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Maximal Androgen Blockade for the Treatment of Metastatic Prostate Cancer

Practice Guideline Report # 3-1

Report Date: February 5, 2003

Members of the Genitourinary Disease Site Group

SUMMARY

Guideline Question

Does maximal androgen blockade (MAB) (orchiectomy or luteinizing hormone-releasing hormone [LHRH] agonist plus administration of an antiandrogen) provide superior overall survival or progression-free survival compared with castration alone (orchiectomy or LHRH agonist) in previously untreated men with metastatic prostate cancer? The outcomes of interest are survival, disease-free or progression-free survival, adverse effects, and quality of life.

Target Population

These recommendations apply to adult men with metastatic prostate cancer (D1 or D2[1], N+/M0 or M1).

Recommendations

- 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 an LHRH agonist, is recommended as standard treatment for patients with metastatic prostate cancer.

Qualifying Statements

- It is the opinion of the Genitourinary Cancer Disease Site Group (GU DSG) that the small statistically significant survival benefit found with 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.

[1] Jewett HJ. The present status of radical prostatectomy for stages A and B prostatic cancer. *Urol Clin North Am* 1975;2:105-24.

Methods

Entries to MEDLINE (1980 through February 2002), CANCERLIT (1980 through October 2001), and Cochrane Library (2001, Issue 4) databases were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's GU DSG and methodologists. This practice guideline report has been reviewed and approved by the GU DSG, which comprises medical and radiation oncologists, urologists, and one patient representative. External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- The GU DSG felt that the most compelling evidence upon which to base a recommendation on 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 (1). 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 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 (2). 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).
- To date, only one RCT has formally assessed quality of life outcomes associated with the use of MAB in patients with metastatic prostate cancer (3,4). 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 MAB reported significantly more diarrhea at three months post-treatment ($p<0.001$) and worse emotional functioning at three and six months post-treatment ($p<0.003$).

Future Research

The GU DSG encourages clinicians to enter patients into randomized trials evaluating MAB using newer agents such as bicalutamide compared with castration alone. These trials should aim to avoid the methodological weaknesses of previous MAB trials and assess quality of life outcomes in addition to survival. Future research could uncover molecular (or other) markers that may identify patients who might benefit from MAB therapy.

For further information about this practice guideline report, please contact: Dr. Himu Lukka, Chair, Genitourinary Cancer Disease Site Group, Hamilton Regional Cancer Centre, 699 Concession Street, Hamilton ON, L8V 5C2; TEL (905) 387-9711 ext. 67699; FAX (905) 575-6326.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

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PREAMBLE: About our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

1. 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.

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Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

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FULL REPORT

I. QUESTION

Does maximal androgen blockade (orchiectomy or luteinizing hormone-releasing hormone [LHRH] agonist plus administration of an antiandrogen) provide superior overall survival or progression-free survival compared with castration alone (orchiectomy or LHRH agonist) in previously untreated men with metastatic prostate cancer (D1 or D2 (5); N+/M0 or M1)? The outcomes of interest are survival, disease-free or progression-free survival, adverse effects, and quality of life.

II. CHOICE OF TOPIC AND RATIONALE

Prostate cancer is currently the most prevalent form of male cancer in Canada, accounting for approximately 25% of all newly diagnosed male cancers (6). In 2001, it was estimated that approximately 17,800 new prostate cancer cases and 4,300 prostate cancer deaths would occur in Canada (6). Over the past several decades, the incidence of prostate cancer has substantially increased. Incidence of the disease dramatically peaked in the late 1980's and early 1990's, followed by a more recent gradual decline in incidence (6). The dramatic rise in prostate cancer incidence has mainly been attributed to prostate specific antigen (PSA) screening and population aging (6,7). As the use of PSA screening has become more widespread, the majority of men are diagnosed at an earlier stage of disease. However, there are still 20-30% of patients who present with advanced or metastatic disease at the time of diagnosis. Of these men, approximately 25% will die from their disease within two years (8). Therapeutic interventions seek not only to increase survival in these patients, but also to improve quality of life (9).

Historically, androgen suppression achieved through surgical castration (orchiectomy) was the gold standard treatment for patients with advanced or metastatic prostate cancer. The advent of medical castration offered an alternative to surgical castration and its associated permanent loss of potency. Early medical interventions to achieve castration involved the administration of diethylstilbestrol, which although effective, was associated with an increase in potentially lethal cardiovascular complications (10). More recent medical interventions have focused on the long-term use of LHRH agonists such as buserelin acetate, goserelin acetate, and leuprolide acetate. These interventions appear to be as effective as surgical castration in removing testicular androgens, with the advantages of causing few side effects and preserving potency (11).

Testicular androgens are the major source of testosterone production; however, the adrenal glands also produce a small but measurable quantity of androgens. It has been hypothesized that removing all effects of circulating androgens by blocking the uptake of adrenal androgens in addition to inhibiting testicular androgen production may be beneficial to patients. Combination treatment in the form of surgical or medical castration plus the administration of an antiandrogen attempts to remove the major source of androgen production and neutralize the effects of the remaining circulating androgens of adrenal origin (8). Combination treatment is commonly referred to as maximal androgen blockade (MAB).

In the early 1980's, Labrie et al were among the first to propose the idea of MAB as a treatment modality for prostate cancer (12). Since this period, an unprecedented number of randomized controlled trials (RCTs) have been conducted to evaluate the efficacy of MAB compared with castration alone. Although these trials have yielded inconsistent results, where the majority of trials have failed to provide convincing evidence of an improved survival benefit with MAB therapy, a few of the larger randomized trials have detected a survival benefit in favour of MAB (13-15). The actual magnitude and clinical significance of this benefit, however, is unclear. Substantial efforts have been made to identify the possible reasons for the discrepant findings of MAB trials. A number of published reports have identified low statistical

power, violation of statistical assumptions, study immaturity, compliance to treatment, and imbalances in prognostic indicators between study arms of individual trials as methodological pitfalls inherent to many of the MAB trials (16-20). More recent attempts to determine the treatment efficacy associated with MAB have involved meta-analyses of the randomized trials (21).

In light of the conflicting evidence surrounding MAB therapy, the Genitourinary Cancer Disease Site Group (GU DSG) felt that it would be useful to both clinicians and patients to systematically review the best available evidence that compares MAB treatment with castration alone and subsequently develop an evidence-based practice guideline based on this evidence.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC) using methods of the Practice Guidelines Development Cycle (22). Evidence was selected and reviewed by two members of the PGI's GU DSG and methodologists. Members of the GU DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on MAB for the treatment of metastatic prostate cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

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. 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 Guidelines Clearinghouse (http://www.guideline.gov/index.asp) 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 RCTs or meta-analyses comparing MAB (orchiectomy or LHRH agonist plus administration of an antiandrogen) with castration alone (orchiectomy or administration of an LHRH 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 RCTs and meta-analyses.
2. Papers published in a language other than English, letters, and editorials were also excluded.

