Acta Oncologica, 2005; 44: 23–31

Taylor & Francis
Taylor & Francis Group

ACTA ONCOLOGICA EXPERT CONSENSUS RECOMMENDATIONS

Aromatase inhibitors in the treatment of early and advanced breast cancer

HEIKKI JOENSUU[1], BENT EJLERTSEN[2], PER E. LØNNING[3] & LARS-ERIK RUTQVIST[4]

[1]*Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland,* [2]*Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark,* [3]*Section of Oncology, Institute of Medicine, Haukeland University Hospital, University of Bergen, Bergen, Norway, and* [4]*Karolinska Institute and Huddinge University Hospital, Sodersjukhuset, Stockholm, Sweden*

Abstract
The third generation aromatase inhibitors anastrozole, exemestane, and letrozole have been compared with tamoxifen and other endocrine therapies in several studies in early and advanced breast cancer. These studies are reviewed in this report. Based on the available evidence, the panel recommends that adjuvant treatment with tamoxifen for 5 years should no longer be considered as the sole standard but that a third-generation aromatase inhibitor should be used either alone or in a sequence with tamoxifen in the adjuvant treatment of postmenopausal women with hormone-receptor-positive breast cancer. Third generation aromatase inhibitors may be considered as the first line therapy of hormone-receptor-positive advanced breast cancer in postmenopausal women, and they may also be used for preoperative therapy of breast cancer.

Background

When ovarian estrogen synthesis ceases at the menopause, estrogens continue to be synthesized in different body compartments from circulating androgens. The key pathway is aromatization of androstenedione into estrone, probably accounting for as much as 90% of the total estrogens synthesized in a postmenopausal woman. The aromatase enzyme may also use testosterone as a substrate converting testosterone into estradiol but since the circulating testosterone levels are lower than those of androstenedione, and aromatase has lower activity for testosterone than for androstenedione, the contribution of this pathway to estrogen synthesis is only modest (see [1] for details and original references). The adrenals are the main source of circulating androgens in postmenopausal women, while the potential role of the postmenopausal ovary remains controversial [2–4].

Although only one gene encodes for the aromatase enzyme in both reproductive and non-reproductive tissues, this gene contains at least 10 different promoters [5]. A possibility of tissue-specific aromatase inhibition exists, because these promoters are expressed differently in different types of normal tissues and in breast cancer, and the promoters are stimulated by different ligands [5–11].

Understanding of the physiological effects of estrogens has improved greatly over recent years due to experimental work as well as clinical observations in individuals who have genetic defects. Development of knock-out mice for the ERα (ERKO) and ERβ [12] has been useful in singling out the biological functions of the different receptors, and the aromatase knock-out mouse (ARKO) has been used to study the effect of total estrogen deprivation [13]. ARKO mice express severe metabolic disturbances including accumulation of abdominal fat, diabetes, and hepatic steathosis [14,15]. For unknown reasons hepatic steathosis is particularly evident in male ARKO mice. These mice are further characterized by a low level of physical activity, which may in part cause their fat accumulation. Observations in humans with germ-line mutations in the aromatase gene have revealed similar types of disturbances but to a somewhat smaller extent [16–18]. Although the relevance of these findings to the treatment of postmenopausal women with aro-

Correspondence: Heikki Joensuu, MD, Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, PO Box 180, FIN-00029 Helsinki, Finland. Tel: +358-9-471 73202. Fax: +358-9-471 74202. E-mail: heikki.joensuu@hus.fi

(Received 8 November 2004; accepted 17 November 2004)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860510007468

matase inhibitors for a limited time period remains unclear at present, they highlight the need for careful assessment of the metabolic status in clinical studies.

Pharmacology of aromatase inhibitors

Pharmacologically, aromatase inhibitors may be divided into two classes: the so-called non-steroidal inhibitors that are either phenobarbitones (such as aminoglutethimide) or imidazole/triazole derivatives (fadrozole, letrozole, and anastrozole), or the steroidal compounds (formestane, exemestane) that are derivatives of androstenedione.

These compounds differ in their effect on the aromatase enzyme. The non-steroidal compounds bind to the p450 domain of the aromatase protein, whereas the steroidal compounds bind to the substrate pocket [19]. While the non-steroidal compounds bind reversibly, the steroidal compounds bind irreversibly, and have therefore been coined as "aromatase inactivators". Another major difference is that the main metabolite of exemestane, 17-hydroexemestane, has androgenic activity. In line with this, exemestane suppresses the sex hormone-binding globulin in a dose-dependent manner in vivo [20]. Oral, but not parenteral, administration of formestane has a similar effect [21].

Several assays are available in vitro for determining the potency of different aromatase inhibitors but such data cannot be directly transferred to the in vivo situation, since efficacy in vivo may depend on pharmacokinetics and tissue uptake. This is illustrated when fadrozole is compared with letrozole; while the former is the most potent compound based on in vitro testing, letrozole turned out to achieve a much better aromatase inhibition in vivo (see below).

