Complete Summary

GUIDELINE TITLE

Maximal androgen blockade for the treatment of metastatic prostate cancer.

BIBLIOGRAPHIC SOURCE(S)

Genitourinary Cancer Disease Site Group. Maximal androgen blockade for the treatment of metastatic prostate cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Feb 5 [online update]. 26 p. (Practice guideline; no. 3-1). [73 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.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Metastatic prostate cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Surgery
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether maximal androgen blockade (MAB) provides superior overall survival or progression-free survival compared with castration alone in previously untreated men with metastatic prostate cancer

TARGET POPULATION

Adult men with metastatic prostate cancer (D1 or D2, N+/M0 or M1)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Maximal androgen blockade (MAB) consisting of orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist plus antiandrogen.

   Note: LHRH agonists considered included buserelin, goserelin, and leuprolide; Antiandrogens considered included flutamide, nilutamide, bicalutamide (Casodex), and cyproterone acetate. Maximum androgen blockade is not recommended as routine treatment.

2. Castration alone (orchiectomy or LHRH agonist)

MAJOR OUTCOMES CONSIDERED

- Survival
- Disease-free/progression-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

MEDLINE (1980 through February 2002), CANCERLIT (1980 through October 2001) and the Cochrane Library databases (2001, Issue 4) were systematically searched. For the most recent searches (1998 through February 2002 in MEDLINE and 1988 through October 2001 in CANCERLIT), "prostatic neoplasms" (Medical subject heading [MeSH]) was combined with "gonadorelin" (MeSH), "androgen antagonists" (MeSH), "diethylstilbestrol" (MeSH), "castration" (MeSH), and each of the following words or phrases used as text words: "leuprolide", "lupron", "goserelin", "zoladex", "buserelin", "suprefact", "flutamide", "eulexin", "nilutamide", "anandron", "nilandron", "bicalutamide", "casodex", "cyproterone acetate", "androcur", "diethylstilbestrol", "DES", "castration", "orchidectomy", "orchiectomy", "prostatic cancer", "prostate cancer". 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. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or on-going trials. Relevant articles were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Genitourinary Disease Site Group (GU DSG) members contributed papers from their personal reprint files. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines.

Inclusion Criteria

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

1. Published reports of randomized controlled trials (RCTs) or meta-analyses comparing MAB (orchiectomy or luteinizing hormone-releasing hormone [LHRH] agonist plus administration of an antiandrogen) with castration alone (orchiectomy or administration of a luteinizing hormone-releasing hormone agonist) in previously untreated men with metastatic prostate cancer.
2. Published reports providing data on overall survival and/or disease progression-related outcomes.

Exclusion criteria

1. Phase I and phase II trials were excluded from this report due to the availability of randomized controlled trials and meta-analyses.
2. Papers published in a language other than English, letters, and editorials were also excluded.

NUMBER OF SOURCE DOCUMENTS

Seven meta-analyses, 27 randomized controlled trials, an updated report of a randomized trial that was originally published in 1993, and an exploratory analysis of another trial were identified.

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

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

It was decided not to pool the results of trials of maximal androgen blockade (MAB) therapy for metastatic prostate cancer due to the availability of up-to-date, published meta-analyses that included recent randomized controlled trials.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In formulating a recommendation for the use of maximal androgen blockade (MAB), the Genitourinary Cancer Disease Site Group (GU DSG) reviewed and discussed the available data on survival, disease progression-related outcomes, adverse effects, and quality of life as presented in the Prostate Cancer Trialists' Collaborative Group (PCTCG) meta-analysis and the review by Aronson et al. Overall, the DSG weighed the evidence of a small but non-significant difference in overall survival at five years for MAB versus castration alone against the available information on adverse effects and quality of life. Although the PCTCG meta-analysis suggested an absolute survival difference of approximately two percent in favour of MAB therapy and a difference of three percent if only nonsteroidal antiandrogens are considered, the GU DSG questioned the clinical significance of this benefit especially given the greater toxicity profile associated with MAB. Faced with this scenario, the GU DSG felt that the current evidence argued against the routine use of MAB. Members of the GU DSG agreed that monotherapy, consisting of either orchiectomy or the administration of a luteinizing hormone-releasing hormone (LHRH) agonist should be recommended as standard treatment for patients with metastatic prostate cancer.

