Complete Summary

GUIDELINE TITLE

Non-hormonal systemic therapy in men with metastatic hormone-refractory prostate cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Winquist E, Waldron T, Berry S, Ernst DS, Hotte S, Lukka H, Genitourinary Cancer Disease Site Group. Non-hormonal systemic therapy in men with metastatic hormone-refractory prostate cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Nov 1. 48 p. (Evidence-based series; no. 3-15). [100 references]

GUIDELINE STATUS

This is the current release of the guideline.

The Evidence-based Series report, initially the full original Guideline, 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.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 29, 2008, Mitoxantrone Hydrochloride (Novantrone, Mitroxone, Neotalem, Onkotrone, and Pralifan): The U.S. Food and Drug Administration (FDA) reminded health care professionals who treat patients with mitoxantrone about recommendations that left ventricular ejection fraction (LVEF) be evaluated before initiating treatment and prior to administering each dose of mitoxantrone. FDA offered additional recommendations for cardiac monitoring to detect late-occurring cardiac toxicity, and provided information for patients with multiple sclerosis who receive the drug.

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SCOPE

DISEASE/CONDITION(S)

Metastatic hormone-refractory prostate cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate which non-hormonal systemic therapies are most beneficial and should be recommended for the treatment of hormone-refractory prostate cancer

TARGET POPULATION

Men with progressive hormone-refractory prostate cancer and evidence of metastases

INTERVENTIONS AND PRACTICES CONSIDERED

First-line cytotoxic and non-cytotoxic systemic therapies

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease control
    - Progression-free survival

    - Time-to-progression
    - Time-to-treatment failure
    - Objective and prostatic-specific antigen (PSA) response rates
- Palliative response rate
- Quality of life
- Toxicity

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

Literature Search Strategy

MEDLINE (1966 through February week 2 2005) and EMBASE (1980 through 2005, week 8) databases were searched for relevant papers. MEDLINE was searched using the following medical subject headings: "prostatic neoplasms," "drug therapy," "antineoplastic agents," and "drug therapy, combination," EMBASE was searched using the following Excerpta Medica tree terms: "prostate tumour," "prostate cancer," "drug therapy," "antineoplastic agent," "drug combination," and "combination chemotherapy". In each database those subject headings were combined with the following disease and treatment-specific text words: "prostat: cancer," "prostat: tumo?r," "prostat: carcinoma," and "chemotherapy". Those terms were then combined with search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials.

In addition, the Cochrane Library databases (2004, Issue 4) and the conference proceedings of the American Society of Clinical Oncology (1999 through 2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by five reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. They were published reports or abstracts of randomized controlled trials (RCTs) or meta-analyses comparing a non-hormonal systemic therapy or

combination (i.e., first-line cytotoxic and non-cytotoxic agents excluding bisphosphonates and radiopharmaceuticals) with either placebo or other drug regimens.

2. They included patients with hormone-refractory prostate cancer (HRPC) and metastases, where HRPC was defined as clinical progression (either symptomatically, radiologically, or biochemically) in the presence of a castrate testosterone level.
3. They included a minimum of 50 patients per trial arm.
4. They reported on at least one of the following outcomes: overall survival, disease control (i.e., progression-free survival [PFS], time-to-progression [TTP], time-to-treatment failure [TTF], and objective tumour and prostate-specific antigen [PSA] response), palliative or symptomatic response, quality of life, or toxicity.

or

5. They were published reports of systematic reviews or evidence-based guidelines that addressed the guideline question.

NUMBER OF SOURCE DOCUMENTS

28 randomized controlled trials (RCTs) were eligible for review

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Reports of randomized controlled trials (RCTs) of systemic therapy in hormone-refractory prostate cancer (HRPC) date back 30 years and are highly heterogeneous in terms of patient populations, interventions, and design. Many different drug interventions have been tested, including a variety of single-agent and combination chemotherapy regimens such as estramustine phosphate (EMP) and non-cytotoxic drugs such as liarazole, suramin, and atrasentan. What constitutes standard therapy in the control arms of trials has been controversial and has included placebo, corticosteroids, estramustine phosphate, and cytotoxics. On the basis of those observations, quantitative statistical pooling of RCT data was felt inappropriate, and an interpretive summary of the data was planned with more weight given to RCTs that were adequately powered.

Although valuable for identifying potential anti-tumour activity, it is well recognized that small RCTs report less reliable results and that studies with positive results are more likely to be subsequently reported and published. Theoretically, the results of such trials require confirmation by larger pragmatic RCTs, but this does not always occur. After considering the endpoints of interest for this guideline, the Genitourinary Cancer Disease Site Group (GU DSG) chose a minimum sample size of 50 patients per trial arm. The statistical justification for this is a minimum requirement for an RCT to be powered to reliably detect a difference between a response rate of 10% versus 30% with one-tailed alpha=0.05 and beta=0.20 (i.e., power of 80%). RCTs without the ability to provide at least this level of discrimination were considered underpowered and their results potentially misleading with regard to the endpoints of interest. Because the natural history and management of hormone-refractory prostate cancer has changed in the last three decades, more contemporary studies were emphasized in this guideline to provide clinicians with the most reliable evidence relevant to their current practice. Furthermore, more emphasis on the results of RCTs demonstrating internally consistent benefits in survival, palliation, and quality of life outcomes was planned. Statistical pooling of tumour response rates for docetaxel-based regimens was performed using Review Manager 4.2.3, available through the Cochrane Collaboration, because individual trials were inadequately powered to detect differences.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

