Complete Summary

GUIDELINE TITLE

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

BIBLIOGRAPHIC SOURCE(S)

Genitourinary Disease Site Group. Use of chemotherapy in advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Jun 19. 20 p. (Practice guideline; no. 3-12). [19 references]

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SCOPE

DISEASE/CONDITION(S)

Advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the optimal chemotherapeutic regimen for patients with advanced unresectable or metastatic cancer of the bladder or urothelium

TARGET POPULATION

Adult patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium

INTERVENTIONS AND PRACTICES CONSIDERED

1. Chemotherapy with gemcitabine-cisplatin (GC) or dose-intense methotrexate, vinblastine, doxorubicin, and cisplatin given with granulocyte colony-stimulating factor (DI-MVAC + G-CSF)
2. Standard MVAC without G-CSF (S-MVAC)
3. Cisplatin-methotrexate-vinblastine (CMV)

MAJOR OUTCOMES CONSIDERED

- Overall and progression-free survival
- Toxicity
- Quality of life
- Clinical improvement

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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 Genitourinary Disease Site Group (GU DSG) member and reviewed by three Genitourinary Disease Site Group 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.

NUMBER OF SOURCE DOCUMENTS

Ten randomized controlled trials were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Statistical pooling was considered. The trials employed different chemotherapy regimens in control and experimental arms, and one regimen (standard methotrexate, vinblastine, doxorubicin, and cisplatin [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 Genitourinary Disease Site Group (GU DSG) decided that statistical pooling would not provide clinically useful data and that such pooling could be misleading.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The two relatively large studies which compared either dose-intense methotrexate, vinblastine, doxorubicin, and cisplatin given with granulocyte colony-stimulating factor (DI-MVAC + G-CSF) versus standard MVAC without G-CSF (S-MVAC) or gemcitabine-cisplatin (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. The Genitourinary Disease Site Group (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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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 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 Genitourinary Disease Site Group (GU DSG) reviewed the results of the survey.

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.

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.

RECOMMENDATIONS

MAJOR 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.

*Details of dose and schedules for recommended treatment regimens are provided in Appendix 1 of the original guideline document.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Standard methotrexate, vinblastine, doxorubicin, and cisplatin (S-MVAC) and cisplatin-methotrexate-vinblastine (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, gemcitabine-cisplatin (GC), and dose-intense MVAC (DI-MVAC) + granulocyte colony-stimulating factor (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% confidence interval [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).

POTENTIAL HARMS

- Toxicity risks differ among chemotherapy regimens, with reported toxic death rates of up to five percent with standard methotrexate, vinblastine, doxorubicin, and cisplatin (S-MVAC), one percent with gemcitabine-cisplatin

(GC), and three percent with dose-intense MVAC (DI-MVAC) + granulocyte colony-stimulating factor (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 $\geq$5% from baseline, 12% versus 3%; $p=0.002$ and weight loss $\geq$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.

QUALIFYING STATEMENTS

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.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Genitourinary Disease Site Group. Use of chemotherapy in advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Jun 19. 20 p. (Practice guideline; no. 3-12). [19 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Jun 19

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Genitourinary Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of chemotherapy in advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- 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.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 23, 2004.

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