In wording their recommendation, the GU DSG felt it was important to make a distinction between the long-term use of MAB for treatment of metastatic prostate cancer and the utility of short-term MAB in the prevention of testosterone flare. In patients treated with medical castration, initial treatment with an LHRH agonist is accompanied by a surge in serum testosterone during the first week(s) of therapy, followed by a decline. There is a concern that this surge may exacerbate

existing metastatic disease. In this clinical situation, short-term use of an antiandrogen is indicated to prevent or block the flare phenomenon. The GU DSG felt that in this clinical situation it was reasonable for antiandrogens to be given to patients for a period of two to four weeks following the first administration of an LHRH agonist.

While the GU DSG does not recommend the use of MAB as treatment for patients with metastatic prostate cancer, they recognized that some clinicians may choose to give MAB to individual patients for the purpose of improving survival. Consequently, the GU DSG felt that their recommendation should include a relatively strong statement against the use of MAB therapy using cyproterone acetate due to the poorer survival outcome associated with this MAB regimen. If MAB is to be administered with the intent of improving survival, the GU DSG suggested that MAB therapy contain a nonsteroidal antiandrogen, such as flutamide or nilutamide. Although evidence from the Casodex Combination Study suggests that MAB treatment containing the newer antiandrogen bicalutamide is associated with lower toxicity, the GU DSG considered this evidence to be preliminary. Before beginning treatment with MAB, individual patients should be advised of the potential adverse effects associated with combined treatment and the impact these adverse affects could have on aspects of quality of life.

The GU DSG's final recommendation on MAB therapy applies to adult men with documented metastatic prostate cancer. The recommendations do not address the role of MAB in patients with a rising prostate specific antigen (PSA) who have no evidence of metastatic disease or MAB as neoadjuvant or adjuvant treatment in patients with non-metastatic prostate cancer. The GU DSG believes that the available evidence on MAB in these clinical situations is insufficient for formulating treatment recommendations. The DSG commented that future research may one day uncover molecular or other markers that may help in identifying subgroups of patients who might benefit from MAB treatment.

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 99 practitioners in Ontario (61 urologists, 15 medical oncologists, and 23 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. The practitioner feedback survey was mailed out on June 4, 2002. 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.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eight of nine members of the PGCC returned ballots. Five PGCC members approved the practice guideline report as written, and three members approved the guideline and provided suggestions for consideration by the GU DSG. One PGCC member commented that the guideline report was rather lengthy and suggested the GU DSG consider streamlining the text for a shorter report.

The GU DSG agreed that there were sections of the guideline report where text could be streamlined without the loss of substantive content. The guideline report was reviewed by the GU DSG and sections of the report where text could be condensed were identified. All editorial changes that were made were minor in nature and did not alter the substantive content of the guideline report.