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

Following review and discussion of sections 1 (clinical practice guideline) and 2 (systematic review) of this evidence-based series, the Genitourinary Cancer Disease Site Group circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Clinician feedback was obtained through a mailed survey of 105 clinicians in Ontario (11 medical oncologists, 19 radiation oncologists, and 75 urologists). The survey consisted of 23 items evaluating the methods, results, and interpretation 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 final practice guideline report was reviewed by one member of the Program in Evidence-based Care (PEBC) Report Approval Panel and was approved with minor editorial changes.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- For men with clinical or biochemical evidence of progression and evidence of metastases, treatment with docetaxel 75 mg/m^2 administered intravenously every three weeks with 5mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation, and quality of life.
- Alternative therapies that have not demonstrated improvement in overall survival but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone (or hydrocortisone).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials (RCTs).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Two recent, large trials have reported improved overall survival with combination docetaxel (75mg/m^2 intravenously every three weeks) over mitoxantrone-prednisone:
    - In a three-arm trial (n=1006), improved median survival was found for docetaxel-prednisone administered every three weeks compared with mitoxantrone-prednisone (median survival, 18.9 versus 16.5 months; two-sided p=0.009), but no statistically significant survival benefit was observed with docetaxel-prednisone given on a weekly schedule. Improvements in palliative and quality-of-life response were observed with both docetaxel-prednisone regimens. The docetaxel-

prednisone arms were associated with more frequent mild toxicities and similar rates of serious toxicities compared with mitoxantrone-prednisone.
    - In the second trial (n=666), survival time was longer with docetaxel-estramustine compared with mitoxantrone-prednisone (median survival, 17.5 versus 15.6 months, respectively; two-sided p=0.02). Estramustine combined therapy was associated with greater grade 3-4 toxicity (54% versus 34%) and more toxic deaths (seven versus two) than mitoxantrone-prednisone.
- The docetaxel trials provide indirect evidence of similar efficacy and increased toxicity with the addition of estramustine to docetaxel.
- Mitoxantrone plus corticosteroid compared with corticosteroid alone has been evaluated in three trials and shown improved palliative and pain response, quality of life, and/or improved time-to-disease progression compared with initial corticosteroid therapy alone. These trials have not shown improvements in survival.
- Single randomized trials have reported improved time-to-progression with estramustine-vinblastine versus vinblastine alone and vinorelbine-hydrocortisone versus hydrocortisone alone and improved time-to-progression and pain response with suramin-hydrocortisone compared with placebo-hydrocortisone.

POTENTIAL HARMS

- Toxicity attributable to mitoxantrone was minimal as evaluated in three trials, and cardiomyopathy was observed in $\leq$5% of patients.
- Toxicities associated with each specific therapy are outlined in the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Docetaxel-based chemotherapy is the only treatment that has demonstrated an overall survival benefit in men with hormone-refractory prostate cancer.
- The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients and individualized based on their clinical status and preferences.
- In the largest randomized trials reviewed for this guideline, the men enrolled continued on gonadal androgen suppression and discontinued the use of antiandrogens. These manoeuvres are recommended for men with hormone-refractory prostate cancer who receive chemotherapy.
- Men with hormone-refractory prostate cancer should have symptom control optimized.
- Use of estramustine in combination with other cytotoxic agents is not recommended due to the increased risk of clinically important toxicities without evidence of improved survival or palliation.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any

kind whatsoever regarding their content or use or application and disclaims any 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)

Winquist E, Waldron T, Berry S, Ernst DS, Hotte S, Lukka H, Genitourinary Cancer Disease Site Group. Non-hormonal systemic therapy in men with metastatic hormone-refractory prostate cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Nov 1. 48 p. (Evidence-based series; no. 3-15). [100 references]

ADAPTATION

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

DATE RELEASED

2005 Nov 1

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is 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

The members of the Genitourinary Cancer Disease Site Group (GU DSG) disclosed potential conflicts of interest relating to this practice guideline. Three of the guideline authors were co-investigators for the recent Tannock et al trial, and one of those authors was also an investigator for three other trials. Two authors reported involvement with the pharmaceutical company that manufactures the chemotherapy agent recommended in the guideline, including advisory boards and receipt of honoraria.

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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:

- Non-hormonal systemic therapy in men with metastatic hormone-refractory prostate cancer. Evidence-based Series. Toronto (ON): Cancer Care Ontario (CCO), 2005 Nov 1. Various p. (Practice guideline; no. 3-15). 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 summary was completed by ECRI on January 25, 2006. The information was verified by the guideline developer on February 23, 2006. This summary was updated by ECRI Institute on August 11, 2008 following the U.S. Food and Drug Administration advisory on mitoxantrone hydrochloride.

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