Synthesizing the Evidence

It was decided not to pool the results of trials of MAB therapy for metastatic prostate cancer due to the availability of up-to-date, published meta-analyses (1,2,23-27) that included recent RCTs.

IV. RESULTS

Literature Search Results

Seven meta-analyses were identified by the literature search and search of personal files (1,2,23-27) (Table 1). The meta-analysis published by the Prostate Cancer Trialists' Collaborative Group (PCTCG) in 2000 (1) is an update to their 1995 meta-analysis (24). In general, the results of the seven meta-analyses suggest that MAB therapy is associated with improvements in overall survival that range from approximately two to 22 percent, depending on the type of antiandrogen used. In the majority of meta-analyses, however, the survival benefits observed failed to reach statistical significance or were only marginally significant. The GU DSG reviewed the seven reports and decided that the most compelling evidence upon which to base a recommendation on MAB, in terms of survival, was the meta-analysis published by the PCTCG (1). The GU DSG took into consideration its methodological weaknesses (25), which include the absence of an initial protocol document, the absence of a clear description of the methods used to exclude trials, and a failure to assess trial quality and perform sensitivity analyses according to trial quality and publication status. Despite these limitations, the GU DSG agreed that the PCTCG meta-analysis is currently the most comprehensive and current with respect to survival data, given that it was based on individual patient data (n=8275) from 27 RCTs (13-15,23,28-49). Among the trials included in the PCTCG meta-analysis (1), five were newly included since the original 1995 PCTCG meta-analysis (38,42,47-49).

Of the remaining six meta-analyses that were identified, the GU DSG considered the report by Aronson et al (2) to be the most thorough with respect to the reporting of disease progression, adverse effects, and quality of life outcomes. Aronson et al systematically reviewed published data on these outcomes according to a prospectively designed protocol that specified the objectives of the review, the literature search strategy, trial eligibility criteria, and assessment of trial quality (2). Two independent reviewers carried out the review protocol, and the final report was subjected to an external expert review. Upon their evaluation of the available data on these outcomes, Aronson et al determined the data insufficient for the

purposes of meta-analysis; therefore they did not statistically pool data on these three outcomes (2).

Since the publication of the PCTCG meta-analysis in 2000 (1), three reports have been published that compare relevant outcomes of MAB compared with castration alone (50-52). The literature search identified one RCT (50), an updated report of a randomized trial that was originally published in 1993 and included in the PCTCG meta-analysis (51), and an exploratory analysis of another trial also included the PCTCG meta-analysis (50).

Table 1. Meta-analyses identified by the literature search.

Meta-analysis	Description
PCTCG, 2000 (1)	Included 27 published and unpublished randomized trials; analyzed individual patient data (8275 pts); update of 1995 PCTCG meta-analysis
Aronson et al., 1999 (2)	Included 20 published randomized trials; analyzed published data (6745 pts)
Bennet et al., 1999 (27)	Included nine published randomized trials; all nine trials contained flutamide in the MAB arm; analyzed published data (4128 pts)
Caubet et al., 1997 (26)	Included seven published randomized trials; all seven trials contained a NSAA in the MAB arm; analyzed published data (2885 pts)
Klotz & Newman, 1996 (25)	Included 20 published randomized trials; analyzed published data (5015 pts)
PCTCG, 1995 (24)	Included 22 published and unpublished randomized trials; analyzed individual patient data (5710 pts)
Bertagna et al., 1994 (23)	Included seven published double-blinded randomized trials; all seven trials contained nilutamide in the MAB arm; analyzed individual patient data (1056 pts)

Note: MAB – maximal androgen blockade, NSAA – nonsteroidal antiandrogens, PCTCG – Prostate Cancer Trialists' Collaborative Group, pts – patients.

Outcomes

Survival

Prostate Cancer Trialists' Collaborative Group Meta-analysis

The PCTCG searched for all randomized trials that compared androgen suppression achieved through surgical or medical castration alone with MAB (castration plus antiandrogen administration) (1). Inclusion criteria included a trial start date prior to 1991 and administration of the antiandrogen for at least one year or until disease progression. The PCTCG located 36 trials, of which one was found to be nonrandomized (53), four administered the antiandrogen for less than one year (54-57), and four were trials for which data could not be obtained (58-61)[2]. Individual patient data, updated for 13 of the 22 trials included in the PCTCG's previous meta-analysis (24), were available for 8275 patients from 27 RCTs. A brief description of the 27 RCTs is provided in Table 2. Twelve trials (4803 patients) used the antiandrogen flutamide, eight trials (1688 patients) used nilutamide, and seven trials (1784 patients) used cyproterone acetate. Combined, there were 5932 reported deaths. Twenty-five of the 27 trials used the same method of androgen suppression in both trial arms, and two trials used surgical castration in the castration only arm and medical castration in the MAB arm.

The PCTCG reported a non-significant overall mortality rate ratio (MRR) of 0.958 (standard error (SE), 0.026; p=0.11), where ratios less than one favoured MAB (1). An analysis of overall mortality at different follow-up periods detected no significant difference in overall mortality at two years and a small, but non-significant difference at five years in favour of MAB

[2] These four trials included 183 (2%) of the total number of patients. Data from two of the four trials (59, 61) was included in the Aronson et al systematic review (2).

(five-year survival, 25.4% versus 23.6%), suggesting an absolute five-year survival difference of approximately two percent (1.8%; SE, 1.3).

The PCTCG performed a number of subgroup analyses to test for heterogeneity. Subgroup analyses were performed by method of androgen suppression (trials with androgen suppression achieved through orchiectomy alone versus all other trials), type of antiandrogen, patient age (three age groups; <65, 65-74, and ≥75), stage of disease (documented metastases versus no metastases), and non-prostate cancer mortality. No significant differences in treatment effect were detected in regards to method of androgen suppression, patient age, and stage of disease. The subgroup analysis by type of antiandrogen detected a non-significant MRR of 0.92 (SE, 0.06; p=0.14) for the eight trials with nilutamide, a statistically significant MRR of 0.92 (SE, 0.03; p=0.02) favouring MAB for the flutamide trials, and a statistically significant MMR of 1.13 (SE, 0.06; p=0.04) favouring castration alone for the trials with cyproterone acetate. In light of the adverse survival outcome associated with cyproterone acetate, further analyses were performed by class of antiandrogen. MAB containing either of the nonsteroidal antiandrogens (flutamide or nilutamide) was associated with a three percent increase in five-year survival over castration alone (27.6% versus 24.7%, respectively; SE, 1.3; p=0.005), and MAB with the steroidal antiandrogen cyproterone acetate was associated with a three percent decrease in five-year survival compared with castration alone (15.4% versus 18.1%, respectively; SE, 2.4; p=0.04). Non-prostate cancer mortality data were available for 20 of the 27 trials; 20% (697 deaths) of the total number of deaths (3475) in these trials was attributed to causes other than prostate cancer. The subgroup analysis of this data detected a small but non-significant increase in non-prostate cancer mortality in the MAB arms of these trials compared with castration alone (logrank observed minus expected (O-E) = 5.6; variance, 162.0; p=0.7), where differences in the distributions of patient age and stage of disease between the two treatment arms did not account for the slight increase in non-prostate cancer death observed with MAB therapy. An examination of non-prostate cancer mortality by type of antiandrogen showed more non-prostate cancer deaths in the MAB arms containing cyproterone acetate; however, this difference was not statistically significant (logrank O-E, 11.7; variance, 35.3).

