versus S-MVAC were designed to demonstrate differences between the experimental regimens, but results from each of the trials indicated no statistically significant difference between experimental and control (S-MVAC) arms. Lack of a statistically significant difference is often interpreted as equivalence of two therapies. It has been suggested that equivalence can be demonstrated in clinical trials, but that such demonstration would require a research question framed in terms of equivalence between the regimens tested; an *a priori* decision which sets a quantitative boundary for what would constitute equivalence; and appropriate sample size calculations and methods of statistical testing (18). The GU DSG recognized that the two large trials comparing DI-MVAC + G-CSF or GC versus S-MVAC chemotherapy were designed to test differences between the control and experimental arms. After prolonged discussion, it was the consensus of the GU DSG that they were comfortable accepting each of the experimental arms as therapeutically equivalent to S-MVAC, given the large size of each trial, reassuring confidence intervals, and well-established reputations of the trial groups.

The medical oncologists in the group had experience using GC and S-MVAC and supported recommending GC on the basis of inferred therapeutic equivalence and observed reduced toxicity. They also concurred that their clinical experience with GC was consistent with the clinical trial report of reduced toxicity, particularly neutropenic complications and mucositis.

As well, GC was considered a regimen more suitable for outpatient administration and less resource-intensive with regard to both administration and management of complications. The experience of members of the GU DSG with DI-MVAC + G-CSF was too limited to allow comment. The study which compared DI-MVAC + G-CSF with S-MVAC did not adjust its survival analysis for imbalance in baseline prognostic factors and did not collect quality of life data; however, on the basis of the maturity and credibility of the study results, the GU DSG decided that it was reasonable to also recommend DI-MVAC + G-CSF as an efficacious and less toxic alternative to S-MVAC.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

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

Target Population

These draft recommendations apply to adult patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium.

Draft Recommendations[2]

Key Recommendations

- Chemotherapy with gemcitabine-cisplatin or dose-intense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) given with granulocyte-colony stimulating factor (G-CSF) should be offered to appropriate patients with advanced unresectable or metastatic cancer of the bladder or urothelium for the purpose of improving survival.
- Standard MVAC remains a chemotherapeutic option and provides similar survival benefits to gemcitabine-cisplatin or high-dose MVAC with G-CSF but with higher risks of toxicity, including toxic death. Statistically and clinically significant differences favouring gemcitabine-cisplatin over standard MVAC in rates of neutropenic sepsis, mucositis, and unfavourable effects on weight were seen in a large randomized trial. Similarly significant differences favouring dose-intense MVAC with G-CSF over standard MVAC in rates of severe leukopenia, neutropenic fever, and mucositis were seen in another large randomized trial.
- Chemotherapy with cisplatin-methotrexate-vinblastine (CMV) is a reasonable alternative for patients who cannot receive doxorubicin or gemcitabine therapy, but has toxicities similar to those of MVAC.

Qualifying Statements

- This guideline does not apply to patients with superficial or locally advanced transitional cell carcinoma of the bladder or bladder cancer of non-transitional histology.

Future Research

As most patients with advanced unresectable or metastatic cancer of the bladder or urothelium die of the disease within two years of diagnosis despite the use of cisplatin-based combination chemotherapy, these patients should continue to be encouraged to participate in controlled clinical trials studying novel agents and drug combinations.

[2] Details of dose and schedules for recommended treatment regimens are provided in Appendix 1.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #3-2-1: *Use of Adjuvant Chemotherapy Following Cystectomy in Patients with Deep Muscle-Invasive 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 119 practitioners in Ontario (83 urologists, 17 medical oncologists, and 19 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. Sixty-five surveys (56%) were returned. Of the 65 returns, 39 respondents (60%) indicated that the practice guideline report was relevant to their clinical practice, three respondents (5%) were unsure, and one respondent (2%) left that question unanswered. Forty-one of the 65 physicians who had returned the questionnaires (63%) completed the survey.

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

Item	Number (%)		
	Strongly agree or agree No. (%)	**Neither agree nor disagree No. (%)**	**Strongly disagree or disagree No. (%)**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	41 (100)	0 (0)	0 (0)
There is a need for a clinical practice guideline on this topic.	36 (87.8)	5 (12.2)	0 (0)
The literature search is relevant and complete.	36 (87.8)	5 (12.2)	0 (0)
The results of the trials described in the report are interpreted according to my understanding of the data.	36 (87.8)	4 (9.8)	1 (2.4)
The draft recommendations in this report are clear.	37 (90.2)	4 (9.8)	0 (0)
I agree with the draft recommendations as stated.	39 (95.1)	2 (4.9)	0 (0)
This report should be approved as a practice guideline.	37 (90.2)	4 (9.8)	0 (0)
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**
	36 (87.8)	2 (4.9)	3 (7.3)