In vivo effects in humans

Studies where plasma estrogen levels have been measured in postmenopausal women treated with aromatase inhibitors have provided divergent results; much of this is probably due to methodological problems related to assay sensitivity. One method of assessing the biochemical efficacy of an aromatase inhibitor in vivo directly is to give a double-tracer injection of ^{3}H-androstenedione and ^{14}C-labelled estrone, and to calculate the total body aromatization from the isotope ratio of the estrogen metabolites [22]. In such studies the first- and the second-generation inhibitors have been found to achieve aromatase inhibition ranging between 50% and 90% [23]. In contrast, the so-called third generation compounds (anastrozole, letrozole, and exemestane) achieved as high as 98% or better aromatase inhibition [24–27]. Interestingly, when anastrozole and letrozole were evaluated in the same patients in a crossover design study, all patients had a more profound aromatase inhibition and a better suppression of plasma estrogens during letrozole treatment [27].

A frequently asked question is how well the total body endocrine evaluation corresponds with the tumor tissue hormone metabolism. This question relates to the observation that tissue estrogen levels, in particular those of estradiol, are higher than the plasma levels in postmenopausal women (see [28] and the references therein). While it is generally assumed that the tissue uptake of estrogens from the circulation is low in postmenopausal women, one should realize that assessment of in vivo aromatization reflects tissue aromatization and that the plasma estrogen levels reflect the tissue levels, since estrogens diffuse from the tissue into the plasma. Many breast cancers express high levels of aromatase and 17-hydro-dehydrogenase [29–34], and cancer tissue hormone levels are often higher than those of the surrounding normal tissue [35,36]. While the mean percentage of estrogen suppression in plasma and tissue is quite similar, there may be individual variation [37,38], and studies evaluating long-term treatment are lacking.

Randomized adjuvant trials

The third-generation aromatase inhibitors anastrozole, letrozole, and exemestane have been evaluated in prospective, randomized trials as adjuvant treatment of early-stage breast cancer. These trials evaluated different ways to incorporate aromatase inhibitors in the adjuvant setting: (1) as monotherapy (anastrozole), (2) as combination therapy with tamoxifen (anastrozole), (3) as sequential therapy with 2–3 years of tamoxifen followed by 2–3 years of the aromatase inhibitor (anastrozole and exemestane), and 4) as sequential therapy with 5 years of tamoxifen followed either by the aromatase inhibitor or placebo (letrozole). A brief description of the available data from these studies is given below.

The ATAC trial included more than 9 000 postmenopausal patients, who were randomly allocated to receive tamoxifen, anastrozole, or tamoxifen plus anastrozole, for a total treatment duration of five years [39]. At a median follow-up of 47 months, the patients allocated to anastrozole had a significantly improved event-free survival compared with the patients allocated to tamoxifen alone (a 14% relative reduction of events). Among hormone-receptor-positive patients (84% of all included patients) the benefit was 2.9% at 4 years from randomization corresponding to a relative reduction of events by

22%. Patients allocated to the combination arm had an event-free survival comparable to that of the patients allocated to tamoxifen alone, that is, a result significantly inferior to that of the patients treated with anastrozole alone. There are as yet no data on overall survival from this trial.

In the ITA trial a total of about 400 postmenopausal patients were first treated with adjuvant tamoxifen for two to three years, and were then allocated to switch to anastrozole or to continue with tamoxifen for a total treatment duration of five years in both groups. The results have been published as a meeting abstract only [40]. At a median treatment time of about three years after randomization, those allocated to the sequential tamoxifen–anastrozole group showed a significantly reduced number of events (10 vs. 26) corresponding to a 64% relative risk reduction, and numerically fewer deaths (2 vs. 5).

The MA-17 trial [41] included more than 5 000 postmenopausal patients who were recurrence-free after 4½–6 years of adjuvant tamoxifen. They were randomly allocated to letrozole or placebo for five years. However, at the first interim analysis after a median follow-up up of 2.4 years after randomization, there was a significant benefit in terms of disease-free survival for the women who had been allocated to the letrozole group with an estimated four-year disease-free survival rate of 93% as compared with 87% in the placebo arm (a 43% reduction in the hazard ratio). There were numerically fewer deaths among those allocated to letrozol (31 vs. 42), but no significant overall survival benefit. After this analysis, the trial was terminated and the results communicated to the participants.

The Intergroup Exemestane Study was a double-blind, randomized trial to test whether after two to three years of tamoxifen therapy switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the five years of treatment [42]. The trial enrolled about 4 700 patients. At a median follow-up of 31 months after randomization, those allocated to exemestane showed a statistically significant 4.7% improvement of disease-free survival estimated at 3 years corresponding to a relative reduction of recurrence of 32%. There were numerically fewer deaths in the exemestane group (93 vs. 106), but no significant difference in overall survival.

In summary, all of these trials show a benefit for patients allocated to receive an aromatase inhibitor with the exception of those who received combination therapy with anastrozole and tamoxifen in the ATAC trial. In that group the results were similar to those achieved among patients treated with tamoxifen alone. This result may have been due to the estrogen agonist effects of tamoxifen, which may have counterbalanced the effect of anastrozole.

Theoretically, part of the benefit achieved with letrozole in the MA-17 trial may have been due to the longer duration of adjuvant endocrine therapy among those allocated to the letrozole group. Two randomized trials have compared five years of tamoxifen versus more than five years of treatment, and both showed negative results. However, the number of events in those trials was relatively small, which resulted in large confidence intervals for the treatment effect. Therefore, it may be argued that the optimal duration of adjuvant endocrine therapy with tamoxifen remains unclear, and that further benefit might be derived from prolonging endocrine treatment beyond five years.

