Complete Summary

GUIDELINE TITLE

Use of adjuvant chemotherapy following cystectomy in patients with deep muscle-invasive transitional cell carcinoma of the bladder.

BIBLIOGRAPHIC SOURCE(S)

Genitourinary Disease Site Group. Segal R, Winquist E, Lukka H, Chin J, Brundage M, Markman B. Use of adjuvant chemotherapy following cystectomy in patients with deep muscle-invasive transitional cell carcinoma of the bladder [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan 22. 18 p. (Practice guideline; no. 3-2-1). [19 references]

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.

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SCOPE

DISEASE/CONDITION(S)

Deep muscle-invasive transitional cell carcinoma of the bladder (pT2b or pT3 or pT4 and pN0-pN2)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of adjuvant chemotherapy in the treatment of patients with deep muscle-invasive transitional cell carcinoma of the bladder (pT2b or pT3 or pT4 and pN0-pN2) who have undergone cystectomy

TARGET POPULATION

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

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant chemotherapy including single-agent cisplatin, and combination chemotherapy regimens including methotrexate-vinblastine-doxorubicin (Adriamycin)-cisplatin (MVAC), cisplatin-methotrexate-vinblastine (CMV), and cisplatin-doxorubicin-cyclophosphamide (CAP)

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease-free survival
- Adverse effects
- Quality of life

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

Inclusion and exclusion criteria

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

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

NUMBER OF SOURCE DOCUMENTS

Five randomized controlled trials were identified, but only four were used to form the basis for the review.

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

The relatively small sample size of the randomized trials and their corresponding limited statistical power to detect clinically significant differences in overall

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

Although the quality of the trials was deemed adequate, they were judged to be clinically heterogeneous as they enrolled patients with different baseline risks of clinical disease progression, and therefore, different potential efficacy of the interventions. For example, nine percent of patients enrolled in the Studer et al trial had involved lymph nodes and 55% had stage T3A disease or less, whereas 70% of patients enrolled in the Freiha et al trial 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 the trials, the consensus of the Genitourinary Disease Site Group was that the clinical heterogeneity of the studies precluded their combination in a meta-analysis.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

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

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

This review of the evidence did not identify any completed randomized trials that directly compared different chemotherapy regimens. Therefore, for individual patients who opt for adjuvant chemotherapy for the purpose of improving disease-free survival, a cisplatin-based combination from one of the randomized trials is recommended. As methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) has been shown to be superior to both single-agent cisplatin and cisplatin-doxorubicin-cyclophosphamide (CAP) in randomized controlled trials (RCTs) in metastatic bladder cancer, it is unlikely most oncologists would use the latter regimens as adjuvant treatment. MVAC and cisplatin-methotrexate-vinblastine (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 and dose-intensive MVAC chemotherapy administered with granulocyte colony-stimulating factor (G-CSF) have similar activity to standard MVAC in terms of survival outcomes, but with less toxicity. The effectiveness of both these treatment regimens in the adjuvant setting after cystectomy is currently being evaluated in a randomized trial (EORTC Protocol 30994).

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

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 123 practitioners in Ontario (86 urologists, 17 medical oncologists, and 20 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations 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 reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Nine PGCC members approved the practice guideline

report as written, and two members approved the guideline conditional on the Genitourinary Disease Site Group addressing specific concerns.

The practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Genitourinary Disease Site Group and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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

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

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

POTENTIAL HARMS

Symptomatic toxicities of adjuvant chemotherapy included nausea and vomiting, dehydration, peripheral neuropathy and impaired renal function, gastrointestinal toxicities (bleeding and mucositis), and death from neutropenic sepsis.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The Genitourinary Cancer Disease Site Group (GU DSG) did not identify any trials that directly compared different chemotherapy regimens in this patient population. If chemotherapy is opted for, the Genitourinary Disease Site Group recommends the use of a cisplatin-based combination chemotherapy regimen such as methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) or cisplatin-methotrexate-vinblastine (CMV).
- Randomized controlled trials of gemcitabine-cisplatin and dose-intensive MVAC plus granulocyte colony-stimulating factor in the setting of metastatic transitional cell bladder cancer provide indirect evidence that these regimens could offer equivalent benefit to MVAC or cisplatin-methotrexate-vinblastine, 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.
- 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
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

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

DATE RELEASED

2001 Oct 9 (revised online 2003 Jan 22)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - 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 Cancer 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

Members of the Genitourinary Cancer Disease Site Group disclosed potential conflict of interest information.

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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 adjuvant chemotherapy following cystectomy in patients with deep muscle-invasive transitional cell carcinoma of the bladder. 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 June 23, 2003. The information was verified by the guideline developer as of July 16, 2003. This NGC summary was updated by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 23, 2004.

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