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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.

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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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