The designs of the available trials do not permit direct efficacy comparisons between the three third-generation aromatase inhibitors. Indirect comparisons of the trial results are difficult due to differences in the study designs; for instance, the relative hazard associated with allocation to an aromatase inhibitor versus tamoxifen immediately after the primary diagnosis (as in the ATAC trial) cannot be compared with a relative hazard among patients who have been disease-free for some years and who are only then randomly allocated to be treated with an aromatase inhibitor or tamoxifen (as in the MA-17 trial and in the Intergroup Exemestane Study). Indirect trial comparisons are also difficult due to the relative lack of statistical precision in the estimates of the treatment effect. In addition, at present there are no data available on whether monotherapy with an aromatase inhibitor is more effective than sequential therapy with tamoxifen followed by an aromatase inhibitor. With sequential therapy, the optimal treatment sequence remains controversial, that is, whether it is better to start with tamoxifen or an aromatase inhibitor.

Toxicity

The main side effects of aromatase inhibitors are related to estrogen withdrawal and include hot flushes, arthralgia, and bone demineralization. Aromatase inhibitors lack the partial estrogen agonist effects of tamoxifen. Therefore, they are not associated with an increased rate of vaginal discharge, vaginal bleeding, and an increased risk of pathological endometrial changes including endometrial cancer. In contrast with tamoxifen, aromatase inhibitors do not appear to increase the risk of thromboembolic disease.

Since aromatase inhibitors have been used to replace tamoxifen in the adjuvant setting, it is relevant to compare their adverse effect profiles in

those trials that permit a direct comparison based on randomization. In the ATAC trial, for instance, patients treated with anastrozole experienced fewer hot flushes, and less vaginal bleeding and thromboembolic disease as compared with patients treated with tamoxifen. On the other hand, musculoskeletal problems were more frequent among the patients treated with anastrozole, including a 2.1% increase in bone fractures. The Intergroup Exemestane Study showed similar results with increased risks for osteoporosis and arthralgia among patients allocated to switch tamoxifen to exemestane, and increased risks of gynaecologic symptoms and thromboembolic disease among those who received continued treatment with tamoxifen.

Potential long-term effects on the cardiovascular system are of particular importance in the adjuvant setting, since cardiovascular disease is a common cause of death among breast cancer patients, particularly among those with low-risk disease. Therefore, even a relatively minor increase in the cardiovascular risk associated with a particular endocrine treatment option might offset the potential treatment benefit in terms of a reduced number of cancer recurrences and breast cancer-related deaths. The partial agonist estrogen properties of tamoxifen might, theoretically, be beneficial in relation to the risk of cardiovascular disease. There is a well-documented early increase in the risk of thromboembolic disease with tamoxifen, but with long-term treatment, it has been hypothesized that tamoxifen may decrease cardiovascular morbidity [43]. It is possible that the mechanism for this reduction is the serum cholesterol-lowering effect of tamoxifen [44]. However, decreased non-breast cancer mortality was not documented in the Oxford overview of adjuvant tamoxifen trials (EBCTCG 1998) [45], nor has it been evident in large breast cancer prevention trials [46], and the cholesterol-lowering effect of tamoxifen may be offset by tamoxifen-related increase in the serum triglyceride levels [44].

So far there are no observations of an increased risk of cardiovascular disease among patients allocated to adjuvant aromatase inhibitor therapy, but long-term data are still scant [39,41,42]. There is relatively little, and to some extent contradictory, information available on the effects of the different aromatase inhibitors on the blood lipid and lipoprotein levels [47–51]. Because of the pharmacological differences between anastrozole, letrozole, and exemestane, it is possible that the effects on the lipid-profile and, therefore, also on long-term cardiovascular risks, might be different for the three compounds, which might have clinical implications as to which one of the aromatase inhibitors is preferable in the adjuvant setting.

Panel consensus on the use of aromatase inhibitors in the adjuvant setting

- There are convincing data, although based on relatively short follow-up, indicating that recurrence-free survival can be improved by using an aromatase inhibitor in the adjuvant therapy of postmenopausal patients with hormone-receptor-positive, early stage breast cancer. Given previous experiences from trials of adjuvant endocrine therapy, it is reasonable to assume that the observed recurrence-free survival benefit will be translated into an overall survival benefit. Therefore, it is reasonable to use aromatase inhibitors in the adjuvant setting as part of routine healthcare.
- Differences in side-effect profiles between tamoxifen and aromatase inhibitors are not such that there is reason to withhold the use of aromatase inhibitors in the adjuvant setting on the basis of frequency or severity of side effects. Both tamoxifen and aromatase inhibitors are generally well-tolerated treatments with a relatively low rate of severe toxicity. Considerations relative to efficacy and cost are probably more relevant.
- Adjuvant aromatase inhibitors can be used as monotherapy where the drug is given up-front, or sequentially after a few years of tamoxifen. Both of these strategies will probably result in clinically worthwhile treatment benefit compared with treatment with tamoxifen alone. Since it cannot at present be determined which one of these strategies is the better, both appear reasonable. However, combination therapy with tamoxifen and an aromatase inhibitor should be avoided. Adjuvant aromatase inhibitor monotherapy might thus be used (1) up-front for 5 years, (2) for 2–3 years after a few years of tamoxifen for a total treatment period of 5 years, or (3) for 2–3 years after 5 years of tamoxifen. There is at present no clinical documentation on sequential therapy with an aromatase inhibitor given up-front for a few years followed by tamoxifen, so this treatment sequence cannot be recommended outside controlled trials.
- Both tamoxifen and the third-generation aromatase inhibitors are relatively low toxic compounds with high patient tolerability and few serious adverse side effects. For tamoxifen, the latter include thromboembolic disease and endometrial cancer, and for the aromatase

