

American Society of Clinical Oncology Endorsement of the Cancer Care Ontario Practice Guideline on Nonhormonal Therapy for Men With Metastatic Hormone-Refractory (castration-resistant) Prostate Cancer

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ABSTRACT

Purpose

In 2006, the American Society of Clinical Oncology (ASCO) Board of Directors (BOD) approved a policy and a set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations.

Methods

The Cancer Care Ontario (CCO) Guideline on Non-Hormonal Therapy for Men With Metastatic Hormone-Refractory Prostate Cancer (HRPC) was reviewed for developmental rigor by methodologists. An ad hoc prostate cancer guideline review panel consisting of prostate cancer experts reviewed the content.

Results

The ASCO ad hoc prostate cancer guideline review panel concurred that the recommendations are clear, thorough, based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients. The CCO guideline was subsequently endorsed by the ASCO BOD. The guideline recommends the use of docetaxel, prednisone/hydrocortisone, and/or mitoxantrone in specific settings. Docetaxel-based chemotherapy is the only treatment that has demonstrated an overall survival benefit in men with HRPC. The use of estramustine in combination with other cytotoxic agents is not recommended. Continued gonadal androgen suppression and discontinuance of antiandrogens is recommended for men receiving chemotherapy.

Conclusion

The review panel agreed with the recommendations as stated in the CCO guideline, with the following qualifications: two of the ASCO content reviewers noted the importance of considering other, nonhormonal therapies in this context that are beyond the scope of this guideline. The review panel notes that CCO has published separate guidelines on radiopharmaceuticals and bisphosphonates in men with castration-resistant (ie, hormone-refractory) metastatic prostate cancer.

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INTRODUCTION

In 2006, the American Society of Clinical Oncology (ASCO) Board of Directors approved a policy and a set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations. The goal of the endorsement policy is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership. Endorsement of guidelines will be considered in selected circumstances, either on request from related professional organizations at the discretion of the ASCO Health Services Committee (HSC), or when ASCO seeks to endorse another organization's guideline in lieu of undertaking its own guideline on the same topic. Of note, any guide-

line that is being considered for endorsement by ASCO must have been developed based on a systematic review of the literature.

OVERVIEW OF THE ASCO GUIDELINE ENDORSEMENT PROCESS

The guideline under endorsement consideration is reviewed and approved by the ASCO HSC and by the ASCO Board. The HSC review includes two parts: methodological review and content review. The methodological review is completed by a member of the HSC's Methodology Subcommittee or by ASCO senior guideline staff using the Rigour of Development subscale of the Appraisal of Guidelines

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for Research and Evaluation (AGREE) instrument. The Rigour subscale consists of seven items that assess the quality of the processes used to gather and synthesize the relevant data, and the methods used to formulate the guideline recommendations (Appendix Fig A1). In addition to this methodological review, ASCO staff conducts literature searches to identify relevant studies and additional systematic reviews, meta-analyses, and guidelines that have been published since the guideline under endorsement was completed.

The content review is completed by an ad hoc review panel (Appendix Table A1). The panel members are asked to complete an eight-item Guideline Endorsement Content Review Form that assesses the perceived clarity and clinical utility of the recommendations, and the degree to which the recommendations are consistent with the content reviewers' interpretation of the available data on the topic in question (Appendix Fig A2). This form was adapted by ASCO from the Cancer Care Ontario (CCO) Program in Evidence-Based Care (PEBC) Practitioner Feedback instrument. Final review and approval is completed by the ASCO Board of Directors pending approval by the ad hoc content review panel and the HSC.

CANCER CARE ONTARIO GUIDELINE ON NON-HORMONAL THERAPY FOR MEN WITH METASTATIC HORMONE-REFRACTORY PROSTATE CANCER

The ad hoc content review panel favors the term "metastatic castration-resistant prostate cancer." For the purposes of this guideline review, the term "hormone-resistant prostate cancer" (used in the CCO guideline) and "castration-resistant prostate cancer" should be considered synonymous, meaning prostate cancer that has progressed despite castrate levels of serum testosterone.

Guideline Clinical Questions and Target Population

The CCO guideline asked "Which nonhormonal systemic therapies are most beneficial and should be recommended for the treatment of hormone-refractory prostate cancer (HRPC)?"¹ The target population included men with progressive hormone-refractory prostate cancer with evidence of metastases.