Table 2. Randomized controlled trials of maximal androgen blockade versus castration alone included in the Prostate Cancer Trialists' Collaborative Group (2000) meta-analysis.

Reference	Total number of patients randomized	MAB arm	Castration arm
Trials containing flutamide			
Delaere et al.,1987 (39)	330	Orchiectomy + flutamide	Orchiectomy + placebo
Schulze et al.,1988 (34)	110	Orchiectomy or LHRH (goserelin) + flutamide	Orchiectomy or LHRH (goserelin)
Crawford et al., 1989 (NCI/INT-0036) (13)	617	LHRH (leuprolide) + flutamide	LHRH (leuprolide) + placebo
Boccardo et al., 1993 (PONCAP) (40)	319	LHRH (goserelin) + flutamide	LHRH (goserelin)
Fourcade et al., 1993 (37)	245	LHRH (goserelin) + flutamide	Orchiectomy + placebo
Iversen et al., 1993 (36)	262	LHRH (goserelin) + flutamide	Orchiectomy
Tyrrell et al., 1993 (35)	586	LHRH (goserelin) + flutamide	LHRH (goserelin)
Ferrari et al., 1996 (41)	122	LHRH (buserelin) + flutamide	LHRH (buserelin)

Reference	Total number of patients randomized	MAB arm	Castration arm
Zalcberg et al., 1996 (38)	223	Orchiectomy + flutamide	Orchiectomy + placebo
Bono et al, 1998 (43)	277	LHRH (leuprolide) + flutamide	LHRH (leuprolide) + flutamide (15 days)
Eisenberger et al., 1998 (NCI/INT-0105) (42)	1385	Orchiectomy + flutamide	Orchiectomy + placebo
Denis et al., 1998 (EORTC 30853) (14)	327	LHRH (goserelin) + flutamide	Orchiectomy
Trials containing nilutamide			
Brisset et al., 1987 (28)	191	Orchiectomy + nilutamide	Orchiectomy + placebo
Navratil, 1987 (29)	208	Orchiectomy or LHRH (buserelin)	Orchiectomy or LHRH (buserelin) + placebo
Knönagel et al., 1989 (32)	51	Orchiectomy + nilutamide	Orchiectomy + placebo
Béland et al., 1990 (30)	208	Orchiectomy + nilutamide	Orchiectomy + placebo
Crawford et al., 1990 (33)	411	LHRH (leuprolide) + nilutamide	LHRH (leuprolide) + placebo
Namer et al., 1990 (31)	151	Orchiectomy + nilutamide	Orchiectomy + placebo
Bertagna et al., 1994 (23)	11	Orchiectomy + nilutamide	Orchiectomy + placebo
Dijkman et al., 1997 (15)	457	Orchiectomy + nilutamide	Orchiectomy + placebo
Trials containing cyproterone acetate			
Di Silverio et al., 1990 (45)	195	LHRH (goserelin) + cyproterone	LHRH (goserelin)
Di Silverio et al., 1990 (45)	133	LHRH (goserelin) + cyproterone	LHRH (goserelin)
Jorgenson et al., 1993 (47)	285	Orchiectomy + cyproterone	Orchiectomy + placebo
Robinson et al., 1995 (44)	238	Orchiectomy + cyproterone	Orchiectomy
Theiβ et al., 1996 (49)	222	LHRH (triptorelin) + cyproterone	LHRH (triptorelin) + placebo
Thorpe et al., 1996 (48)	343	LHRH (goserelin) +cyproterone	LHRH (goserelin)
De Voogt et al., 1998 (46)	368	Orchiectomy or LHRH (buserelin) + cyproterone	Orchiectomy or LHRH (buserelin) + cyproterone (14 days)

Note: MAB – maximal androgen blockade, LHRH – luteinizing hormone-releasing hormone agonist.

Disease Progression

Aronson et al Systematic Review

Similarly to the PCTCG meta-analysis, Aronson et al also restricted trial eligibility in their review to RCTs comparing MAB with castration alone (orchiectomy or LHRH agonist). Aronson et al summarized 23 trials (seven of which were not included in the PCTCG meta-analysis) that reported data on disease progression-related outcomes, either time to disease progression or progression-free survival (2). Nineteen trials (28-31,33,34,40-42,44,45,47,61-67) reported no significant difference between MAB and castration alone on measures related to disease progression. Three trials (13,15,68) reported statistically significant differences in favour of MAB; all three of these trials included nonsteroidal antiandrogens in the MAB arm. Two of the

three trials (13,15) also reported progression-free survival data: one trial compared orchiectomy plus placebo versus orchiectomy plus nilutamide (median progression-free survival, 15 months versus 21 months; progression-free survival at two years, 34% versus 46% of patients; at five years, 13% versus 21% of patients; p=0.0024) (15), and one trial compared leuprolide plus placebo versus leuprolide plus flutamide (median progression-free survival, 14 months versus 21 months; progression-free survival at two years, 35% versus 43% of patients; at five years, 20% versus 20% of patients; p=0.039) (13). The third trial reported time to disease progression data for a comparison of orchiectomy versus goserelin plus flutamide (median time to progression, 20 months versus 30 months; progression-free survival at two years, 43% versus 58% of patients; at five years, 22% versus 34% of patients; p=0.0024) (68). Another trial, which included cyproterone acetate in the MAB arm, reported a statistically significant advantage to castration alone over MAB for time to 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% of patients; p=0.0160) (48).

Adverse Effects

Aronson et al Systematic Review

Aronson et al grouped adverse effects into three classes of evidence that included adverse effects by category, adverse effects by degree of severity, and adverse effects leading to withdrawal from treatment (2). Data on adverse effects were extracted from all of the RCTs included in their review, although they found this data to be limited due to incomplete reporting of categories of adverse effects across the trials. Consequently, Aronson et al supplemented the adverse effects data with data from the package inserts that accompany therapeutic agents marketed in the United States. Adverse effects within a category were summed across trials if they were reported in at least three trials and used the same class of treatment. Table 3 shows the combined data of adverse effects by category from the Aronson et al report (2). Adverse effects were categorized as cardiovascular, endocrine, gastrointestinal, hepatic, and ophthalmologic. Treatment was grouped as castration alone (orchiectomy or LHRH agonist), castration plus a nonsteroidal antiandrogen, castration plus cyproterone acetate, or any MAB therapy. While the authors advised caution in interpreting the estimates of specific adverse effects by category due to the previously mentioned limitations, it appears that patients treated with MAB that included nonsteroidal antiandrogens suffered more gastrointestinal-related problems compared with patients treated with castration alone. In contrast, patients treated with MAB containing cyproterone acetate demonstrated more complications related to endocrine function than patients receiving castration only.