The 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

Maximal androgen blockade (MAB) should not be routinely offered as treatment for patients with documented metastatic prostate cancer beyond the purpose of blocking testosterone flare. Monotherapy, consisting of orchiectomy or a luteinizing hormone-releasing hormone (LHRH) agonist, is recommended as standard treatment for patients with metastatic prostate cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Seven meta-analyses were identified by the literature search and search of personal files. Since the publication of the Prostate Cancer Trialists' Collaborative Group (PCTCG) meta-analysis in 2000, three reports have been published that compare relevant outcomes of maximal androgen blockade (MAB) compared with castration alone. The literature search identified one randomized controlled trial (RCT), an updated report of a randomized trial that was originally published in 1993 and included in the PCTCG meta-analysis, and an exploratory analysis of another trial also included the PCTCG meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- The Genitourinary Cancer Disease Site Group (GU DSG) felt that the most compelling evidence upon which to base a recommendation on maximal androgen blockade (MAB) for the treatment of patients with metastatic prostate cancer, with survival as the endpoint, was the individual patient data meta-analysis published by the Prostate Cancer Trialists' Collaborative Group (PCTCG) in 2000. This meta-analysis evaluated patients with advanced prostate cancer; however, 88% of the patients included in the meta-analysis had documented metastatic disease.
- The PCTCG meta-analysis, which included 8275 patients from 27 randomized controlled trials (RCTs), detected no significant improvement in overall survival with MAB therapy (orchiectomy or luteinizing hormone-releasing hormone [LHRH] agonist plus administration of either a steroidal or nonsteroidal antiandrogen) compared with castration alone (overall mortality rate ratio [MRR], 0.958; standard error [SE], 0.026; p=0.11). An analysis of survival at different follow-up periods indicated no significant difference in survival at two years and a small but non-significant difference at five years in favour of MAB versus castration alone (25.4% versus 23.6%), suggesting an absolute five-year survival difference of approximately two percent (1.8%; SE, 1.3).
- A subgroup analysis performed on the 20 RCTs that included a nonsteroidal antiandrogen (flutamide or nilutamide) in the MAB arm indicated this form of MAB therapy was associated with a statistically significant improvement in five-year survival of approximately three percent compared with castration alone (27.6% versus 24.7%; SE, 1.3; p=0.005).
- A subgroup analysis performed on the seven RCTs that included a steroidal antiandrogen (cyproterone acetate) in the MAB arm indicated this MAB regimen was associated with a statistically significant reduction in five-year survival of approximately three percent compared with castration alone (15.4% versus 18.1%; SE, 2.4; p=0.04).
- A recent systematic review of the literature indicated that 19 of 23 randomized trials that provided data on measures related to disease progression reported no significant differences between MAB and castration alone. Of the four trials that detected significant differences, three reported a statistically significant difference in favour of MAB with nonsteroidal antiandrogens. The other trial, which included cyproterone acetate in the MAB arm, reported a statistically significant advantage to castration alone over MAB for time to disease progression (median time to progression, 11.5 months for castration alone versus 10.8 months for MAB; progression-free survival at two years, 31% versus 21%; p=0.0160).

POTENTIAL HARMS

- To date, only one randomized controlled trial has formally assessed quality of life outcomes associated with the use of maximum androgen blockade (MAB) in patients with metastatic prostate cancer. Measures of quality of life assessed in this trial included three treatment-related symptoms (diarrhea, gas pain, and body image), physical functioning, and emotional functioning. Compared with patients treated with castration alone, patients receiving

maximum androgen blockade reported significantly more diarrhea at three months post-treatment ($p<0.001$) and worse emotional functioning at three and six months post-treatment ($p<0.003$).

- The Casodex Combination Study did not meet the inclusion criteria of this review but was included because it provided data on the newer antiandrogen bicalutamide. Data from this study suggests that differences in toxicity might exist between different luteinizing hormone-releasing hormone (LHRH) agonists and nonsteroidal antiandrogens. In this trial, a greater number of patient withdrawals were observed among patients receiving MAB with flutamide compared to bicalutamide. While there is definitely the possibility of an improved toxicity profile with bicalutamide, this data should be interpreted with caution as the trial was not designed or powered to make comparisons among the four MAB treatment groups.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 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.
- It is the opinion of the Genitourinary Cancer Disease Site Group (GU DSG) that the small statistically significant survival benefit found with maximal androgen blockade (MAB) using nonsteroidal antiandrogens (flutamide or nilutamide) is of questionable clinical significance and does not outweigh the negative side effects of MAB treatment. Patients to whom MAB may be offered should be advised of the small survival benefit and potential adverse effects associated with combined treatment and the impact these adverse effects could have on aspects of quality of life.
- MAB containing the steroidal antiandrogen cyproterone acetate should not be used as this form of MAB treatment has been found to reduce survival compared with castration alone.
- The current evidence does not permit a recommendation regarding the role of MAB in the following clinical situations beyond the purpose of blocking testosterone flare: MAB using the newer antiandrogen bicalutamide, MAB in patients with prostate-specific antigen relapse who have no documented evidence of metastatic disease, and MAB as neoadjuvant or adjuvant hormonal treatment for patients with non-metastatic prostate cancer.

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
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Genitourinary Cancer Disease Site Group. Maximal androgen blockade for the treatment of metastatic prostate cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Feb 5 [online update]. 26 p. (Practice guideline; no. 3-1). [73 references]

ADAPTATION

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

DATE RELEASED

2003 Feb

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 (GU DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

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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 is available:

- Maximal androgen blockade for the treatment of metastatic prostate cancer. 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 July 21, 2003. The information was verified by the guideline developer as of August 6, 2003.

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