inhibitors, possibly bone fractures as observed in the ATAC trial. Since long-term clinical data on potential adverse effects of aromatase inhibitors are scant, it appears reasonable to offer adjuvant aromatase inhibitor therapy primarily to patients who have (1) a history of thromboembolic disease or who have been diagnosed with pathological proliferative endometrial changes (which contraindicates tamoxifen), (2) who cannot continue with tamoxifen due to tamoxifen-related adverse effects, and (3) who present with breast cancer where a maximal treatment effect is particularly desirable (e.g. node-positive disease; or node-negative, high-risk disease).
- Aromatase inhibitors should not be used in the adjuvant treatment of premenopausal women or of patients who have hormone-receptor-negative breast cancer. Safety and efficacy of administration of aromatase inhibitors following ovarian function suppression in premenopausal women is being investigated in ongoing clinical trials.

Preoperative treatment of breast cancer with aromatase inhibitors

Aromatase inhibitors given prior to breast cancer surgery have consistently been found to be active in phase II trials [52–54]. Results are available from two larger trials in which aromatase inhibitors were given preoperatively. One of these two trials was a double-blind multicenter study, where 337 postmenopausal women with ER and/or PgR positive untreated breast cancer were randomly allocated to receive either tamoxifen 20 mg or letrozole 2.5 mg daily [55]. At four months of treatment, OR was superior in the letrozole group, 34% vs. 17% as assessed using mammography. The rate of breast-conserving surgery was significantly more frequent in the letrozole group (45% vs. 35%). Endocrine therapy given preoperatively gives a unique opportunity for translational research, since tumor tissue is often available both before and during therapy, as was elegantly demonstrated by Ellis et al. [56].

Another large multi-center trial randomized 314 patients with large operable or locally advanced hormone-receptor-positive breast cancer to receive anastrozole, given 1 mg daily, or tamoxifen, administered 20 mg daily [57]. Preliminary results from this trial suggests that anastrozole is as effective as tamoxifen; an objective response as determined by breast ultrasound examination was achieved in 39% of the patients allocated to anastrozole and in 27% of those allocated to tamoxifen (odds ratio 1.57; 95% CI, 0.97–2.55). Similar results were obtained in a smaller trial [58]. Preoperatively-given exemestane compared favorably to tamoxifen in a small trial [59]. Results from trials that compare survival when aromatase inhibitors are given both pre- and postoperatively to postoperative (adjuvant) use have not been reported.

Panel consensus on the preoperative use of aromatase inhibitors in the treatment of breast cancer

- Aromatase inhibitors are active when used as primary therapy prior to breast surgery for cancer. In this setting, their activity and tolerability appear comparable to or superior to that of tamoxifen.
- When preoperative endocrine therapy is indicated, use of a third-generation aromatase inhibitor is recommended.

Aromatase inhibitors as first-line therapy for advanced breast cancer

Full reports have been published from three randomized trials that compared anastrozole with tamoxifen, and from one trial that compared letrozole with tamoxifen as first-line therapy for advanced breast cancer. In addition, a full report from a combined analysis of the results from two of the anastrozole trials has been published.

The three randomized anastrozole trials include two double-blind multicenter trials and one open-label single-center trial. The Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability trial (TARGET) and the North American Trial (NAT) had a similar design. Both were multicenter, multinational, double-blind, and placebo-controlled trials, and both randomized postmenopausal women with advanced breast cancer to anastrozole 1 mg daily versus tamoxifen 20 mg daily [60,61]. These two anastrozole versus tamoxifen trials were designed as non-inferiority trials, and the specified primary endpoints were time to progression (TTP; time from randomization until objective disease progression or death), objective response rate (OR), and tolerability. Adjuvant tamoxifen within 12 months of study entry and prior chemotherapy for advanced disease were not allowed. According to the design of these trials, equivalence was established when a 20% or greater advantage for tamoxifen could be ruled out concerning TTP, and a difference in OR of more than 10% in favor of tamoxifen could be ruled out. Crossover to the alternative regimen was not incorporated in the design. In TARGET 340 patients were randomized to receive anastrozole and 328 tamoxifen. Equivalence was established for TTP

(8.2 vs. 8.3 months) and for OR (33% in each group). In addition, both groups had a 56% clinical benefit rate (CB). No significant differences were observed in any adverse event, and both drugs were considered to be well tolerated.