Summary of Guideline Development Methodology and the Key Evidence

The CCO guideline was developed under the auspices of CCO's PEBC by five members of the PEBC's Genitourinary Cancer Disease Site Group and methodologists. The literature search of MEDLINE spanned 1966 to February 2005. Additional databases searched included the Cochrane Library databases (through 2004, issue 4), ASCO Annual Meeting proceedings, the Canadian Medical Association Infobase, EMBASE (1980 to 2005), and the National Guideline Clearinghouse.² Details of the search strategies and the study inclusion criteria are available at <http://www.cancercare.on.ca/pdf/pebc3-15f.pdf>.

The searches identified 83 unique randomized clinical trials (RCTs), 28 of which satisfied the inclusion criteria. These 28 trials, published between 1979 and 2004 and representing a total of 7,627 eligible men, formed the basis for the guideline. A qualitative versus a quantitative (meta-analytic) synthesis of the data was done by the Genitourinary Cancer Disease Site Group given the high degree of heterogeneity among trials in terms of study design, patient populations, and interventions.

Major Guideline Recommendations and Qualifying Statements

The CCO guideline recommendations for nonhormonal therapy in men with castration-resistant (ie, hormone-refractory) prostate cancer are as follows, and are taken verbatim from the CCO guideline:

- For men with clinical or biochemical evidence of progression and evidence of metastases, treatment with docetaxel 75 mg/m² administered intravenously every 3 weeks with 5 mg 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).

The CCO guideline also included the following qualifying statements, which are taken verbatim from the CCO guideline:

- 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 clinical trials reviewed for this guideline, the men enrolled continued on gonadal androgen suppression and discontinued the use of antiandrogens. These maneuvers 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.

RESULTS OF THE ASCO METHODOLOGICAL REVIEW

The methodological review of the CCO guideline was completed independently by three ASCO guideline staff members using the Rigour of Development subscale from the AGREE instrument, as discussed. The score for the Rigour of Development domain is calculated by summing the scores across individual items in the domain and standardizing the total score as a proportion of the maximum possible score. Detailed results of the scoring for this guideline are available on request from guidelines@asco.org. Overall, the CCO guideline scored very high (86%) in terms of methodological quality, with only minor deviations from the ideal (eg, lack of stated exclusion criteria for study selection) as reflected in the AGREE items.

METHODS AND RESULTS OF THE ASCO UPDATED LITERATURE SEARCH

A search for new evidence was conducted by ASCO guidelines staff to identify relevant RCTs, systematic reviews, meta-analyses, and guidelines that have been published since the CCO guideline was completed. Following the strategies described in the CCO

Nonhormonal Therapy in Castration-Resistant Prostate Cancer

Table 1. Summary of Articles From the ASCO Updated Search of the Literature on Nonhormonal Systemic Therapy for Metastatic Hormone-Refractory Prostate Cancer

Reference	Publication Type	No. of Patients	Intervention(s)	Conclusions
Beer et al, ³ 2007	Report of double-blind, placebo-controlled randomized phase II trial	250	DN-101, a new high-dose oral formulation of calcitriol, plus docetaxel v placebo and docetaxel	PSA response rate in the DN-101/docetaxel group was 63% v 52% in the placebo and docetaxel group ($P = .07$). Data suggest that DN-101 was associated with improved survival (a secondary end point). DN-101 did not increase toxicity of weekly docetaxel.
Berry et al, ⁴ 2006	Report of randomized phase III trial	674	Docetaxel and estramustine v mitoxantrone and prednisone	No differences between docetaxel and estramustine v mitoxantrone and prednisone on measures of global quality of life or pain palliation.
Collins et al, ⁵ 2006	Report of systematic review	7 trials representing 2,656 patients	Docetaxel plus prednisolone v other chemotherapy regimens, active supportive care, or placebo	Based on the limited available evidence, 3-weekly docetaxel plus prednisone is superior to mitoxantrone plus prednisone in terms of overall survival, pain and PSA decline, and quality of life. Mitoxantrone plus a corticosteroid does not improve survival compared with a corticosteroid alone.
Fizazi et al, ⁶ 2006	Report of individual patient data meta-analysis	5 trials representing 610 patients	Chemotherapy (docetaxel, paclitaxel, ixabepilone, vinblastine) plus estramustine v chemotherapy alone	Overall survival was significantly better in the estramustine plus chemotherapy arm (HR = 0.82; 95% CI, 0.69 to 0.97; $P = .02$). Estimated 1-year overall survival rate was 57% in estramustine group, 50% in control arm. Combining estramustine with chemotherapy increases overall survival v chemotherapy alone.
Shelley et al, ⁷ 2006	Report of systematic review	47 trials representing 6,929 patients	Chemotherapy (eg, docetaxel, vinblastine, mitoxantrone, fluorouracil) ± hormone therapies	Data from recently completed randomized trials, especially those that evaluated docetaxel, have reported improvements in overall survival, symptom palliation, and quality of life. Chemotherapy should be considered as an option. Informed decision making that considers risks and benefits of therapy is key.