Only three of the RCTs included in the Aronson et al review measured adverse effects by degree of severity. Given the small number of patients included in these trials, they considered this data insufficient for making valid comparisons between treatments. There were, however, sufficient data available from randomized trials to combine data on adverse effects leading to withdrawal from treatment. The authors suggested that these data, which they considered more reliable than the data for adverse effects by category, might function as an indicator of severity. For this comparison, Aronson et al also included data from non-randomized phase II studies if they reported the frequency of patients withdrawing from treatment. Table 4 lists the combined data for adverse effects leading to withdrawal from treatment. Compared to patients in the castration only arms, patients receiving MAB therapy with a nonsteroidal antiandrogen withdrew from treatment much more frequently, and patients receiving MAB therapy consisting of cyproterone acetate demonstrated a withdrawal pattern similar to patients receiving castration only.

Table 3. Adverse effects by category, combined results.

Adverse effect	Castration only			MAB: Castration + NSAA			MAB: Castration + cyproterone			Any MAB		
	No. pts	%	No. studies	No. pts	%	No. studies	No. pts	%	No. studies	No. pts	%	No. studies
CARDIOVASCULAR												
Cardiovascular, nonspecified	570	4.0	4	387	4.9	3	175	1.7	1	562	3.9	4
Edema	569	3.2	3	293	2.0	1	277	6.5	2	570	4.2	3
ENDOCRINE												
Hot flashes	2594	40.1	16	2789	40.0	12	488	52.7	4	3277	41.9	16
Gynecomastia	1441	9.4	10	1987	7.0	9	257	17.5	2	2244	8.2	11
Breast tenderness/pain	649	7.7	5	1206	5.1	5	257	6.6	2	1463	5.4	7
Impotence	515	71.1	5	362	66.0	4	156	82.1	1	518	70.8	5
Decreased libido	519	70.1	5	367	65.4	4	156	78.8	1	523	69.4	5
GASTROINTESTINAL												
Gastrointestinal, nonspecified	959	2.3	7	768	10.3	6	175	0.6	1	943	8.5	7
Nausea/vomiting	1872	3.2-7.1	8	1851	5.6-9.2	8	0	0	0	1851	5.6-9.2	8
Diarrhea	1464	2.2	6	1458	8.2	6	0	0	0	1458	8.2	6
GI pain	124	1.6	2	122	7.4	2	0	0	0	122	7.4	2
HEPATIC												
Hepatic, nonspecified	1197	1.3	4	2004	5.0	6	0	0	0			
Increased liver enzymes	483	2.7	3	474	6.8	3	0	0	0		NR	
OPTHALMOLOGIC	**Orchiectomy**			**Orchiectomy + nilutamide**								
Opthalmologic, nonspecified	407	5.4	3	396	29.0	3		NR			NR	

Note: MAB – maximal androgen blockade, NSAA – nonsteroidal antiandrogen, NR-not reported, pts – patients.

Adapted from: Aronson N, Seidenfeld J, Samson DJ et al. *Relative Effectiveness and Cost-Effectiveness of Methods of Androgen Suppression in the Treatment of Advanced Prostate Cancer*. Evidence Report/Technology Assessment No. 4. (Prepared by Blue Cross/Blue Shield Association Evidence-based Practice Center under Contract No. 290-97-0015.) AHCPR Publication No. 99-E0012. Rockville, MD: Agency for Health Care Policy and Research. May 1999, Appendix II, Tables II-6 to II-10, pp. II-28 – II-30.

Table 4. Adverse effects leading to withdrawal from treatment, combined results.

Treatment	Number of studies	Number of patients in treatment group	Withdrawals from treatment	
			Number of patients	%
Leuprolide 1 daily	1	268	0	0.0
Goserelin 3.6 1 month	11	1679	33	2.0
Goserelin 10.8 3 months	2	77	1	1.3
Buserelin 0.4	1	72	3	4.2
Orchiectomy + nilutamide 150	2	271	38	14.0
Orchiectomy + nilutamide 300	3	209	24	11.5
Orchiectomy + cyproterone 150	1	102	3	2.9
Orchiectomy + cyproterone 300	1	20	2	10.0
Orchiectomy/ LHRH agonist	28	4275	82	1.9
Goserelin 3.6 1 mo + flutamide 750	5	846	94	11.1
Orchiectomy/LHRH agonist + flutamide 750	9	2804	233	8.3
Orchiectomy/LHRH agonist + bicalutamide 50	1	401	41	10.2
Orchiectomy/LHRH agonist + nilutamide 150/300	5	480	62	12.9
Orchiectomy/LHRH agonist + cyproterone 150/300	2	122	5	4.1

Source: Aronson N, Seidenfeld J, Samson DJ et al. *Relative Effectiveness and Cost-Effectiveness of Methods of Androgen Suppression in the Treatment of Advanced Prostate Cancer*. Evidence Report/Technology Assessment No. 4. (Prepared by Blue Cross/Blue Shield Association Evidence-based Practice Center under Contract No. 290-97-0015.) AHCPR Publication No. 99-E0012. Rockville, MD: Agency for Health Care Policy and Research. May 1999, Appendix II, Table II-11, pp. II-30.

Quality of Life

Aronson et al (2) reported that among all the RCTs they reviewed, only one formally assessed quality of life outcomes. They summarized two reports of one sub-study (3,4) of the large NCI INT-0105 SWOG/ECOG trial (42), which compared orchiectomy plus flutamide to orchiectomy plus placebo. Measures of quality of life assessed in the trial included three treatment-related symptoms (diarrhea, gas pain, and body image), physical functioning, and emotional functioning and were administered at one, three, and six months after the start of treatment. Patients treated with MAB reported significantly more diarrhea at three months ($p<0.001$) and worse emotional functioning at three and six months ($p<0.003$) than did those in the castration only arm. Aronson et al also reported that there were non-significant trends towards poor functioning in the MAB arm on measures of physical functioning, fatigue, abdominal gas, overall pain, and body image.

Casodex Combination Study

The Casodex Combination Study, a large (n=813) randomized multi-centre trial, which was included in the Aronson et al review (2) but excluded from the PCTCG report (1), provides data on treatment with MAB therapy involving the administration of bicalutamide, a newer antiandrogen (66). The Casodex Combination Study does not meet the inclusion criteria of this review because it does not include a traditional castration only control arm. However, it is described in this report because it is the only trial conducted to date that compares two different LHRH agonists with two nonsteroidal antiandrogens and also provides information on toxicity associated with the two antiandrogens.