Recruitment into the NAT was stopped following randomization of 171 patients to anastrozole and 182 to tamoxifen. The decision to stop recruitment followed the completion of recruitment into TARGET. TTP was significantly longer among participants who received anastrozole as compared with tamoxifen (11.1 vs. 5.6 months; $p = 0.005$), but OR was not significantly different (21% vs. 17%). The CB rate was significantly higher among patients treated with anastozole as compared with those who received tamoxifen (59% vs. 46% in a retrospective analysis, respectively; $p = 0.0098$). Both drugs were considered to be well tolerated, and anastrozole was associated with a smaller incidence of thomboembolic events and vaginal bleeding as compared with tamoxifen (4.1% vs. 8.2%, and 1.2 vs. 3.8%, respectively).

A third trial, an open-labeled single-center trial from Barcelona, randomized 238 patients to 1 mg anastrole versus 40 mg tamoxifen daily [62]. Adjuvant endocrine therapy or any prior therapy for advanced disease were not allowed. CB, TTP in patients who achieved a CB, survival, and side effects were specified as the primary endpoints. TTP was not reported except for the CB subgroup. After a median follow-up of 13.3 months CB was encountered in 100 (83%) of the 121 patients randomized to anastrozole as compared with 65 (56%) of the 117 patients randomized to receive tamoxifen ($p < 0.001$). Patients who received anastrozole had a significant survival benefit; their median survival was 17.4 versus 16.0 months among those treated with tamoxifen ($p = 0.003$). The incidence of thromboembolic events, ocular disorders, fluid retention, somnolence, sweating, hot flashes, vaginal bleeding, and vaginal discharge were higher in patients who received tamoxifen.

A large multicenter, multinational double-blind and placebo-controlled trial randomly allocated 454 patients to tamoxifen 20 mg daily and 453 to letrozole 2.5 mg daily with pre-specified crossover at the time when progressive disease was detected [63]. This trial was designed and powered as a superiority trial with TTP as the primary endpoint. Appearance of new lesions, an increase of 25% or more in the size of the existing lesions, clinical deterioration due to breast cancer within 6 weeks of treatment, or death were considered as signs of progression. The proportion of patients with estrogen receptor (ER) and/or progesterone receptor (PgR) positive cancer was 66%, and 18% had received prior adjuvant tamoxifen. Women who used letrozole had a longer TTP as compared with those who were administered tamoxifen in an intention-to-treat analysis (9.6 vs. 6.0 months; $p < 0.0001$), and letrozole performed consistently better than tamoxifen in all prespecified subgroups. Letrozole was also found to be superior in terms of the secondary endpoints, OR (32% vs. 21%, $p = 0.0002$), and CB (50% vs. 38%, $p = 0.0004$). The median survival time was not significantly different between the groups (34 months vs. 30 months, $p = 0.53$), and the clinical impact of an early survival benefit found in a later exploratory analysis among the patients who first received letrozole remains speculative [64].

Exemestane has also been compared with tamoxifen in an open-label, multicenter, phase II randomized trial [65]. Among the 61 patients randomized to receive exemestane the OR was 41% (95% CI, 29–53) as compared with 17% (95% CI, 7–27) in 59 patients randomized to receive tamoxifen. The corresponding CB rate was 57% among patients treated with exemestane and 42% among those treated with tamoxifen. This study was extentend into a phase III study, and the progression-free survival has been reported to be longer in the exemestane group as compared with the tamoxifen group (10.7 vs. 6.7 months; $p = 0.04$) [66].

The TARGET and the NAT trials have twice been combined into one single analysis [67,68]. The methodology used for combining the study results is not straightforward owing to multiple testing, despite this being preplanned. To facilitate the combined analyses both studies used the same patient eligibility criteria, but the patient characteristics nevertheless appeared to be different and may not support the combined analysis approach. The subgroup analysis of patients with ER and/or PgR positive cancer also need to be interpreted with some caution, since this analysis contained only 45% of the patients enrolled on TARGET but 89% of those enrolled on NAT.

Aromatase inhibitors as second-line therapy for advanced breast cancer

Results have been published from five randomized trials that compared megestrol acetate with either letrozole (two trials), anastrozole (two trials), or exemestane (one trial) after tamoxifen failure. The five trials were all controlled multicenter trials, and they all demonstrated either equivalence or superiority of the aromatase inhibitor to megestrol in terms of OR and TTP [69–73]. Patients who received megestrol more often reported weight gain and dyspnea than those who received an aromatase inhibitor. One meta-analysis that combined the data

from the two anastrozole trials reported a survival gain among patients treated with anastrozole, but the analysis used the same methodology as described above for the two first-line therapy trials with anastrozole. Another meta-analysis that used a traditional meta-analysis approach has also been published, and this analysis combined individual patient data from one trial with each of the three third-generation aromatase inhibitors [74]. The relative risk of death following therapy with an aromatase inhibitor as compared with megestrol acetate was in this meta-analysis 0.79 (95% CI, 0.69–0.91, $p = 0.001$), corresponding to approximately four months' prolongation of median survival time.

Only one trial compared a third-generation aromatase inhibitor with aminoglutethimide. In this study 555 patients were randomized to receive either aminoglutethimide or letrozole (0.5 or 2.5 mg per day, respectively). Survival and TTP were significantly improved with the 2.5 mg dose of letrozole as compared with aminoglutethimide [75].

