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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
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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 CANCERLIT (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.

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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.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:
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FULL REPORT

I. QUESTION

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

II. CHOICE OF TOPIC AND RATIONALE

In women with hormone-receptor-positive advanced breast cancer, endocrine therapy is often very effective and is associated with fewer side effects than chemotherapy. In patients who initially respond to hormonal interventions, the choice of subsequent therapy usually follows a sequential trial of endocrine strategies. The standard approach has been to begin this pathway with tamoxifen, which has a well-established efficacy and safety profile. Recently, a new class of endocrine agents, the selective aromatase inhibitors, has become available for use in postmenopausal women with advanced breast cancer. These agents have been compared to tamoxifen and to other endocrine therapies as a first-, second- and third-line treatment of hormone-responsive disease. Aromatase inhibitors are effective and well-tolerated but are significantly more expensive than tamoxifen and the other agents.

Selective aromatase inhibitors may be classified according to their structure as steroidal or non-steroidal agents (1). The steroidal agents include formestane, a second-generation drug requiring parenteral administration, which is no longer available, and exemestane, an oral agent. The third-generation non-steroidal agents include anastrozole and letrozole. These two classes of agents differ in their mechanism of interaction with aromatase. The steroidal agents competitively bind to the active enzyme site and cause irreversible inhibition of enzyme activity, whereas the binding of the non-steroidal agents is reversible. This difference may be of clinical relevance since there is some evidence of a lack of cross-resistance between the steroidal and non-steroidal agents.

Selective aromatase inhibitors are contraindicated in premenopausal women. The use of these agents in premenopausal women is associated with incomplete suppression of estrogen synthesis and with ovarian hyperstimulation syndrome (2).

This practice guideline was developed to review the evidence for the use of selective aromatase inhibitors as a treatment for postmenopausal women with advanced breast cancer and to make recommendations for their placement in the hormonal therapy pathway.

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, using the methods of the Practice Guidelines Development Cycle (3). Evidence was selected and reviewed by a member of the CCOPGI's Breast Cancer Disease Site Group (Breast DSG) and methodologists. Members of the Breast Cancer 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 selective aromatase inhibitors in the management of metastatic breast 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 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

The MEDLINE (from 1966) and CANCERLIT (from 1975) databases were searched to December 2001 using disease-specific terms (breast or mammary, cancer, carcinoma or neoplasm(s), and metastasis, metastatic or advanced), treatment-specific terms (anti-aromatase or aromatase inhibitors or endocrine therapy or anastrozole or arimidex or exemestane or aromasin or letrozole or femara or megestrol acetate or aminoglutethimide), and design-specific terms (meta-analysis or randomized controlled trial or randomized controlled trials or random). The searches were not restricted by language of publication. Issue 2 (2002) of the Cochrane Library, the Physician Data Query database (http://www.clinicaltrials.gov), clinical trial and practice guideline Internet sites, conference proceedings from the American Society of Clinical Oncology (ASCO) (1997-2001), the European Society for Medical Oncology (ESMO) (1998-2000) and the San Antonio Breast Cancer Symposium (2000-2001), bibliographies, and personal files were also searched.

An update search of the MEDLINE database and the proceedings of the 2002 ASCO meeting was conducted in June 2002, after the practitioner feedback survey.

Update

The original literature search has been updated using MEDLINE and CANCERLIT (through October 2003), the Cochrane Library (Issue 4, 2003), the Physician Data Query database, clinical trial and practice guideline Internet sites, proceedings of the annual meeting of ASCO (2003), proceedings of ESMO (2001-2002), and proceedings of the San Antonio Breast Cancer Symposium (2002).

Inclusion Criteria

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

- Selective aromatase inhibitors as first-, second- or third-line hormonal therapy in postmenopausal patients with stage IV breast cancer were evaluated using a randomized controlled design, meta-analysis, evidence-based clinical practice guideline format, or non-comparative design (in the absence of randomized controlled trials).
- Reported outcomes of interest included survival, quality of life, tumour response, time to disease progression, and adverse effects of treatment.
- Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. These data often appear first in meeting abstracts and may not be published for several years.

Exclusion Criteria

Articles excluded from this systematic review included:

- Trials of aminoglutethimide (a first-generation aromatase inhibitor) compared to non-aromatase-inhibitor hormonal therapies.
- Trials of fulvestrant, formestane, vorozole, or fadrozole, selective aromatase inhibitors that are not available in Ontario.

- Trials of aromatase inhibitors as adjuvant or neo-adjuvant therapy.
- Letters and editorials.

Synthesizing the Evidence

To estimate the overall effect of aromatase inhibitors versus tamoxifen as first-line therapy on response and time to disease progression, data were abstracted from the published reports of individual randomized trials and pooled using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview© Update Software). For the pooled analysis of tumour response, the numbers of patients with a complete or partial response were abstracted from the text or tables in published reports, abstracts, or poster presentations. Time-to-progression data were obtained by estimating the number of patients who progressed or died within 12 months after randomization from the Kaplan-Meyer probability curves presented in each report. These numbers and the numbers randomized were used for the meta-analysis.

Results are expressed as relative risks (also known as risk ratios) with 95% confidence intervals (CI). For tumour response, a relative risk (RR) >1.0 indicates that patients in the experimental treatment group (aromatase inhibitor) had a higher probability of a complete or partial response compared with those in the control group (tamoxifen); conversely, a relative risk <1.0 favours tamoxifen over the aromatase inhibitor. For disease progression, a RR <1.0 indicates that the patients in the experimental treatment group (aromatase inhibitor) experienced delayed progression compared with those in the control group (tamoxifen); a RR >1.0 favours tamoxifen over the aromatase inhibitor. The random-effects model was used for pooling across studies in preference to the fixed-effects model, as the more conservative estimate of effect (4).

Data from second-line trials were not pooled by the guideline developers because a published meta-analysis, based on individual patient data from randomized trials of aromatase inhibitors versus megestrol acetate as second-line therapy, was available.

IV. RESULTS

Literature Search Results

Twelve randomized trials (5-19,30), three phase II trials (20-22) and three published meta-analyses (13,23,24), were eligible for inclusion in this systematic review of the evidence. No relevant evidence-based practice guidelines were found.

Update

The update searches found published reports of updates for two publications that had been included in the original evidence summary: the first was an update to a large randomized trial (9,1u), and the second was a meta-analysis of individual-patient data from two trials (23,2u).