Survival

The Casodex Combination study used a 2X2 factorial design that paired LHRH agonists leuprolide or goserelin with bicalutamide or flutamide. At a median follow-up of 160 weeks, median survival time for the bicalutamide and flutamide arms were 180 weeks and 148 weeks, respectively. The mortality hazard ratio (HR) for patients treated with bicalutamide plus LHRH agonist versus flutamide plus LHRH agonist was 0.87 (95% confidence interval [CI], 0.72 to 1.05; p=0.15).

In exploratory analyses of the Casodex Combination Study data, Sarosdy and colleagues (69) assessed the relative efficacy of the two LHRH agonists (goserelin plus antiandrogen versus leuprolide plus antiandrogen) and compared the four MAB treatments. Although there were slightly more deaths in the leuprolide combination arms versus the goserelin combination arms (57% versus 54% of patients), the difference was not statistically significant. Comparison of the four MAB treatment groups indicated a statistically significant difference in overall survival (p=0.008 logrank). Patients in the leuprolide plus flutamide arm had a poorer survival outcome compared with patients in any other arm. The difference between the leuprolide plus flutamide arm and the goserelin plus flutamide arm was statistically significant (p=0.047), but there were no significant differences between goserelin plus flutamide versus goserelin plus bicalutamide or goserelin plus bicalutamide versus leuprolide plus bicalutamide. The authors noted that these data should be interpreted with caution as the trial was not designed or powered to make comparisons among the four MAB treatment groups.

Disease Progression

Median time to progression was reported to be 97 and 77 weeks for the bicalutamide and flutamide arms, respectively (66). At a median follow-up of 160 weeks, there was disease progression in 71% of patients in the bicalutamide plus LHRH agonist group and 72% of patients in the flutamide plus LHRH agonist group. The HR for time to progression was 0.93 (95% CI, 0.79 to 1.10, p=0.41) favouring bicalutamide plus LHRH agonist.

The same exploratory analyses carried out for overall survival were also performed for disease progression (69). Compared to goserelin combination therapy, there was slightly more disease progression in the leuprolide combination arm (73% versus 71% of patients), but this difference was not statistically significant. Comparison of the four MAB treatments indicated the following disease progression rates: leuprolide plus bicalutamide, 69% of patients; leuprolide plus flutamide 77%; goserelin plus bicalutamide, 72%; goserelin plus flutamide, 70% of patients.

Adverse Effects

In the Casodex Combination Study, antiandrogen-LHRH agonist combinations were generally well tolerated. The most frequent adverse event was hot flashes (53% of patients in each group). The adverse effects seen more frequently in the flutamide versus bicalutamide arms were diarrhea (26% versus 12% of patients, p<0.001) and treatment-related abnormal liver function test results (11% versus 7% of patients, no significance level reported). Incidence of hematuria was significantly higher in patients receiving bicalutamide versus flutamide (12% versus 6%, p=0.007). Overall, more patients who received flutamide compared to bicalutamide combination therapy withdrew from treatment (16% versus 10% respectively) (66).

Reports Published After the PCTCG (2000) Meta-analysis

Since the publication of the PCTCG meta-analysis (1), one RCT comparing MAB with castration alone has been published (50). In this trial, Kotake et al randomized patients with stage C or D prostate cancer to one of four treatment arms to investigate the efficacy and toxicity associated with long-term medical castration compared with long-term or short-term MAB. Three hundred and ninety patients were randomized to receive goserelin alone, goserelin plus short-term use (eight weeks) of the antiandrogen chlormadinone acetate (CMA), goserelin

plus long-term use (28 months) of CMA, or goserelin plus short-term use (eight weeks) of diethylstilbestrol diphosphate (DES-DP). Three hundred and sixty-one patients were evaluable for response, overall survival, progression-free survival, disease-specific survival, and toxicity. After three years of follow-up, there were no significant differences between the four treatment groups with respect to response rates (at 12 weeks p=0.186; at years one, two, and three, no significant differences, no p-values reported), overall survival (p=0.4324), progression-free survival (p=0.1046), and disease-specific survival (p=0.4914). Subgroup analyses were carried out for all outcomes by clinical stage, tumour differentiation, performance status, and extent of disease. For response, patients with poorly differentiated tumours (p=0.022) and patients with stage D2 disease who were treated with goserelin plus long-term CMA (p=0.001) had significantly poorer response rates at 12 weeks compared to similar patients in the other three treatment groups. The authors advised caution in the interpretation of the subgroup analyses of response rates as the total number of patients included in the subgroups was small. All subgroup analyses carried out for overall survival, progression-free survival, and disease-specific survival were not statistically significant. Kotake et al measured toxicity associated with the four treatment groups as the type and number of adverse drug reactions (ADR) and the number of withdrawals due to ADR. The most prevalent ADR in all treatment groups were endocrine disorders, which included hot flashes, breast swelling and/or tenderness, impotence, and loss of libido. However, patients treated with goserelin plus short-term DES-DP had a significantly higher incidence of breast swelling and/or tenderness compared with the other three treatment groups (p<0.05) and a higher frequency of cardiovascular disorders compared with the goserelin alone and goserelin plus short-term CMA treatment groups (p<0.05). Altogether, 16 patients withdrew from treatment due to ADR (five patients receiving goserelin plus long-term CMA, one patient receiving goserelin plus short-term CMA, and 10 patients receiving goserelin plus DES-DP). There was one reported ADR-related death; a patient in the goserelin plus DES-DP treatment group developed congestive heart failure. Results from this recent randomized trial are in accordance with the findings of the PCTCG meta-analysis (1).

As an update to their RCT originally published in 1993 (35) that was included in the PCTCG meta-analysis (1), Tyrrell et al (51) recently published the long-term results of their trial which compared MAB containing goserelin plus flutamide with goserelin alone in 583 patients with locally advanced (M0, 45% of patients) or metastatic prostate cancer (M1,55% of patients). After approximately 11 years of follow-up, Tyrrell et al detected no significant difference between the two treatment groups with respect to overall survival (HR=0.88; 95% CI, 0.73 to 1.06; p=0.172). A subgroup analysis by stage of disease further revealed that there was also no significant difference in overall survival between patients with locally advanced disease versus those with metastatic disease (HR for M0 patients=0.92; 95% CI, 0.68 to 1.25; HR for M1 patients=0.85 95% CI, 0.66 to 1.08) indicating that the efficacy of treatment was not significantly different in these two subgroups of patients (p=0.685). The updated results from this trial also support the findings of the PCTCG meta-analysis (1).