In an open-label multicenter trial 713 breast cancer patients were randomized to receive either letrozole 2.5 mg daily or anastrozole 1 mg daily [76]. TTP, the primary endpoint, was similar in the two groups (median, 5.7 months). OR was significantly higher in the letrozole group (19% vs. 12%), but no significant differences were observed in other secondary endpoints that included CB, time to treatment failure, or survival.

Panel consensus on the use of aromatase inhibitors in overtly metastatic breast cancer

- The efficacy of the third-generation aromatase inhibitors in the treatment of postmenopausal women with hormone-receptor-positive metastatic breast cancer is comparable to or superior to that of tamoxifen. Like tamoxifen, the third-generation aromatase inhibitors are well tolerated when administered in this setting. Third-generation aromatase inhibitors should be considered as the first-line endocrine treatment in postmenopausal women with hormone-receptor-positive, overtly metastatic breast cancer.
- Third-generation aromatase inhibitors are superior in efficacy and tolerability to megestrole acetate when used as the second-line treatment of women whose cancer has progressed on tamoxifen.
- Clinically important differences may exist between different third-generation aromatase inhibitors but at present direct comparative data on which to base preference of one compound over another are scant, and no recommendation for one compound over another is made.
- The use of aromatase inhibitors is not recommended in the treatment of hormone-receptor-negative breast cancer or in the treatment of premenopausal women.

References

[1] Lønning PE, Dowsett M, Powles TJ. Postmenopausal estrogen synthesis and metabolism: Alterations caused by aromatase inhibitors used for the treatment of breast cancer. J Steroid Biochem 1990;35:355–66.

[2] Dowsett M, Cantwell B, Lal A, Jeffcoate SL, Harris AL. Suppression of postmenopausal ovarian steroidogenesis with the luteinizing hormone-releasing hormone agonist goserelin. J Clin Endocrinol Metab 1988;66:672–7.

[3] Sluijmer AV, Heineman MA, Jong FHD, Evers JLH. Endocrine activity of the postmenopausal ovary: The effects of pituitary down-regulation and oophorectomy. J Clin Endocrinol Metab 1995;80:2163–7.

[4] Couzinet B, Meduri G, Lecce MG, et al. The postmenopausal ovary is not a major androgen-producing gland. J Clin Endocrinol Metab 2001;86:5060–6.

[5] Bulun SE, Sebastian S, Takayama K, Suzuki T, Sasano H, Shozu M. The human CYP19 (aromatase P450) gene: update on physiologic roles and genomic organization of promoters. J Steroid Biochem Molec Biol 2003;86:219–24.

[6] Reed MJ, Topping L, Coldham NG, Purohit A, Ghilchik MW, James VHT. Control of aromatase activity in breast cancer cells: The role of cytokines and growth factors. J Steroid Biochem Mol Biol 1993;44:589–96.

[7] Agarwal VR, Bulun SE, Leitch M, Rohrich R, Simpson ER. Use of alternative promoters to express the aromatase cytochrome p450 (CYP19) gene in breast adipose tissues of cancer-free and breast cancer patients. J Clin Endocrinol Metab 1996;81:3843–9.

[8] Zhao Y, Mendelson CR, Simpson ER. Characterization of the sequences of the human CYP19 (aromatase) gene that mediate regulation by glucocorticoids in adipose stromal cells and fetal hepatocytes. Mol Endocrinol 1995;9:340–9.

[9] Zhao Y, Nichols JE, Valdez R, Mendelson CR, Simpson ER. Tumor necrosis factor-alpha stimulates aromatase gene expression in human adipose stromal cells through use of an activating protein-1 binding site upstream of promoter 1.4. Mol Endocrinol 1996;10:1350–7.

[10] Simpson E, Jones M, Davis S, Rubin G. Do intracrine mechanisms regulate aromatase expression? J Steroid Biochem Mol Biol 1999;69:447–52.

[11] Singh A, Purohit A, Ghilchik MW, Reed MJ. The regulation of aromatase activity in breast fibroblasts: the role of interleukin-6 and prostaglandin E2. Endocrine-Rel Cancer 1999;6:139–47.

[12] Couse JF, Hewitt SC, Korach KS. Receptor null mice reveal contrasting roles for estrogen receptor alpha and beta in reproductive tissues. J Steroid Biochem Mol Biol 2000;74: 287–96.

[13] Fisher CR, Graves KH, Parlow AF, Simpson ER. Characterization of mice deficient in aromatase (ArKO) because of targeted disruption of the cyp19 gene. Proc Natl Acad Sci USA 1998;95:6965–70.

[14] Hewitt KN, Boon WC, Murata Y, Jones MEE, Simpson ER. The aromatase knockout mouse presents with a sexually dimorphic disruption to cholesterol homeostasis. Endocrinology 2003;144:3895–903.