Clinical Trials

The trials identified for inclusion in this guideline report, summarized in Table 1, include five randomized trials comparing selective aromatase inhibitors with tamoxifen as first-line treatment (5-11), six randomized trials comparing selective aromatase inhibitors with megestrol acetate or aminoglutethimide as second-line treatment (12-19), and three phase II trials of exemestane as third- or greater-line therapy for metastatic breast cancer (20-22). The study by Dirix et al was identified as a phase II randomized trial by the investigators (11). For the Milla-Santos et al trial of anastrozole versus tamoxifen (7,8), the Buzdar et al (12,13) and Jonat et al (13,14) trials of anastrozole versus megestrol acetate, and the Dombernowsky et al trial of letrozole versus megestrol acetate (15,16), relevant data were available from two separate reports or abstracts. The main results of two trials have been reported only in abstract form (7,8,11). Quality-of-life data were reported separately, in abstract form, for two trials (10,16). Results of a randomized

trial of letrozole versus anastrozole as second-line treatment for advanced breast cancer were added to the guideline report in June 2002 (30).

The characteristics of patients enrolled in these trials are summarized in Table 2. Median follow-up ranged from 11 to 37 months for the randomized trials. Seven of 12 randomized trials were double-blind (5-7,9,15,17,19). Outcomes related to quality of life were assessed for six randomized trials (10,12,14-17,19).

Update

The updated clinical trial compared selective aromatase inhibitors with tamoxifen as first-line treatment (1u).

Table 1. Clinical trials of selective aromatase inhibitors included in this systematic review of the evidence.

Author	Year of publication	Patients enrolled	Comparisons	Reference
First-line treatment (randomized trials)				
Bonneterre et al	2000	668	anastrozole vs. tamoxifen*	5
Nabholtz et al	2000	353	anastrozole vs. tamoxifen*	6
Milla-Santos et al	2001	238	anastrozole vs. tamoxifen*	7,8 [abstracts]
Mouridsen et al	2001, 2003	939	letrozole vs. tamoxifen*	9,1u,10
Dirix et al	2001	122	exemestane vs. tamoxifen (phase II)	11 [abstract]
Second-line treatment (randomized trials)				
Buzdar et al	1997, 1998	386	anastrozole vs. megestrol acetate	12,13
Jonat et al	1996, 1998	378	anastrozole vs. megestrol acetate	13,14
Dombernowsky et al	1998	551	letrozole vs. megestrol acetate*	15,16
Buzdar et al	2001	602	letrozole vs. megestrol acetate*	17
Gershanovich et al	1998	555	letrozole vs. aminoglutethimide	18
Rose et al	2002	713	letrozole vs. anastrozole	30 [abstract]**
Kaufmann et al	2000	769	exemestane vs. megestrol acetate*	19
Third or greater-line treatment (single-cohort phase II trials)				
Thurlimann et al	1997	80	exemestane	20
Jones et al	1999	92	exemestane	21
Lonning et al	2000	242	exemestane	22

* double-blind

** added after draft guideline circulated for practitioner feedback (see page 17).

Published Meta-analyses

Bonneterre et al (23) combined individual-patient data from two trials of anastrozole versus tamoxifen as first-line therapy (5,6). Buzdar et al (13) combined individual-patient data from the American (12) and European (14) trials of anastrozole versus megestrol acetate as second-line

therapy. Messori et al (24) pooled individual-patient data from four of the trials of aromatase inhibitors versus megestrol acetate listed in Table 1 above (12,14,15,19).

Update

The pooled-analysis update (2u) provided an initial survival analysis and update of the safety data from two trials of anastrozole versus tamoxifen as a first-line therapy (5,6).

Table 2. Clinical trials of selective aromatase inhibitors–treatments and patient characteristics.

Author (Reference)	# cases analyzed	Treatments	Daily dose (mg)	% PgR/ER status unknown	Adjuvant endocrine therapy	% of patients with prior therapy		
						Adjuvant anti-estrogen	Adjuvant chemotherapy	Chemotherapy for advanced disease
First-line (randomized trials)								
Bonneterre (5) et al	668	anastrozole tamoxifen	1 20	55%	No tamoxifen <12 months	11%	23%	not allowed
Nabholtz et al (6)	353	anastrozole tamoxifen	1 20	11%	No tamoxifen <12 months	20%	27%	not allowed
Milla-Santos et al (7) [abstract]	238	anastrozole tamoxifen	1 40	0%	None allowed	0%	NR	not allowed
Mouridsen et al (9,1u)	907	letrozole tamoxifen	2.5 20	34%	If no recurrence and >12 months	18%	>22%	≤1 course 10%
Dirix (11) [abstract]	122	exemestane tamoxifen	25 20	NR	Allowed	NR	NR	≤1 course
Second-line (randomized trials)								
Buzdar et al (12)	386	anastrozole anastrozole megestrol acetate	1 10 160	13%	Allowed	42%	NR	≤1 course
							prior chemotherapy: 45%	
Jonat et al (14)	378	anastrozole anastrozole megestrol acetate	1 10 160	37%	Allowed	43%	NR	≤1 course
							prior chemotherapy: 28%	
Dombernowsky et al (15)	551	letrozole letrozole megestrol acetate	0.5 2.5 160	43%	Allowed	33%	>21%	≤1 course 16%
Buzdar et al (17)	602	letrozole letrozole megestrol acetate	0.5 2.5 160	18%	Allowed	38%	30%	≤2 courses 15%
Gershanovich et al (18)	555	letrozole letrozole aminoglutethimide	0.5 2.5 500	44%	Allowed	37%	>26%	≤1 course 22%
Rose et al (30) [abstract]	713	letrozole anastrozole	2.5 1	52%	Allowed	NR	NR	≤1 course
Kaufmann et al (19)	769	exemestane megestrol acetate	25 160	32%	Allowed	NR	>28%	≤1 course 16%
Third-line (phase II trials)								
Thurlimann et al (20)	78	exemestane	200	14%	NR	NR	NR	≤1 course 36%
Jones et al (21)	91	exemestane	25	8%	Allowed	NR	NR	≤1 course 24%
Lonning et al (22)	241	exemestane	25	30%	Allowed	NR	NR	≤1 course

PgR, progesterone receptor; ER, estrogen receptor; NR, not reported

Clinical Outcomes

Study results, in terms of tumour response, time to progression/failure and survival, for 15 randomized trials are summarized in Table 3. Objective response includes complete response (CR) or partial response (PR). Time to progression (TTP) is the time from randomization to objective disease progression or death. Several of the outcomes reported are related to each other. For example, clinical benefit includes objective response and stable disease for ≥24 weeks, and time to treatment failure (TTF) is the time from randomization to the earliest occurrence of one of three outcomes: progression, death, or withdrawal from randomized treatment.