In light of the limited amount of quality of life data available from randomized MAB trials, Rosendahl et al (52) conducted an exploratory analysis of EORTC trial 30853 (14), which was included in the PCTCG meta-analysis (1), using the quality-adjusted time without symptoms of disease and toxicity of treatment (QTWiST) method. In brief, QTWiST analysis adjusts survival data by the quality of life patients experience while in various health states during and following treatment (52). In the EORTC trial, patients were randomized to receive orchiectomy or goserelin plus flutamide. Results from this study showed that both overall survival (p=0.04) and time to disease progression (p=0.009) were significantly longer in the MAB treatment group compared with orchiectomy alone; median duration of survival was 27 months versus 34 months for orchiectomy and MAB, respectively (14). In terms of adverse effects, hot flashes were the most commonly reported treatment-related symptom, and they occurred much more frequently in patients receiving MAB therapy. The objective of the exploratory QTWiST analysis

was to compare between treatment groups the tradeoff between adverse effects, time to disease progression, and overall survival by assigning values to different health states (e.g. time spent with hot flashes as a result of treatment, time spent without progression of disease and side effects of treatment, and time spent with progression of disease) (52). The values assigned to the various health states were derived from a separate, but similar cohort of prostate cancer patients. After seven years of follow-up, quality-adjusted survival (QAS) was 5.3 months longer in the MAB treatment group compared to castration alone, a benefit equivalent in magnitude to what was reported in the original analysis by Denis et al (14). This finding suggests that the presence of hot flashes had little impact on the quality of life of patients undergoing MAB. It should be noted, however, that the findings of this trial are limited to the impact hot flashes have on QAS, since other and possibly more severe adverse effects that are associated with MAB therapy, such as cardiovascular and gastrointestinal adverse effects, were not incorporated into the QTWiST analysis.

V. INTERPRETIVE SUMMARY

To date, a large number of RCTs have been conducted to compare survival, disease progression, adverse effects, and quality of life associated with MAB and castration alone in patients with metastatic prostate cancer. Results from these trials have been contradictory, and MAB therapy has been associated with both a survival benefit and lack of benefit when compared with castration alone. Contradictory evidence on the use of MAB could be the consequence of a number of methodological factors that, when present, may impede the ability of a study to detect statistically and clinically meaningful differences in treatment effect. Such factors include low statistical power, study immaturity, compliance to treatment, imbalances in prognostic indicators between individual study arms or across trials, and chance (16-20). The conflicting evidence and the sheer number of available randomized trials has led to the publication of a number of meta-analyses in an attempt to overcome the shortcomings of individual trials and determine whether or not MAB therapy provides superior overall survival compared with castration alone in patients with metastatic prostate cancer.

Due to the availability of recent meta-analyses, the GU DSG decided not to pool the results of individual RCTs of MAB therapy. This review of the evidence located seven meta-analyses comparing MAB with castration alone in previously untreated men with metastatic prostate cancer (1,2,23-27). After a review of the seven published reports, the GU DSG decided to use two of these reports as the evidence base for comparisons of MAB therapy with castration alone (1,2).

The PCTCG meta-analysis failed to detect an overall survival advantage in favour of MAB therapy versus castration alone, indicating an absolute difference in survival of two percent (95% CI, 0 to 4) (1). Further, this finding was not influenced by method of androgen suppression, patient age, or stage of disease. A subgroup analysis by type of antiandrogen indicated no difference between treatment arms when the MAB arm contained nilutamide, a statistically significant survival advantage to MAB when the combined arm contained flutamide, and a statistically significant survival advantage favouring castration alone for the trials with cyproterone acetate in the MAB arm. Additional analysis by class of antiandrogen indicated that compared to castration alone, MAB with nonsteroidal antiandrogens improved survival by approximately three percent (95% CI, 0.4 to 5.4) and MAB with the steroidal antiandrogen cyproterone acetate decreased survival by approximately three percent. The final conclusion of the PCTCG meta-analysis was that MAB therapy improved five-year survival in the range of two to three percent depending on the type of antiandrogen used. It should be noted, however, that the lower confidence limit surrounding this benefit included zero when all antiandrogens were included and just exceeded zero if only nonsteroidal antiandrogens were considered, suggesting the possibility that there may be no significant survival difference between the two treatments and that the small difference observed may have occurred by chance. Alternatively,

if the small statistical survival benefit associated with MAB is real, it is questionable whether a survival difference of a few percent translates into a clinically meaningful difference in survival.

The fact that the PCTCG meta-analysis detected a significant survival advantage with MAB containing flutamide highlights the greater methodological issue of whether or not the results of a meta-analysis should take precedence over a large RCT with sufficient follow-up. In the case of MAB, the large SWOG trial (42), which compared orchiectomy with and without flutamide, failed to detect a significant difference between the two treatment groups with respect to survival (one-tailed p=0.14) (HR=0.91; 90% CI, 0.81 to 1.01). This finding is in contrast to the subset analysis of flutamide trials performed by the PCTCG, which included the large SWOG trial in addition to smaller, less powerful studies. In light of this conflicting evidence, the GU DSG felt that conclusions concerning the impact of flutamide-containing MAB treatment on survival should be drawn cautiously.

Disease progression data provided by Aronson et al (2) indicated that 19 of 23 trials reported no significant difference between MAB and castration only arms. Three trials reported a statistically significant difference in favour of MAB with nonsteroidal antiandrogens (13,15,68), and one trial that included cyproterone acetate in the MAB arm reported a statistically significant advantage to castration alone (48). Since the majority of MAB trials failed to demonstrate significant differences in disease progression in favour of MAB, data on disease progression can be considered further supporting evidence that MAB does not provide superior treatment efficacy over castration alone.

Aronson et al provided pooled data on the adverse effects associated with castration alone and MAB (2). It appeared that patients treated with MAB that included nonsteroidal antiandrogens suffered more gastrointestinal-related problems compared with patients treated with castration only. In contrast, patients treated with MAB containing cyproterone acetate showed more complications related to endocrine function than patients receiving castration only. A substantial number of patients on nonsteroidal antiandrogens withdrew from treatment (ranging from 8.3% to 14%), and it is reasonable to assume that the significant numbers of withdrawals were likely attributable to the adverse effects associated with this regimen of MAB. Aronson et al also summarized the data from the only study that has reported quality of life outcomes associated with MAB (3,4). Patients treated with MAB reported significantly more diarrhea at three months post-treatment and worse emotional functioning at three and six months post-treatment than did those in the castration only arm. Although adverse effects and quality of life outcomes have not been extensively studied in randomized trials, the current data do suggest an increased toxicity profile and a concomitant decline in quality of life in patients who are treated with MAB versus castration alone.

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 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.