[15] Murata Y, Robertson KM, Jones MEE, Simpson ER. Effect of estrogen deficiency in the male: The ArKO mouse model. Mol Cell Endocrinol 2002;193:7–12.
[16] Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 1995;80:3689–98.
[17] Maffei L, Murata Y, Rochira V, et al. Dysmetabolic syndrome in a man with a novel mutation of the aromatase gene: Effects of testosterone, alendronate, and estradiol treatment. J Clin Endocrinol Metab 2004;89:61–70.
[18] Carani C, Qin K, Simoni M, et al. Brief report: Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med 1997;337:91–5.
[19] Miller WR, Dixon JM. Antiaromatase agents: preclinical data and neoadjuvant therapy. Clin Breast Cancer 2000; 1(Suppl 1):s9–s14.
[20] Johannessen DC, Engan T, Salle ED, et al. Endocrine and clinical effects of exemestane (PNU 155971), a novel steroidal aromatase inhibitor, in postmenopausal breast cancer patients: A phase I study. Clin Cancer Res 1997;3: 1101–8.
[21] Dowsett M, Mehta A, King N, et al. An endocrine and pharmacokinetic study of four oral doses of formestane in postmenopausal breast cancer patients. Eur J Cancer 1992; 28:415–20.
[22] Jacobs S, Lønning PE, Haynes B, Griggs L, Dowsett M. Measurement of aromatisation by a urine technique suitable for the evaluation of aromatase inhibitors in vivo. J Enzyme Inhibition 1991;4:315–25.
[23] Lønning PE. Pharmacology of new aromatase inhibitors. Breast 1996;5:202–8.
[24] Dowsett M, Jones A, Johnston SRD, Jacobs S, Trunet P, Smith IE, et al. In vivo measurement of aromatase inhibition by letrozole (CGS 20267) in post menopausal patients with breast cancer. Clin Cancer Res 1995;1:1511–5.
[25] Geisler J, King N, Dowsett M, et al. Influence of anastrozole (Arimidex®), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in postmenopausal women with breast cancer. Br J Cancer 1996;74:1286–91.
[26] Geisler J, King N, Anker G, et al. In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. Clin Cancer Res 1998;4:2089–93.
[27] Geisler J, Haynes B, Anker G, Dowsett M, Lønning PE. Influence of letrozole (Femara) and anastrozole (Arimidex) on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over-designed study. J Clin Oncol 2002;20: 751–7.
[28] Lønning PE. Aromatase inhibitors in breast cancer. Endocrine Relat Cancer 2004;11:179–89.
[29] Brodie A, Long B, Lu Q. Aromatase expression in the human breast. Breast Cancer Res Treat 1998;49:S85–91.
[30] Santen RJ, Martel J, Hoagland M, et al. Demonstration of aromatase activity and its regulation in breast tumor and benign breast fibroblasts. Breast Cancer Res Treat 1998;49: S93–9.
[31] Sasano H, Murakami H. Immunolocalization of aromatase in human breast disorders using different antibodies. Breast Cancer Res Treat 1998;49:S79–84.
[32] Shenton KC, Dowsett M, Lu Q, et al. Comparison of biochemical aromatase activity with aromatase immunohistochemistry in human breast carcinomas. Breast Cancer Res Treat 1998;49:S101–7.
[33] Poutanen M, Isomaa V, Peltoketo H, Vihko R. Role of 17 beta-hydroxysteroid dehydrogenase type 1 in endocrine and intracrine estradiol biosynthesis. J Steroid Biochem Mol Biol 1995;55:525–32.
[34] Sasano H, Frost AR, Saitoh R, et al. Aromatase and 17ß-hydroxysteroid dehydrogenase type 1 in human breast carcinoma. J Clin Endocrinol Metab 1996;81:4042–6.
[35] Van Landeghem AAJ, Poortman J, Nabuurs M, Thijssen JHH. Endogenous concentration and subcellular distribution of estrogens in normal and malignant breast tissue. Cancer Res 1985;45:2900–4.
[36] Vermeulen A, Deslypere JP, Paridaens R, Leclerco G, Roy F, Heuson JC. Aromatase, 17ß-hydroxysteroid dehydrogenase and intratissular sex hormone concentrations in cancerous and normal glandular breast tissue in postmenopausal women. Eur J Cancer Clin Oncol 1985;22:515–25.
[37] Miller WR, Stuart M, Sahmoud T, Dixon JM. Anastrozole ('Arimidex') blocks oestrogen synthesis both peripherally and within the breast in postmenopausal women with large operable breast cancer. Br J Cancer 2002;87:950–5.
[38] Geisler J, Detre S, Berntsen H, et al. Influence of neoadjuvant anastrozole (Arimidex) on intratumoral estrogen levels and proliferation markers in patients with locally advanced breast cancer. Clin Cancer Res 2001;7:1230–6.
[39] ATAC Trialists Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: Results of the ATAC trial efficacy and safety update analyses. Cancer 2003;98:1802–10.
[40] Boccardo F, Rubagotti A, Amoroso D, et al. Anastrozole appears superior to tamoxifen in women already receiving adjuvant tamoxifen treatment. Breast Cancer Res Treat 2003;82(Suppl 1):S6 (abstract).
[41] Goss PE, Ingle JN, Martino S, et al. A Randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;19:349–58.
[42] Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–92.
[43] Rutqvist L E, Mattsson A. for the Stockholm Breast Cancer Study Group. Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. J Natl Cancer Inst 1993;85:1398–406.
[44] Love RR, Newcomb PA, Wiebe DA, et al. Effects of tamoxifen on lipids and lipoprotein levels in postmenopausal patients with node negative breast cancer. J Natl Cancer Inst 1990;82:1327–32.
[45] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: An overview of the randomised trials. Lancet 1998;351:1451–67.
[46] Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
[47] Atalay G, Dirix L, Biganzoli L, et al. The effect on serum lipid profile in postmenopausal women with metastatic breast cancer: a companion study to EORTC trial 10951, "randomized phase II study in first line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients". Ann Oncol 2004;15:211–7.
[48] Dewar J, Nabholtz J-M, Bonneterre J. The effect of anastrozole (Arimidex) on serum lipids: Data from a randomized comparison of anastrozole versus tamoxifen in

postmenopausal women with advanced breast cancer. Breast Cancer Res Treat 2001;69:224 (abstract 124).