Investigators identified time to disease progression as a primary outcome variable for eight trials (5,6,8,9,12,13,20,30), along with objective tumour response for six trials (5,6,8,12,13,20) and overall survival for one trial (7) as additional primary outcomes. Tumour response was identified as the sole primary outcome for seven trials (11,15,17-19,21,22). Response and clinical benefit rates were reported as a primary or secondary outcome for all 15 studies. Time-to-event analyses were reported for disease progression for 13 trials (5,6,8,9,12,13,15,17-22) and for treatment failure for nine trials (5,6,9,12,15,17-19,22). Overall survival data were available for only nine of the 15 trials (8,9,12,13,15,17-19,21). In general, adjustments of p-values for the multiple comparisons that arise from the analysis of several outcome variables or comparison of two doses of the experimental drug with control do not appear to have been made. There were, however, two exceptions. For the trial of anastrozole versus megestrol acetate by Buzdar et al, 97.5% or 97.7% confidence intervals were reported for the hazard ratios (HR) for disease progression, treatment failure, and death (12). Jonat et al (14), adjusted the level of significance to 0.024 for TTP and response rate to compensate for an interim analysis and the comparison of each of two doses of anastrozole to megestrol acetate.

Table 3. Results of clinical trials of selective aromatase inhibitors.

Author (Reference)	# of pts/ arm	Treatments	Daily dose (mg)	Response rate (CR+PR)	Clinical benefit rate	Median TTF (months)	Median TTP (months)	Median survival (months)
First-line (randomized trials)								
Bonneterre et al (5)	340 328	anastrozole tamoxifen	1 20	33% 33%	56% 56%	6.2 6.0	8.2 8.3	NR NR
Nabholtz (6)	171 182	anastrozole tamoxifen	1 20	21% 17%	59%* 46%	7.6 5.4	11.1* 5.6	NR NR
Milla-Santos (8) [abstract]	121 117	anastrozole tamoxifen	1 40	34% 27%	82%* 55%	NR NR	12.3* 5.3	alive, 35 mos: 39%* 8%
Mouridsen (9,1u)	453 454	letrozole tamoxifen	2.5 20	32%* 21%	50%* 38%	9.0* 5.7	9.4* 6.0	34[+] 30[Ŧ]
Dirix (11) [abstract]	N= 122	exemestane tamoxifen	25 20	45% 14%	55% 39%	NR NR	NR NR	NR NR
Second-line (randomized trials)								
Buzdar (12,13)	128 130 128	anastrozole anastrozole megestrol acetate	1 10 160	10% 5% 5%	37% 29% 35%	5.5 4.4 4.1	5.6 4.7 5.0	alive, 24 mos: 62% 58% 53%
Jonat (13,14)	135 118 125	anastrozole anastrozole megestrol acetate	1 10 160	10% 13% 10%	34% 34% 33%	NR NR NR	4.8 5.3 4.6	alive, 24 mos: 51% 51% 39%
Dombernowsky (15)	188 174 189	letrozole letrozole megestrol acetate	0.5 2.5 160	13% 24%** 16%	27% 35% 32%	3.2 5.1** 3.9	5.1 5.6[+] 5.5	22 25[+] 22
Buzdar (17)	202 199 201	letrozole letrozole megestrol acetate	0.5 2.5 160	21% 16% 15%	33% 27% 24%	5* 3 3	6* 3 3	33 29 26
Gershanovich (18)	192 185 178	letrozole letrozole aminoglutethimide	0.5 2.5 500	17% 20% 12%	33% 36% 29%	~3 ~3* ~3	3.3 3.4* 3.2	21 28*** 20
Rose (30) [abstract]	356 357	letrozole anastrozole	2.5 1	19%[++] 12%	27% 23%	NR	NR	NR
Kaufmann (19)	366 403	exemestane megestrol acetate	25 160	15% 12%	37% 35%	3.8* 3.6	4.7* 3.8	not reached* 28
Third-line (phase II trials)								
Thurlimann (20)	78	exemestane	200	26%	39%	NR	4.8	NR
Jones (21)	91	exemestane	25	13%	30%	NR	2.0	26
Lonning (22)	241	exemestane	25	7%	24%	13.0	14.7	NR

pts, patients; CR, complete response; PR, partial response; TTF, time to treatment failure; TTP, time to treatment progression; NR, not reported; mos, months.

Ŧ Data presented at the 2001 San Antonio Breast Cancer Symposium and cited with permission of the author;

* $p<0.05$ vs. control;

** $p<0.05$ for letrozole 2.5 mg vs. megestrol acetate and vs. letrozole 0.5 mg;

*** $p<0.05$ for letrozole 2.5 mg vs. aminoglutethimide and vs. letrozole 0.5 mg;

[+] $p<0.05$ for letrozole 2.5 mg vs. letrozole 0.5 mg;

[++] $p=0.014$ for letrozole vs. anastrozole.

First-line Therapy

Randomized trials

There have been three large (5,6,9) and two smaller (7,11) randomized controlled trials comparing highly selective aromatase inhibitors to tamoxifen as first-line hormonal therapy for metastatic breast cancer (Table 3). The large trials are comparable with respect to the proportion of subjects who received prior adjuvant hormonal therapy or prior systemic therapy for advanced disease (5,6,9) (Table 2).