It is important to recognize that the majority of patients included in the MAB trials had metastatic disease, largely stage D2 disease. Currently, hormonal intervention for prostate cancer is indicated when there is a rise in PSA; a rise in PSA generally occurs at a much earlier stage of recurrent or metastatic disease than occurs in patients with D2 disease. It is unknown whether the results from MAB trials including patients with D2 disease are generalizable to patients with a rising PSA. There is some evidence from subgroup analyses of individual MAB trials to suggest that MAB administered as neoadjuvant or adjuvant treatment may be of benefit to patients with non-metastatic or a minimal extent of metastatic disease. Unfortunately, the

majority of MAB trials have only included patients with metastatic prostate cancer, and few trials have actually analyzed relevant outcomes by extent of metastatic involvement (13,18,42). In the PCTCG meta-analysis, only 12% of patients (approximately 1000 patients) had documented non-metastatic prostate cancer. Analysis of these patients showed a slightly worse survival outcome with MAB when compared with castration alone, but this difference did not reach statistical significance (MRR=1.06; SE, 0.10; 95% CI, 0.87 to 1.29) (1). The PCTCG meta-analysis did not analyze outcomes by extent of metastatic disease. Given the limited data on the use of MAB in these subgroups of patients, prospective randomized trials are warranted to investigate the efficacy of MAB in these groups of patients.

VI. ONGOING TRIALS

The GU DSG is not aware of any ongoing RCTs comparing MAB with castration alone in previously untreated patients with metastatic prostate cancer.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

In formulating a recommendation for the use of MAB, the GU DSG reviewed and discussed the available data on survival, disease progression-related outcomes, adverse effects, and quality of life as presented in the PCTCG meta-analysis (1) and the review by Aronson et al (2). 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 an 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 (70,71). In this clinical situation, short-term use of an antiandrogen is indicated to prevent or block the flare phenomenon (72). 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 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.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the GU DSG drafted the following recommendations:

Target Population

These recommendations apply to adult men with metastatic prostate cancer (C or D1 or D2 (5); N+/M0 or M1 or T3-4, N0 or Nx, M0 (73)).

Draft Recommendations

Key Recommendations

- Recent evidence from a large individual patient data meta-analysis including 8275 patients from 27 randomized trials does NOT support the routine use of MAB as treatment for patients with documented metastatic prostate cancer beyond the purpose of blocking testosterone flare. Monotherapy, consisting of orchiectomy or an LHRH agonist is recommended as standard treatment for patients with metastatic prostate cancer.
- In this meta-analysis, MAB did not significantly improve survival when compared with castration alone. Although a subgroup analysis by class of antiandrogen indicated that five-year overall survival was significantly improved by approximately three percent with MAB when combination therapy included nonsteroidal antiandrogens, the clinical significance of this benefit is questionable. Maximal androgen blockade containing the steroidal antiandrogen cyproterone acetate was associated with a significant reduction in five-year survival of approximately three percent when compared with castration alone.
- Data on adverse affects and quality of life associated with MAB therapy are limited, but evidence from one randomized trial showed gastrointestinal toxicity and emotional functioning to be significantly worse with MAB therapy compared with castration alone.
- If MAB is to be administered with the intent of improving survival, the steroidal antiandrogen cyproterone acetate should not be used. Before initiation of treatment for this purpose, individual patients should be made aware of the potential adverse effects associated with combined treatment and the impact these adverse affects could have on aspects of quality of life.

Qualifying Statements

- The GU DSG felt that the most compelling evidence upon which to base a recommendation concerning the use of 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 PCTCG in 2000 (1). This meta-analysis evaluated patients with advanced prostate cancer; however, 88% of patients included in the meta-analysis had documented metastatic disease. Accordingly, these recommendations on the use of MAB are applicable to patients with documented metastatic prostate cancer.

- The current evidence does not permit a recommendation regarding the administration of MAB using the newer antiandrogen bicalutamide, which is associated with less toxicity.
- The current evidence does not permit a recommendation regarding the use of MAB beyond the purpose of controlling testosterone flare in patients with prostate-specific antigen relapse who have no documented evidence of metastatic disease.
- The current evidence does not permit a recommendation regarding the use of MAB beyond the purpose of blocking testosterone flare as neoadjuvant or adjuvant hormonal treatment for patients with non-metastatic prostate cancer.

Future Research

Future research could uncover molecular (or other) markers that may identify patients who might benefit from MAB therapy.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

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 GU DSG reviewed the results of the survey.

Results

Fifty-seven responses were received out of the 99 surveys sent (58% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 48 indicated that the report was relevant to their clinical practice and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 5.

Table 5. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	44 (93.6)	1 (2.1)	2 (4.3)
There is a need for a clinical practice guideline on this topic.	43 (91.5)	4 (8.5)	0 (0)
The literature search is relevant and complete.	40 (85.1)	4 (8.5)	3 (6.7)
The results of the trials described in the report are interpreted according to my understanding of the data.	43 (91.4)	1 (2.1)	3 (6.4)
The draft recommendations in this report are clear.	45 (93.8)	0 (0)	3 (6.3)
I agree with the draft recommendations as stated.	42 (89.3)	1 (2.1)	4 (8.6)
This report should be approved as a practice guideline.	39 (81.3)	3 (6.3)	6 (12.5)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	41 (87.2)	2 (4.3)	4 (8.6)

Summary of Written Comments

Nineteen respondents (40%) provided written comments. The main points contained in the written comments were:

1. One practitioner commented that since most patients on an antiandrogen are prescribed bicalutamide, many practicing urologists will be confused by the recommendations contained in the guideline and will probably view the evidence as outdated. This practitioner also noted that qualifying statements three and four are awkwardly worded and confusing.
2. One practitioner suggested that the GU DSG should consider adding to their recommendation a statement about entering patients into an "ideally" designed and conducted large trial that evaluates MAB using newer agents (e.g. bicalutamide) compared with castration alone.
3. One practitioner commented that the guideline does not address the role of peripheral androgen blockade in obvious T3-4 patients who have chosen to undergo LHRH agonist treatment.
4. One practitioner commented that although bicalutamide is currently the most commonly used nonsteroidal antiandrogen, the recommendations contained in the guideline are premature; he/she stated that further evidence is required before a guideline on MAB using bicalutamide is developed. The practitioner also stated some concerns around the interpretation of the evidence contained in the guideline. His/her first concern pertained to the interpretation of the conclusions of the PCTCG meta-analysis. The practitioner asked, "why is an approximate three percent improvement in five-year overall survival with combination therapy consisting of nonsteroidal antiandrogens considered 'of questionable clinical significance' and an approximate three percent decrease in five-year overall survival with combination therapy consisting of cyproterone acetate is considered "of non-clinical significance"? The practitioner felt that the statistics quoted in the guideline are not applied consistently. The practitioner's second concern dealt with the single randomized trial of MAB therapy that provided data on quality of life. The practitioner commented that if the GU DSG is making the recommendation of monotherapy (other than the use of MAB to prevent testosterone flare) to improve quality of life, there is only one trial to support this recommendation and this trial did not include patients on bicalutamide.
5. One practitioner was concerned with using the PCTCG meta-analysis as the evidence base of the guideline since this practitioner believes this meta-analysis to be methodologically flawed. The practitioner listed three trials that he/she believes should have been excluded from the meta-analysis due to insignificant numbers and insufficient follow-up (Knonagel et al, 1989; Bertagna et al, 1994; Schulze et al, 1988). The practitioner commented that a meta-analysis is only as good as the individual studies included in it. For the same reasons stated above, the practitioner also thought that the other meta-analyses identified and examined as part of the guideline should be re-examined and at least one or two meta-analyses discarded.
6. One practitioner commented that he/she disagrees that survival benefit is the yardstick with which to measure the effectiveness of MAB therapy. This practitioner uses MAB in his/her practice to rapidly reduce the effect of testosterone on prostate cancer with the intent to stop treatment as soon as maximal benefit to the reduction of the cancer has been achieved. The practitioner noted that not all anti-hormone treatments are equivalent (e.g. cyproterone acetate is not nearly as effective as standard treatment; orchiectomy cannot be reversed) and therefore, comparing all forms of MAB treatment is not appropriate. With respect to the meta-analysis performed by the PCTCG, the practitioner commented that the studies included are so varied in terms of their

methodology and outcome measurement that doing a meta-analysis only serves to magnify their shortcomings.