[49] Elisaf MS, Bairaktari ET, Nicolaides C, et al. Effect of letrozole on the lipid profile in postmenopausal women with breast cancer. Eur J Cancer 2001;37:1510–3.

[50] Harper-Wynne C, Ross G, Sacks N, et al. Effects of the aromatase inhibitor letrozol on normal breast epithelial cell proliferation and metabolic indices in postmenopausal women: a pilot study for breast cancer prevention. Cancer Epidemiol Biomarkers Prev 2002;11:614–21.

[51] Krag L, Geisler J, Lønning P E, et al. Lipid and coagulation profile in postmenopausal women with early breast cancer at low risk treated with exemestane: A randomized, placebo-controlled study. Am Soc Clin Oncol 2004;23:39 (abstract 650).

[52] Dixon JM, Renshaw L, Bellamy C, Stuart M, Hoctin-Boes G, Miller WR. The effects of neoadjuvant anastrozole (Arimidex) on tumor volume in postmenopausal women with breast cancer: a randomized, double-blind, single-center study. Clin Cancer Res 2000;6:2229–35.

[53] Dixon JM, Love CD, Bellamy CO, et al. Letrozole as primary medical therapy for locally advanced and large operable breast cancer. Breast Cancer Res Treat 2001;66: 191–9.

[54] Miller WR, Dixon JM. Endocrine and clinical endpoints of exemestane as neoadjuvant therapy. Cancer Control 2002; 9(2 Suppl):9–15.

[55] Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001;12:1527–32.

[56] Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for erbB-1- and/or erbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001;19:3808–16.

[57] Cataliotti L, Buzdar A, Noguchi S, Bines I. Efficacy of preoperative Arimidex (anastrozole) compared with tamoxifen (PROACT) as neoadjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer. Eur J Cancer 2004;2(Suppl 3):69 (abstract).

[58] Smith I, Dowsett M. Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: the IMPACT trial. Breast C Res Treatm 2003;82(Suppl.):S6 (abstract).

[59] Semiglazov VF, Semiglazov VV, Ivanov VG, et al. Neoadjuvant endocrine therapy: exemestane (E) vs tamoxifen (T) in postmenopausal ER+breast cancer patients (T1-4N1-2MO). Breast Cancer Res Treat 2003;82(Suppl.):S22 (abstract).

[60] Bonneterre J, Thürlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18:3748–57.

[61] Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 2000;18:3758–76.

[62] Milla-Santos A, Milla L, Portella J, et al. Anastrozole versus tamoxifen as first-line therapy in post menopausal patients with hormone-dependent advanced breast cancer. Am J Clin Oncol 2003;26:317–22.

[63] Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 2001;19:2596–606.

[64] Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 2003;21:2101–9.

[65] Paridaens R, Dirix L, Lohrisch C, et al. Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. Ann Oncol 2003;14: 1391–8.

[66] Paridaens R, Dirix L, Beex L, et al. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane or tamoxifen in postmenopausal patients (pts): A randomised phase III trial of the EORTC group. J Clin Oncol 2004;22(Suppl):14S (abstract).

[67] Bonneterre J, Buzdar A, Nabholtz JM, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. Results of two randomized trials designed for combined analysis. Cancer 2001;92:2247–58.

[68] Nabholtz JM, Bonneterre J, Buzdar A, Robertson JF, Thurlimann B. Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur J Cancer 2003;39:1684–9.

[69] Jonat W, Howell A, Blomqvist C, et al. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. Eur J Cancer 1996;32A:404–12.

[70] Buzdar AU, Jones SE, Vogel CL, Wolter J, Plourde P, Webster A. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. Cancer 1997;79:730–9.

[71] Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol 1998;16:453–61.

[72] Kaufmann M, Bajetta E, Dirix LY, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: Results of a phase III randomized double-blind trial. The Exemestane Study Group. J Clin Oncol 2000;18:1399–411.

[73] Buzdar A, Douma J, Davidson N, et al. A phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol 2001;19:3357–66.

[74] Messori A, Cattel F, Trippoli S, Vaiani M. Survival in patients with metastatic breast cancer: Analysis of randomized studies comparing oral aromatase inhibitors versus megestrol. Anticancer Drugs 2000;11:701–6.

[75] Gershanovich M, Chaudri HA, Campos D, et al. Letrozole, a new oral aromatase inhibitor: Randomised trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. Ann Oncol 1998;9:639–45.

[76] Rose C, Vtoraya O, Pluzanska A, et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer: Comparison of the aromatase inhibitors letrozole and anastrozole. Eur J Cancer 2003;39:2318–27.