Two concurrent trials of anastrozole versus tamoxifen, carried out in North America and Europe, have been published in peer-reviewed journals (5,6). In the North American trial reported by Nabholtz et al (6), 89% of the study participants were known to have estrogen- or progesterone-receptor-positive disease. In this trial, the TTP (the primary end point) was 11.1 months with anastrozole and 5.6 months with tamoxifen, a statistically significant difference (p=0.005). There was no significant difference between treatments in objective response rate (a primary outcome variable for this trial), but the clinical benefit rate (defined as objective response or stable disease for at least six months) was found to be higher with anastrozole (p=0.0098) in an unplanned comparison. The European trial, reported by Bonneterre et al was of identical design (5). In contrast to the North American study, the receptor status of the primary tumour was unknown for more than half of the patients. Overall, there was no significant difference in TTP, objective response rate, or clinical benefit rate between treatment groups in the European trial. An exploratory, subgroup analysis of data from the patients with receptor-positive disease suggested a small benefit in TTP in the anastrozole group. These two trials were designed with the intention of pooling the data. A pooled analysis (23), which was based on data from 1021 women, failed to detect significant differences in TTP (median, 8.5 months with anastrozole versus [vs.] 7.0 months with tamoxifen), response rate (29.0% vs. 27.1%) or clinical benefit (57.1% vs. 52.0%). Survival data were not reported because the median duration of follow-up was only 18 months.

Results of a smaller trial of anastrozole vs. tamoxifen as first-line therapy for metastatic breast cancer were presented in two meeting abstracts by Milla-Santos et al (7,8). In this trial, treatment with anastrozole was superior to tamoxifen in terms of clinical benefit (p=0.0287), TTP (HR, 0.77; 95% CI, 0.56 to 0.91; p=0.047), and survival (HR, 0.63; 95% CI, 0.51 to 0.89; p=0.036) (8).

A multicentre trial of letrozole versus tamoxifen as first-line therapy in over 900 patients with metastatic breast cancer was reported by Mouridsen et al in a published report (9) and at the 2001 San Antonio Breast Cancer Symposium (25). The receptor status was unknown in about one third of the patients. In this trial, the primary endpoint of median TTP was significantly better in the letrozole group (p=0.001). The objective response rate (p=0.0006), TTF (p=0.0001), and clinical benefit rate (p=0.001) were also superior in the patients treated with letrozole (9). Approximately 20% of patients in this trial had received adjuvant anti-estrogen therapy. An unplanned subgroup analysis of objective response rate in this subset of 167 patients with a history of prior anti-estrogen therapy detected response rates of 29% with letrozole and only 8% with tamoxifen (9). Final results were presented at the San Antonio Symposium (25) but have not yet been published in abstract form or in a peer-reviewed journal. The developers of this guideline report have obtained permission from the investigators to cite the data presented at San Antonio in this guideline. The final analysis detected response rates (32% with letrozole vs. 21% with tamoxifen, p<0.05), clinical benefit rates (50% vs. 38%, p<0.05), median TTF (9.0 months vs. 5.7 months, p<0.05) and median TTP (9.4 months vs. 6.0 months, p<0.05) that were very similar to those in the published report (9) (Table 3). Unpublished survival data were also presented at San Antonio. Overall, the median duration of survival was 34 months for the letrozole group, and 30 months for the tamoxifen group. This difference was not statistically significant. Of note, this protocol contained an optional crossover to the other treatment upon disease progression. Approximately one half of the patients in each

treatment arm crossed over to the other treatment. Exploratory analyses suggested that two-year survival rates were higher among patients randomized to letrozole than among those randomized to tamoxifen and that survival was superior for letrozole when the data were censored at crossover. However, these data have not been published and should be interpreted with caution.

Tamoxifen has also been compared to exemestane as first-line therapy in a randomized phase II trial with 122 patients, reported in abstract form by Dirix et al (11). The only reported outcomes were response and clinical benefit rates. The observed response rate was higher in the exemestane group than in the tamoxifen group, but a p-value was not reported.

Update

Survival and efficacy results for the updated clinical trial (1u) are included in Table 3. Results changed only slightly from their previous report (9).

In the update (2u) to the pooled analysis (23), survival data was reported. There was no difference in time to death (median, 39.2 months with anastrozole vs. 40.1 months with tamoxifen). Subgroup analysis by hormone-receptor-status did not reveal any differences in death rates between the two groups.

Meta-analysis

A pooled analysis of published response and TTP data from all the first-line trials was performed by the guideline developers. The numbers of patients who were alive and progression free 12 months after randomization were estimated from TTP curves in published reports (5,6,9) and in one case, from a poster presented at the 2000 San Antonio Breast Cancer Symposium (7); these data were not available from the abstract report of the fifth trial (11). Response data were available for all five trials, from full reports in three cases (5,6,9) and from meeting abstracts in two (8,11).

Figures 1 and 2 show the RR of tumour response and disease progression for the individual trials and overall. Both the pooled response and 12-month progression-free-survival data demonstrate the superiority of first-line aromatase-inhibitor therapy over tamoxifen. There was statistically significant heterogeneity among studies in terms of response data (p=0.0048 on test for heterogeneity), with the risk ratio for the Dirix et al trial being noticeably different from the other four trials. The study by Dirix et al was a phase II open-label trial, while the other four were double-blind phase III trials. When the analysis was repeated without the Dirix et al trial, the p-value for the test of heterogeneity was increased to 0.11 and the overall risk ratio was of borderline significance (RR, 1.23; 95% CI, 1.00 to 1.52; p=0.05).

Because data from abstracts may be less reliable than those from published reports, the meta-analysis was repeated without the Milla-Santos et al (7) and Dirix et al (11) trials. This sensitivity analysis detected pooled risk ratios of 1.23 (95% CI, 0.93 to 1.61) for response and 0.82 (95% CI, 0.77 to 0.88) for progression. The pooled result for progression is consistent with that for the full set of four studies, but the overall risk ratio for response becomes non-significant when the analysis is restricted to the three studies reported in full.

Update

Updated data for response rates and TTP (1u) were included in the meta-analyses.

Figure 1. Pooled response rates from randomized trials of aromatase inhibitors versus tamoxifen as first-line therapy for metastatic breast cancer.