Summary of Written Comments

Eight respondents (19.5%) provided written comments. The main points contained in the written comments were:

1. One practitioner commented that the GU DSG should note that the performance status of patients eligible for participation in the trials described in the guideline is an important issue. The practitioner noted that the performance status of patients in the trial of GC versus S-MVAC was Karnofsky >70%. In contrast, many patients referred to this practitioner have much lower performance status scores. The physician suggested that patients with low performance status scores should not be offered any chemotherapy.
2. One practitioner commented that the Sternberg et al trial (reported in abstract form) is not reported in terms of its nuances and the abstract did not provide data on dose intensity in each trial arm (presumably higher in the G-CSF arm). The practitioner raised two issues: (a) Was toxicity reduced in the G-CSF arm due to G-CSF or due to the relative reduction of scheduled doses of vinblastine and methotrexate? Would dose reductions of those agents in the non G-CSF arm have led to a more favorable toxicity profile without sacrificing any of the observed disease control in this arm? He/she commented that the data do not permit an examination of this question, but the answer might colour a final guideline recommendation. (b) Will this guideline lead to the approval of G-CSF under section 8, if sought for patients receiving S-MVAC?
3. One practitioner commented that the statement about the improved toxicity profile for GC relative to S-MVAC should be linked to a stronger statement about the use of GC to replace S-MVAC.
4. One practitioner asked what "stage II or III transitional cell carcinoma of the bladder" meant on page 1 of the Full Report, Choice of Topic and Rationale section, and suggested that conventional wording or TNM classification be used instead.
5. One practitioner commented that he/she is already using GC and another physician indicated that he/she is not aware of practices that use chemotherapy other than S-MVAC or GC for metastatic transitional cell carcinoma of the bladder. The second practitioner questioned the need to produce this guideline report, but indicated that the recommendation is acceptable as stated. One practitioner indicated that the document looks like a reasonable guideline.

Modifications/Actions

The GU DSG responded to the questions relating to the data and its interpretation as follows:

1. The GU DSG agreed that performance status is an important factor to consider when treating patients with advanced or metastatic bladder cancer. It is well recognized that clinical trials tend to exclude patients with reduced performance status. Accordingly, clinicians need to interpret data from clinical trials within this context. Without being prescriptive, the GU DSG felt it was important to emphasize the need to individualize chemotherapy treatment based on important prognostic indicators, including performance status.
2. After the practice guideline report was disseminated to practitioners, the full report of the Sternberg trial was published (19). Intended dose intensities for the two trial arms were provided in the published report. Compared to dose intensities in the S-MVAC arm, dose intensities of doxorubicin and cisplatin were doubled in the DI-MVAC + G-CSF arm, and dose intensities of methotrexate and vinblastine were reduced by 30%. The dose intensities ($mg/m^2/wk$) for methotrexate, vinblastine, doxorubicin, and cisplatin were 22.5, 2.25, 7.5, and 17.5, respectively, for the S-MVAC arm, and 15, 1.5, 15, and 35, respectively, for the DI-MVAC + G-CSF arm. As was noted by one practitioner, it is impossible to determine from the Sternberg data why toxicity was reduced in the DI-MVAC + G-CSF arm. The

addition of G-CSF and/or the reduction of scheduled doses of vinblastine and methotrexate are both plausible explanations. The GU DSG recognizes that further research is required to examine the relative contribution of G-CSF to S-MVAC in patients with advanced or metastatic bladder cancer. Approval of G-CSF for use with S-MVAC will ultimately be the responsibility of the Ministry of Health and Long-Term Care.

3. Although an improved toxicity profile has been demonstrated with GC combination chemotherapy compared to S-MVAC, the GU DSG felt that it is premature to recommend one treatment regimen over the other. More specifically, in the absence of a properly designed equivalence trial, the superiority of GC to S-MVAC remains unproven.
4. Stage II and III transitional cell carcinoma of the bladder refer to the TNM tumour classification system, where stage II and stage III are classified as T2a/T2bN0M0 and T3a/T4aN0M0, respectively.

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. Seven PGCC members approved the practice guideline report as written and four members approved the guideline conditional on the GU DSG addressing specific concerns. Prior to the approval of the guideline report, a few PGCC members requested that the GU DSG consider making some modifications to the guideline recommendations. Some PGCC members questioned why the GU DSG did not recommend GC as the preferred chemotherapy option over DI-MVAC + G-CSF, given the lower toxicity associated with GC. Members of the PGCC suggested that the GU DSG modify the wording of the recommendations to include a statement that GC and DI-MVAC + G-CSF are both acceptable chemotherapy options, but that GC is preferred because it is associated with less toxicity. Other suggestions made by the PGCC included some editorial changes to the guideline recommendations and outcomes section of the full report to improve clarity.