7. One practitioner commented that the target population of the guideline includes patients with T3-4, N0, M0 prostate cancer. This practitioner does not think of this patient population as having metastatic disease.
8. One practitioner commented that cyproterone acetate may be used to try and treat hot flashes resulting from castration.
9. One practitioner thought that the guideline dealt with an "old, already generally accepted clinical practice habit", one practitioner stated that he/she already follows the protocol outlined in the guideline, and another practitioner commented that some urologists still strongly believe in the use of MAB.
10. Two practitioners viewed the guideline as an excellent summary of the current evidence and fully supported the draft recommendations.

Modifications/Actions

The GU DSG responded to the comments provided by practitioners as follows:

1. The GU DSG is aware that some clinicians may prescribe bicalutamide as LHRH agonist treatment based on the toxicity data from the Casodex Combination Study. In this trial, bicalutamide was associated with fewer adverse effects than was MAB with flutamide, and fewer patients on bicalutamide withdrew from treatment. The GU DSG has acknowledged in the guideline report that bicalutamide may have a lower toxicity profile compared to other commonly used nonsteroidal antiandrogens, but the group feels strongly that before recommendations can be made on MAB therapy using bicalutamide further randomized trials that are adequately powered and compare MAB to monotherapy are required. Qualifying statements three and four have been combined and reworded to improve clarity.
2. The GU DSG added a statement to the Future Research section of the guideline report to encourage patient enrolment in randomized trials of MAB therapy using newer agents.
3. The GU DSG has explicitly stated that the guideline recommendations are applicable to men with metastatic prostate cancer. In the meta-analysis performed by the PCTCG, which the DSG selected as the primary evidence source upon which to base their recommendation, only 12% (approximately 1000 patients) of patients were classified as having locally advanced disease without any evidence of definitive metastases. In this subset of patients, overall mortality at five years was slightly, but not significantly, higher with MAB therapy compared to castration alone (MRR=1.06; 95%CI 0.87-1.29). At this time, the DSG believes that the small number of patients with non-metastatic disease included in the randomized trials of MAB therapy does not provide a sufficient level of evidence to permit recommendations on the use of MAB in these patients.
4. In response to the practitioner's concerns around the GU DSG's interpretation of the conclusions of the PCTCG meta-analysis (specific to the results of the subgroup analysis done by class of antiandrogen), the GU DSG believes that the use of the word "significant" in the second bullet of the recommendations to describe differences in five-year survival between treatment and control arms (MAB with nonsteroidal antiandrogens versus castration alone, MAB with steroidal antiandrogens versus castration alone) has caused the confusion. The word significant was meant to refer to statistical significance. As indicated in the guideline report, MAB containing either of the nonsteroidal antiandrogens (flutamide or nilutamide) was associated with a three percent increase in five-year survival over castration alone (27.6% versus 24.7%; p=0.005) and MAB with the steroidal antiandrogen cyproterone acetate was associated with a three percent decrease in five-year survival compared with castration alone (15.4% versus 18.1%; p=0.04). The DSG questions whether these small differences in overall survival,

although statistically significant, translate into clinically meaningful differences in survival. To avoid further misinterpretation, the GU DSG reworded the recommendation so that the issue of statistical versus clinical significance was more explicit. This practitioner also questioned the DSG's interpretation of the single randomized trial that assessed quality of life outcomes. The DSG disagrees that they have misinterpreted or relied too heavily on the results of this trial. The trial, which compared orchiectomy plus flutamide with orchiectomy plus placebo, was a large (1385 patients), well-conducted study that is the only trial conducted to date to prospectively collect data on the quality of life associated with MAB. The GU DSG has stated in the guideline recommendations that data on quality of life is currently limited. As more evidence becomes available, the DSG is aware that the results from this trial will have to be reviewed within the context of other trials that also report quality of life outcomes.

5. The DSG has acknowledged and described in the guideline report some of the inherent weaknesses of the PCTCG meta-analysis; however, despite these weaknesses, the GU DSG feels that it is currently the best available evidence upon which to base a recommendation. This practitioner is particularly concerned with the PCTCG's decision to include specific trials that he/she has identified as methodologically flawed. The DSG admits that the meta-analysis is undermined by the fact that individual trials were not assessed for quality and sensitivity analyses were not performed by trial quality. However, the GU DSG disagrees with the practitioner's suggestion of excluding particular trials on the basis of poor quality; the GU DSG feels that this kind of trial selection could potentially bias the results of the meta-analysis.
6. The DSG agrees with this practitioner that survival is not the only outcome of interest to be considered when measuring the effectiveness of MAB. In formulating their recommendation, the GU DSG reviewed all outcomes for which data were available; this included a review of survival and disease-free survival data, toxicity, and quality of life. The DSG is unaware of any trials that have assessed the use of MAB in the short-term as a means of tumour control through rapid reductions in testosterone levels.
7. The DSG has revised the target population of the guideline so that patients with metastatic prostate cancer are defined as having D1 or D2, N+/M0 or M1 stage disease.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Co-ordinating 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 stream-lining the text for a shorter report.

Modifications/Actions

The GU DSG agreed that there were sections of the guideline report where text could be stream-lined 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.

IX. PRACTICE GUIDELINE

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.

Target Population

These recommendations apply to adult men with metastatic prostate cancer (D1 or D2[1]; N+/M0 or M1).

Recommendations

- 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 an LHRH agonist, is recommended as standard treatment for patients with metastatic prostate cancer.

Qualifying Statements

- It is the opinion of the GU DSG that the small statistically significant survival benefit found with 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 affects 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.

Future Research

The GU DSG encourages clinicians to enter patients into randomized trials evaluating MAB using newer agents such as bicalutamide compared with castration alone. These trials should aim to avoid the methodological weaknesses of previous MAB trials and assess quality of life outcomes in addition to survival. Future research could uncover molecular (or other) markers that may identify patients who might benefit from MAB therapy.

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For a complete list of the Genitourinary Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our web site at http://www.cancercare.on.ca/access_PEBC.htm.

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