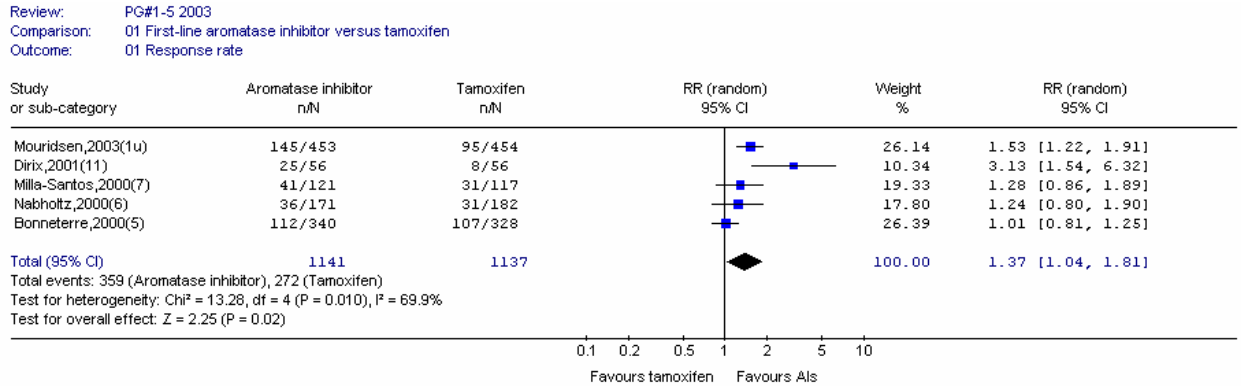
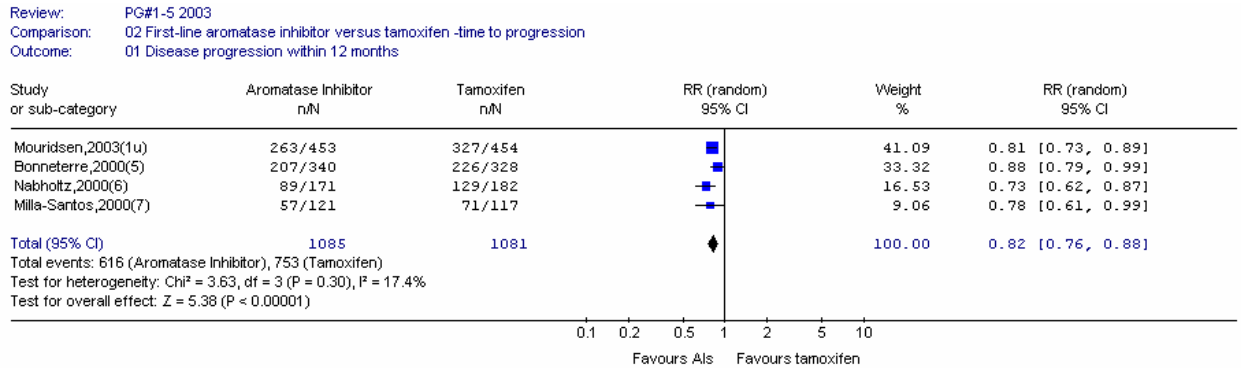


Figure 2. Pooled 12-month disease-progression rates from randomized trials of aromatase inhibitors versus tamoxifen as first-line therapy for metastatic breast cancer.



Second-line Therapy

Randomized trials

Results from seven randomized trials of the selective aromatase inhibitors as second-line hormonal therapy for metastatic breast cancer (12-19,30) are presented in Table 3.

Two multicentre trials conducted in North America and Europe compared anastrozole (1 mg or 10 mg daily) to megestrol acetate in women whose disease had progressed after treatment with tamoxifen (12,14). A pooled analysis of the data from these two trials has been reported by Buzdar et al (13). No difference was detected in any of the efficacy endpoints in either individual trial. The pooled analysis detected a small but statistically significant survival advantage in the 1 mg anastrozole arm but not the 10 mg anastrozole arm, compared to megestrol acetate (median survival: 26.7 months with 1 mg anastrozole, 25.5 months with 10 mg anastrozole, 22.5 months with megestrol; p<0.025, 1mg anastrozole vs. megestrol).

Dombernowsky et al compared two doses of letrozole (0.5 mg and 2.5 mg) to megestrol acetate as second-line therapy in women with advanced breast cancer (15). Letrozole 2.5 mg was better than megestrol acetate in time to treatment failure (p=0.04) and objective response rate (p=0.04), but there was no survival advantage or difference in TTP.

In a trial of similar design, Buzdar et al randomized more than 600 women to letrozole 0.5 mg, letrozole 2.5 mg, or megestrol acetate 160 mg per day (17). Treatment with letrozole 0.5 mg daily was associated with a prolonged TTP (p=0.041) and TTF (p=0.018) compared with megestrol acetate, but there were no significant improvements in response rate or survival.

Letrozole (0.5 mg or 2.5 mg) was compared to aminoglutethimide in patients previously treated with anti-estrogens for advanced disease in a randomized trial by Gershanovich et al (18). No significant differences were detected among treatment arms for the primary endpoint of objective response rate. The median TTP and time to treatment failure was just over three months in all treatment groups, but Cox regression analysis detected a statistically significant advantage favouring letrozole 2.5 mg over aminoglutethimide (p=0.008 for TTP, adjusted for baseline covariates; unadjusted p=0.05 for TTP; adjusted p=0.003 for TTF; unadjusted p=0.01 for TTF). Similarly, the higher dose of letrozole was associated with improved overall survival compared with aminoglutethimide (p=0.002).

Each of the five trials described above evaluated two doses of an aromatase inhibitor (12-15,17,18). The trials by Buzdar et al and Jonat et al did not detect any statistically significant differences between doses of anastrozole of 1.0 mg and 10 mg in outcome variables associated with response, progression, or survival (12-14). Three trials compared letrozole 0.5 mg and letrozole 2.5 mg versus either megestrol or aminoglutethimide (15,17,18). In the trials by Dombernowsky et al and Gershanovich et al, only the higher dose of letrozole was associated with significantly improved TTF, TTP, and median survival. In contrast, Buzdar et al found the lower dose of letrozole to be better. There were no statistically significant differences in outcomes when the higher and lower doses were compared to each other in any of these trials. Although different dose levels of letrozole were evaluated in these trials, it is generally accepted that the standard dose is 2.5 mg daily.

The largest individual randomized trial of an aromatase inhibitor as second-line therapy, by Kaufmann et al, compared exemestane to megestrol acetate in 769 women (19). There was no significant difference between groups in the primary endpoint of overall response but exemestane was associated with a longer TTP (p=0.037), TTF (p=0.042), and survival (p=0.039) than megestrol acetate .