Modifications/Actions

The GU DSG decided not to change the wording of the recommendations, in terms of stating that GC is the preferred chemotherapy regimen over DI-MVAC + G-CSF. The GU DSG felt that since these two regimens have not been directly compared in a properly designed equivalence trial, it is speculative to state that GC is the preferred option because it is less toxic than DI-MVAC + G-CSF. The current data suggest that survival outcomes are similar for GC, DI-MVAC + G-CSF, and S-MVAC, but S-MVAC is associated with increased toxicity compared with the other two regimens.

Upon review of the individual comments made by members of the PGCC, the GU DSG felt that some members may have confused outcomes associated with S-MVAC and DI-MVAC + G-CSF. Therefore, to facilitate clarity the DSG developed acronyms for the different chemotherapy regimens, and incorporated these acronyms throughout the entire guideline [gemcitabine-cisplatin (GC); standard MVAC without G-CSF (S-MVAC); dose-intensive MVAC with G-CSF (DI-MVAC + G-CSF)]. The DSG also made the suggested editorial changes to the recommendations and outcomes section of the full report of the guideline.

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 advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium.

Recommendations
- Chemotherapy with gemcitabine-cisplatin (GC) or dose-intense methotrexate, vinblastine, doxorubicin, and cisplatin given with granulocyte-colony stimulating factor (DI-MVAC + G-CSF) should be offered to patients with advanced unresectable or metastatic cancer of the bladder or urothelium for the purpose of improving survival.
- Standard MVAC without G-CSF (S-MVAC) remains a chemotherapeutic option and provides similar survival benefits to GC or DI-MVAC + G-CSF but with higher risks of toxicity, including toxic death. In a recent large randomized trial comparing GC with S-MVAC, statistically and clinically significant differences in toxicity favouring GC over S-MVAC were seen; rates of neutropenic sepsis, mucositis, and unfavourable effects on weight were significantly less with GC. Similar significant differences in toxicity were observed in another large randomized trial that compared DI-MVAC + G-CSF with S-MVAC; in this trial, rates of severe leukopenia, neutropenic fever, and mucositis were significantly less with DI-MVAC + G-CSF compared with S-MVAC.
- Chemotherapy with cisplatin-methotrexate-vinblastine (CMV) is a reasonable alternative for patients who cannot receive doxorubicin or gemcitabine therapy, but has toxicities similar to those of S-MVAC.

Qualifying Statements
- This guideline does not apply to patients with superficial or locally advanced transitional cell carcinoma of the bladder or bladder cancer of non-transitional histology.

Future Research
As most patients with advanced unresectable or metastatic cancer of the bladder or urothelium die of the disease within two years of diagnosis despite the use of cisplatin-based combination chemotherapy, these patients should continue to be encouraged to participate in controlled clinical trials studying novel agents and drug combinations.

Related Guidelines
Practice Guidelines Initiative's Practice Guideline Report #3-2-1: *Use of Adjuvant Chemotherapy Following Cystectomy in Patients with Deep Muscle-Invasive Transitional Cell Carcinoma of the Bladder.*

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For a complete list of the Genitourinary 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. Doses and schedules of recommended treatment regimens.

Regimen	Dose, route, days of administration	Frequency	Reference(s)
Gemcitabine-cisplatin Gemcitabine Cisplatin	 1000 mg/m^2 iv days 1,8,15 70 mg/m^2 iv day 2	every 28 days	17
Dose-intense MVAC with G-CSF Methotrexate Vinblastine Doxorubicin Cisplatin Granulocyte-colony stimulating factor	 30 mg/m^2 iv day 1 3 mg/m^2 iv day 2 30 mg/m^2 iv day 2 70 mg/m^2 iv day 2 300 μg sc days 3-11	every 14 days	16
MVAC Methotrexate Vinblastine Doxorubicin Cisplatin	 30 mg/m^2 iv days 1,15,22 3 mg/m^2 iv days 2,15,22 30 mg/m^2 iv day 2 70 mg/m^2 iv day 2	every 28 days	12-14, 16,17
CMV Methotrexate Vinblastine Cisplatin Folinic acid	 30 mg/m^2 iv days 1,8 4 mg/m^2 iv days 1,8 70 mg/m^2 iv day 2 15 mg po every 6 hours x 4, days 2,9	every 21 days	15

Notes: iv – intravenous, po – orally, sc - subcutaneous