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## The Role of Aromatase Inhibitors in the Treatment of Postmenopausal Women with Metastatic Breast Cancer Practice Guideline Report #1-5

*Members of the Breast Cancer Disease Site Group*

ORIGINAL GUIDELINE: September 3, 2002 MOST RECENT LITERATURE SEARCH: October 2003 NEW EVIDENCE ADDED TO GUIDELINE REPORT: October 2003 RECOMMENDATIONS MODIFIED: October 2003
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### SUMMARY

#### **Guideline Question**

What is the role of aromatase inhibitors as first-, second-, and third-line treatment of postmenopausal women with stage IV (metastatic) breast cancer?

#### **Target Population**

These recommendations apply to postmenopausal women with stage IV breast cancer who are candidates for hormonal therapy.

#### **Recommendations**

##### ***First-line Therapy***

- Anastrozole and letrozole are modestly superior to tamoxifen (in terms of objective response rate and time to disease progression) as first-line therapy for postmenopausal women with stage IV breast cancer and are the preferred treatment option in this setting.
- Tamoxifen remains an acceptable alternative.
- There are insufficient data to recommend any one aromatase inhibitor over others in this setting.

##### ***Second-line Therapy***

- Anastrozole, letrozole, and exemestane are superior to megestrol acetate or aminoglutethimide as second-line hormonal therapy and are the preferred treatment option in this setting.
- There are insufficient data to recommend any one aromatase inhibitor over others in this setting.

##### ***Third- or Greater-line Therapy***

- For postmenopausal women with advanced breast cancer who have been heavily pretreated with hormonal agents and chemotherapy, exemestane is an acceptable therapy.

#### **Qualifying Statement**

- Selective aromatase inhibitors are contraindicated in premenopausal women.

## Methods

Entries to MEDLINE and CANCELIT (through October 2003), the Cochrane Library (2003, Issue 4), and databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by a member of the Practice Guidelines Initiative's Breast Cancer Disease Site Group and a research methodologist. This practice guideline report has been reviewed and approved by the Breast Cancer Disease Site Group, which comprises surgeons, medical oncologists, radiation oncologists, pathologists, a research methodologist, a medical sociologist, a nurse representative, and patient/survivor representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the 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 consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

## Key Evidence

- There are three randomized trials comparing anastrozole with tamoxifen, one of letrozole versus tamoxifen and one of exemestane versus tamoxifen as first-line therapy for metastatic breast cancer. Treatment with selective aromatase inhibitors was associated with higher objective response rates and prolonged time to progression compared to tamoxifen, but definitive survival and quality-of-life data are not available. The toxicity profile of the aromatase inhibitors is acceptable.
- There are three randomized trials comparing letrozole to megestrol acetate or aminoglutethimide, two of anastrozole versus megestrol acetate, and one of exemestane versus megestrol acetate as second-line hormonal therapy for metastatic breast cancer. Women eligible for these trials included those who relapsed during or within 6 months of completion of adjuvant anti-estrogen therapy and those who progressed on first-line anti-estrogen therapy for metastatic disease. Treatment with selective aromatase inhibitors was associated with equivalent or better objective response rates and time to progression, and a superior toxicity profile, compared to megestrol acetate or aminoglutethimide. Two individual trials and a meta-analysis of individual-patient data from four trials detected a modest but statistically significant survival advantage for aromatase inhibitors, compared to control. There were no consistent differences in measures of quality of life between aromatase inhibitors and control therapy in randomized trials. There were no significant differences between doses of anastrozole of 1.0 and 10 mg, but two of three trials detected significantly higher survival rates with letrozole 2.5 mg compared to 0.5 mg.
- A non-blinded randomized trial of letrozole versus anastrozole, reported only in abstract form, detected a statistically significant increase in response rate with letrozole compared to anastrozole as second-line treatment but no difference in time to progression. No survival or quality-of-life data are available from this trial.
- Data from three phase II trials indicate that exemestane therapy, as third- or greater-line hormonal therapy, is associated with modest but appreciable rates of objective response and is well tolerated. There are no data from clinical trials of other aromatase inhibitors in this setting.

*For further information about this practice guideline, please contact:*

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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.<sup>1</sup> 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:

- <sup>1</sup> 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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