An abstract by Rose et al for ASCO 2002 reported a significant difference in response rate between letrozole and anastrozole as second-line treatment (19% for letrozole vs. 12% for anastrozole, p=0.014), but no significant difference in clinical benefit rate, TTP or TTF (30). Survival data were not reported.

Meta-analysis

Messori et al (24) published a meta-analysis of survival data from four of the randomized trials of aromatase inhibitors versus megestrol acetate described above (12,14,15,19). The trial of letrozole versus megestrol acetate by Buzdar et al (17) was not included because it was published after completion of the meta-analysis. The authors of the meta-analysis pooled individual-patient data from the North American and European trials of anastrozole (12,14), a trial of letrozole (15), and a trial of exemestane (19). This analysis found that treatment with aromatase inhibitors prolonged survival, compared to megestrol acetate, with a RR of death of 0.79 (95% CI, 0.69 to 0.91; p=0.0011). A second meta-analysis, included in the same report but based on published data from these four trials, obtained similar results (24).

Third-line Therapy

The results of three phase II studies of the steroidal selective aromatase inhibitor exemestane as third-line (or greater) therapy for metastatic breast cancer (20-22) confirm that a meaningful response to treatment can be obtained in this setting (Table 3). In addition, the data suggest that there may be a lack of cross resistance between exemestane and the non-steroidal aromatase inhibitors.

Thurlimann et al found a response rate of 26% in 78 heavily pretreated patients given 200 mg exemestane who had progressed after treatment with tamoxifen, aminoglutethimide and in some cases additional hormonal manipulation (20). Of note, the response rate was 12% in those patients who displayed resistance to aminoglutethimide.

A more modest response to exemestane was seen in a phase II trial in patients with progressive disease following treatment with tamoxifen and megestrol acetate (21). In this trial, the objective response rate was 13%; clinical benefit was observed in almost one third of patients.

Lonning et al evaluated the effect of exemestane in 241 women with metastatic breast cancer who had disease progression following therapy with aminoglutethimide or one of the novel, non-steroidal selective aromatase inhibitors (22). The majority of these patients received exemestane as third-line therapy. Although the objective response rate was low, 24.3% of the patients experienced a clinical benefit.

Quality of Life

Variables related to quality of life were measured for one randomized trial of first-line therapy with aromatase inhibitors (10) and five randomized trials of second-line therapy (12,14-17,19).

Karnofsky Performance Status (KPS) was measured before and after treatment for all but one participant in the double-blind randomized trial by Mouridsen et al (10). Fifteen percent of women treated with letrozole as first-line therapy experienced an improvement of 20 points or more in KPS score compared with 9% on tamoxifen ($p=0.066$). The median time to a worsening of KPS score by 20 points or more was not reached in the letrozole group and was 30 months in the tamoxifen group (log-rank $p=0.002$).

The Rotterdam Symptom Checklist and other measures were used to assess quality of life during the first year after randomization in the North American (12) and European (14) open-label trials of anastrozole versus megestrol acetate as second-line therapy. Buzdar et al (12) reported significantly better physical and psychological scores with anastrozole compared to megestrol ($p<0.025$). Jonat et al found the opposite effect (14), reporting better scores on the psychological dimension of the quality-of-life questionnaire with megestrol ($p=0.008$ vs. anastrozole 1 mg, $p=0.003$ vs. anastrozole 10 mg) among 75% of trial participants who completed the questionnaire 12 weeks after randomization. Patients on anastrozole 10 mg experienced less bone pain than those on megestrol ($p=0.011$), and those on anastrozole 1 mg had better performance status scores at 12 weeks ($p=0.007$ vs. megestrol).

The European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30) scale was used to assess quality of life during the first 24 months of participation in the double-blind trial of two doses of letrozole versus megestrol acetate by Dombernowsky et al (15,16). No significant differences in quality-of-life scores were found among treatment groups but fewer patients on letrozole 2.5 mg experienced a deterioration in World Health Organization (WHO) performance status (41% vs. 55% with megestrol, $p=0.01$). Buzdar et al used a similar approach in their double-blind trial of letrozole versus megestrol acetate but found no significant differences among treatment groups in measures of quality of life (17).

Kaufmann et al also assessed subjective response and quality of life in their double-blind trial of exemestane versus megestrol acetate (19). There was no significant difference between treatments in improvement in pain score or tumour-related signs and symptoms. Some of the quality-of-life domains on the EORTC QLQ-C30 were better in the exemestane group ($p<0.01$ compared with megestrol for physical functioning, role functioning, global health, fatigue, dyspnea, and constipation) while others improved more in the megestrol acetate group (emotional function, appetite, and pain; p-values not reported).

Toxicity of Selective Aromatase Inhibitors

In general, therapy with selective aromatase inhibitors is very well tolerated. Toxicity data from full reports of clinical trials are summarized in Table 4. There were no reported deaths that were considered by the investigators to be related to the use of aromatase inhibitors in these trials.

In randomized trials of anastrozole and letrozole compared to tamoxifen as first-line therapy for metastatic disease (5,6,9), approximately 5% of patients in both treatment groups experienced serious adverse effects that led to withdrawal from the trial. Overall, the patients receiving aromatase inhibitors in these trials reported the same or slightly higher numbers of hot flashes but less vaginal bleeding and fewer thromboembolic events than those receiving tamoxifen. The tumour flare phenomenon was reported with similar frequency for the anastrozole (3.0%) and tamoxifen groups (3.5%) in the trials by Bonneterre et al and Nabholtz et al (23).

In trials of anastrozole, Letrozole, or exemestane versus megestrol acetate or aminoglutethimide as second-line therapy (12,14,15,17,18,19), serious adverse events leading to study withdrawal were also uncommon. Fewer women receiving aromatase-inhibitor therapy experienced weight gain, dyspnea, or thromboembolic events but more had gastrointestinal symptoms (nausea, vomiting, and diarrhea) compared to control.

Nausea, fatigue, and hot flashes were the most commonly reported adverse effects in the phase II trials of exemestane as third- (or greater-) line therapy (20-22).

Update

Updated toxicity data results for the International Letrozole Breast Cancer Group (1u) are described in Table 4. Results changed only slightly from the previous report (9).

Table 4. Toxicity data from full reports of clinical trials of selective aromatase inhibitors: % patients with adverse effects.