Abbreviations: ASCO, American Society of Clinical Oncology; PSA, prostate-specific antigen; HR, hazard ratio.

guideline, MEDLINE, and the Cochrane Library databases were searched from 2004 to April 2007. The search was restricted to papers published in English and the CCO guideline inclusion criteria were applied to review of the literature search results. Table 1 provides a summary of the relevant evidence identified by the updated search.

RESULTS OF THE ASCO CONTENT REVIEW

The ASCO ad hoc prostate cancer guideline review panel has reviewed the guideline in question and concurs that the recommendations are clear, thorough, are based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients. Overall, the ad hoc review panel agrees with the recommendations as stated in the CCO guideline, with the following qualifications:

- Two of the ASCO content reviewers noted the importance of considering other, nonhormonal therapies in this context that are beyond the scope of this guideline. The ad hoc review panel notes that CCO has published separate guidelines on radiopharmaceuticals and bisphosphonates in men with castration-resistant (ie, hormone-refractory) metastatic prostate cancer, which are available at www.cancercare.on.ca/pdf/pebc14-1f.pdf and www.cancercare.on.ca/pdf/pebc3-14f.pdf, respectively.

ENDORSEMENT RECOMMENDATION

The ASCO ad hoc prostate cancer guideline review panel has reviewed the CCO guideline and endorses the adoption of the guideline.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

Table A1. Members of the Ad Hoc Guideline Content Review Panel

Panel Member	Institution
Howard I. Scher, MD, <i>Chair</i>	Memorial Sloan-Kettering Cancer Center
Ethan M. Basch, MD, ASCO Health Services Committee Liaison	Memorial Sloan-Kettering Cancer Center
Tomasz M. Beer, MD	Oregon Health & Science University
Michael A. Carducci, MD	Johns Hopkins School of Medicine
Celestia S. Higano, MD	University of Washington
Maha H.A. Hussain, MD	University of Michigan

Abbreviation: ASCO, American Society of Clinical Oncology.

Nonhormonal Therapy in Castration-Resistant Prostate Cancer

RIGOUR OF DEVELOPMENT SUBSCALE

Systematic Methods were use to search for evidence.

Strongly Agree			Strongly Disagree
4	3	2	1

Comments

The criteria for selecting the evidence are clearly described.

Strongly Agree			Strongly Disagree
4	3	2	1

Comments

The methods used for formulating the recommendations are clearly described.

Strongly Agree			Strongly Disagree
4	3	2	1

Comments

The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly Agree			Strongly Disagree
4	3	2	1

Comments

There is an explicit link between the recommendations and the supporting evidence.

Strongly Agree			Strongly Disagree
4	3	2	1

Comments

The guideline has been externally reviewed by experts prior to its publication.

Strongly Agree			Strongly Disagree
4	3	2	1

Comments

A procedure for updating the guideline is provided.

Strongly Agree			Strongly Disagree
4	3	2	1

Comments

Fig A1. Rigour of Development scale.

American Society of Clinical Oncology
Practice Guideline Endorsement Content Review Form*

Guideline Title: _____

Organization: _____

Reviewer Name: _____

Background and Instructions. ASCO considers clinical practice guidelines developed by other professional organizations for endorsement. This is done by ASCO most often in lieu of undertaking its own guideline on the same topic. You have been asked to provide a content review of a guideline that is under consideration for endorsement by ASCO. Please check the box that best applies for each of the following items.

	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	Unsure
The results of the studies described in this guideline are interpreted according to my understanding of the data.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The recommendations in this report are clear.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I agree with the recommendations as stated in the guideline.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The recommendations are suitable for the patients for whom they are intended.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The recommendations are too rigid to apply to individual patients.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
When applied, the recommendations will produce more benefits for patients than harms.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The guideline presents options that will be acceptable to patients.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The guideline should be endorsed by ASCO.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*This form was adapted from the Cancer Care Ontario Program in Evidence-Based Care Practitioner Feedback instrument.

Fig A2. American Society of Clinical Oncology Practice Guideline Endorsement Content Review Form.