Author (Reference)	# of pts/ arm	Treatments	Daily Dose (mg)	Hot flashes	Vaginal bleeding	Weight gain	Thrombo-embolic events	Dyspnea	Fatigue	GI symptoms
First-line										
Bonneterre et al (5)	340 328	anastrozole tamoxifen	1 20	21% 21%	1% 2%	2% 2%	5% 7%	NR	NR	24% 28%
Nabholtz (6)	171 182	anastrozole tamoxifen	1 20	38% 28%	1% 4%	3% 1%	4% 8%	NR	NR	54% 57%
Mouridsen (9,1u)	453 454	letrozole tamoxifen	2.5 20	19% 16%	NR	NR	1% 2%	18% 17%	13% 13%	15% 16%*
Second-line										
Buzdar (12)	128 130 128	anastrozole anastrozole megestrol acetate	1 10 160	23% 18% 21%	NR	1% 5% 16%	3% 2% 5%	13% 15% 24%	NR	38% 43% 27%
Jonat (14)	135 118 125	anastrozole anastrozole megestrol acetate	1 10 160	3% 5% 6%	NR	2% 3% 8%	4% 1% 5%	NR	NR	22% 22% 16%
Dombernowsky (15)	188 174 189	letrozole letrozole megestrol acetate	0.5 2.5 160	6% 6% 4%	NR	2% 2% 9%	1% 0% 8%	11% 9% 16%	6% 11% 11%	19% 11% 9%*
Buzdar (17)	202 199 201	letrozole letrozole megestrol acetate	0.5 2.5 160	15% 12% 12%	3% 1% 8%	3% 3% 12%	NR	2% 2% 9%	4% 6% 9%	13% 11% 10%*
Gershanovich (18)	192 185 178	letrozole letrozole aminoglutethimide	0.5 2.5 500	3% 5% 3%	NR	NR	NR	NR	3% 3% 3%	7% 10% 10%*
Kaufmann (19)	366 403	exemestane megestrol acetate	25 160	13% 5%	NR	8% 17%	NR	0.3% 3%	8% 10%	9% 5%*
Third-line										
Thurlimann(20)	78	exemestane	200	21%	NR	NR	NR	NR	NR	19%*
Jones (21)	91	exemestane	25	20%	NR	NR	NR	NR	7%	20%*
Lonning (22)	241	exemestane	25	7%	NR	NR	NR	2%	7%	10%*

pts, patients; NR, not reported;
* nausea.

V. INTERPRETIVE SUMMARY

First-line Therapy

Results are available from five randomized trials of selective aromatase inhibitors versus tamoxifen as first-line therapy for women with advanced breast cancer and from a pooled analysis performed for this guideline. In the trial of letrozole, and two of the three anastrozole trials, treatment with the aromatase inhibitor was associated with higher rates of clinical benefit and prolonged TTP of approximately three to seven months. In the smaller exemestane trial, treatment with this agent also resulted in a superior clinical benefit rate, but this result was not statistically significant. Preliminary data on survival are available from two of the trials. One relatively small trial of anastrozole versus tamoxifen, reported in abstract form, detected survival results in favour of anastrozole. There was no apparent overall survival advantage in the crossover trial of letrozole versus tamoxifen in the first-line setting when all patients were considered. The pooled analysis of four trials revealed a statistically significant improvement in 12-month progression-free survival with aromatase inhibitors. Overall, the incidence of adverse effects in the aromatase-inhibitor- and tamoxifen-treated patients was similar, with slightly fewer thromboembolic events observed in the former group. There are very limited data on quality of life from these trials.

Second-line Therapy

Mature data are available from two randomized trials of anastrozole versus megestrol acetate, two trials of letrozole versus megestrol acetate, and a large trial of exemestane versus megestrol acetate in the treatment of women who have progressed on tamoxifen and up to one chemotherapy regimen given for advanced breast cancer. In the individual anastrozole and letrozole trials, the objective response rates achieved with the aromatase inhibitor were as good as, or better than, those with megestrol acetate, but there was no statistically significant survival difference. A pooled analysis of individual-patient data from the two anastrozole trials detected a statistically significant improvement in overall survival rate at two years of about 10% (56.1% for anastrozole 1 mg vs. 46.3% for megestrol acetate). The single trial of exemestane versus megestrol acetate demonstrated equivalent objective response rates and significant but modest improvements in both TTP and median survival. A published individual-patient-data meta-analysis found that treatment with aromatase inhibitors in the second-line setting was associated with a 4.1-month improvement in mean survival. Four trials found no consistent evidence of differences in quality of life between aromatase inhibitors and megestrol acetate. In general, fewer patients experienced weight gain, dyspnea, and thromboembolic events with aromatase-inhibitory therapy than with megestrol acetate as second-line therapy.

Early results, reported in abstract form, are available from the only head-to-head comparison of two non-steroidal aromatase inhibitors. There was no pre-planned blinded assessment of response in this randomized open-label trial. A modest but statistically significant improvement in objective response rate in favour of letrozole was detected, but there were no reported differences between letrozole and anastrozole in the other outcomes of interest.

Third- and Greater-line Therapy

In three phase II studies of third-line hormonal therapy for advanced breast cancer, exemestane therapy was associated with modest but appreciable rates of objective response and clinical benefit and was well tolerated. Some activity was observed in patients who had progressed on treatment with the non-steroidal aromatase inhibitors.

Optimal Sequencing of Hormonal Agents in Metastatic Breast Cancer

The generalizability of results from these trials to clinical practice has been questioned for several reasons. In the studies conducted in the first-line setting, only a minority of patients had

received adjuvant tamoxifen. Thus, the overall objective response rates to tamoxifen observed in the trials may have been higher than would be expected, because of high response rates among women without prior exposure to tamoxifen. An additional problem arises from the scarcity of data on objective response after crossover to an aromatase inhibitor from tamoxifen, or vice versa, in the first-line trials. The only trial with a pre-defined blinded crossover to the alternate agent compared letrozole to tamoxifen. The lack of survival benefit observed in this trial when all patients were considered suggests that meaningful responses to aromatase inhibitors after first-line tamoxifen, and to tamoxifen after first-line aromatase inhibitors, are possible.

VI. ONGOING TRIALS

No relevant ongoing trials were identified.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Breast Cancer DSG reviewed draft guideline reports at two meetings in 2001. At the first meeting, the discussion centred on the role of aromatase inhibitors versus tamoxifen, which aromatase inhibitor to use, the role of evidence from clinical trials funded by drug companies, and the lack of evidence for second-line treatment options if aromatase inhibitors were to be used as first-line therapy. After reviewing and discussing the original evidence, the DSG members had difficulty reaching consensus on recommendations for the use of aromatase inhibitors. They requested that data from the first-line trials be pooled before reviewing the evidence again.

At their next meeting, the DSG considered the optimum dose of letrozole, which is marketed as 2.5 mg tablets, as second-line therapy. It is not clear from the data if the doses evaluated in clinical trials (0.5 and 2.5 mg) are equally effective. The DSG reviewed original toxicity data from randomized trials and noted that the rates of thromboembolism favour aromatase inhibitors over tamoxifen, but the rates were low with both treatments. They also discussed the use of aromatase inhibitors in premenopausal women, and added the biologic rationale for not treating these patients with aromatase inhibitors to section II of the guideline report. After discussing the role of economic analyses in guideline development, the DSG decided not to include any detailed description of these studies but to list references for them in the guideline report.

The DSG members reviewed the original evidence available from the randomized trials and meta-analysis and concluded that there was no clear evidence of a difference in survival between aromatase inhibitors and tamoxifen as first-line therapy. Treatment with aromatase inhibitors, however, was associated with higher objective response rates and prolonged TTP compared to tamoxifen. When tumour response or time-to-disease progression are the outcomes of interest, the DSG recommended that aromatase inhibitors are an acceptable alternative to tamoxifen as first-line therapy for metastatic breast cancer. During these discussions, DSG members acknowledged that their involvement in a clinical trial of tamoxifen versus exemestane presented a potential conflict of interest that could make them reluctant to recommend aromatase inhibitors in the first-line setting.

The draft guideline report was subsequently reviewed by Cancer Care Ontario's Policy Advisory Committee on New Cancer Drugs, who provided feedback that suggested a stronger recommendation for aromatase inhibitors in the first-line setting. In response to this feedback, the recommendation was revised from "acceptable alternative" to "preferred treatment option" and approved by the Breast Cancer DSG.

VIII. IMPLICATIONS FOR POLICY

The Breast Cancer Disease Site Group is aware of five economic evaluations of aromatase inhibitors for the treatment of metastatic breast cancer (24,26-29) that may be of interest to

policy makers. A full description and evaluation of these studies is outside the scope of this guideline report.

Update
An additional economic evaluation of letrozole versus tamoxifen was identified during the literature search update (3u).

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Practice Guideline
Based on the original evidence described above, the Breast Cancer DSG drafted the following practice guideline:

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

Draft Recommendations

Key recommendations

First-line therapy

- The selective aromatase inhibitors 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

- Selective aromatase inhibitors are superior to megestrol acetate or aminoglutethimide as second-line hormonal therapy.
- There are insufficient data to recommend any one aromatase inhibitor over others in this setting.

Third- or greater-line therapy

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

Qualifying statement

- The selective aromatase inhibitors are contraindicated in premenopausal women.

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 121 practitioners in Ontario (81 medical oncologists and 40 radiation oncologists). The survey consisted of 21 questions about the quality of the practice-guideline-in-progress (PGIP) report. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The guideline report and questionnaire were mailed

on May 14, 2002. Follow-up reminders were sent two weeks (post card) and four weeks (complete package mailed again) later. The Breast Cancer DSG reviewed the results of the survey.

Results

Seventy-six responses were received out of the 121 surveys sent (63% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 53 indicated that the report was relevant to their clinical practice and 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
2. The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	53 (100%)	0	0
3. There is a need for a clinical practice guideline on this topic.	53 (100%)	0	0
4. The literature search is relevant and complete.	48 (92%)	2 (4%)*	2 (4%)
6. The results of the trials described in the report are interpreted according to my understanding of the data.	53 (100%)	0	0
7. The draft recommendations in this report are clear.	52 (98%)	1 (2%)	0
8. I agree with the draft recommendations as stated.	50 (94%)	2 (4%)	1 (2%)
20. This PGIP report should be approved as a practice guideline.	48 (91%)	4 (7%)	1 (2%)
21. If this PGIP 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
	47 (92%)	3 (6%)**	1 (2%)

* plus 1 missing; ** plus 2 missing

Summary of Written Comments

Twelve respondents (23%) provided written comments. The main points contained in the written comments were:

1. Two practitioners questioned the strength of the recommendation for aromatase inhibitors as first-line therapy, suggesting that aromatase inhibitors are an acceptable alternative to tamoxifen but not necessarily the preferred option.
2. Practitioners were concerned about the lack of evidence related to crossover from one drug to another and to the sequencing of treatments.
3. One practitioner suggested that data from a randomized trial of letrozole versus anastrozole, presented at ASCO 2002, should be added.
4. One practitioner criticized the inclusion of data from abstracts.

Modifications/Actions

The DSG discussed the issues described above and responded as follows:

1. The DSG stands by the recommendation for aromatase inhibitors as the preferred option for first-line hormonal therapy. Although there is no clear evidence of a difference in survival between aromatase inhibitors and tamoxifen as first-line therapy, randomized trials detected higher objective response rates and prolonged TTP with aromatase inhibitors compared to tamoxifen.
2. After the feedback survey, a discussion on the optimal sequencing of hormonal agents in metastatic breast cancer was added to the Interpretive Summary section.
3. Results from the ASCO abstract report of the letrozole versus anastrozole trial were added to the guideline report (30).
4. The rationale for including data from abstracts was added to the Inclusion Criteria section of the Full Report. A sensitivity analysis was performed to assess the impact of abstract data on the pooled risk ratios for tumour response and disease progression (page 9).

X. 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 Breast Cancer DSG and the Practice Guidelines Coordinating Committee.

Target Population

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

Recommendations

First-line therapy

- Letrozole and anastrozole 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

- Letrozole, anastrozole, and exemestane inhibitors 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.

XI. JOURNAL REFERENCE

Eisen A, Prichard K, Johnston M, Oliver T; Breast Cancer Disease Site Group. Role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Curr Oncol. 2004;11(2):41-52.

XII. ACKNOWLEDGMENTS

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For a complete list of members of the Breast Cancer Disease Site Group and the Practice Guidelines Coordinating Committee, please visit the Program in Evidence-based Care Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Update

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