The Emerging Role of the New Aromatase Inhibitors in the Treatment of Breast Cancer

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The role of hormonal therapy as an effective therapeutic modality in breast cancer has long been recognized, dating back to the late 19th century when Beatson [1] reported on the beneficial effects of a surgical oophorectomy in a patient with advanced breast cancer. Hormonal manipulations are effective in breast cancer patients whose tumors are rich in estrogen receptors and are thus estrogen-dependent. Modern approaches with hormone therapy rely either on blocking estrogen receptors or suppressing the synthesis of estrogens. The former is achieved with drugs known as selective estrogen receptor modulators, with tamoxifen as the gold standard, while the latter relies on the use of aromatase inhibitors. This review will focus on the expanding role of aromatase inhibitors in the treatment of breast cancer in postmenopausal patients.

While the ovaries represent the main source for estrogen synthesis in premenopausal women, it is the enzymatic activity of aromatase that allows for the production of estrogens in older females. Aromatase catalyses the conversion of androgens, testosterone and androstenedione to estrogens, estrone and estradiol. In postmenopausal patients, high levels of aromatase are found in peripheral tissues such as fat, muscle, healthy breast tissue, as well as within breast tumors [2]. Aromatase inhibitors have no role in the treatment of breast cancer in premenopausal patients and are prescribed exclusively for postmenopausal women. Their administration in this setting achieves a near total (>98%) ablation in estrogen synthesis [3].

Aminoglutethimide was the first aromatase inhibitor in clinical use, but it often resulted in undesirable side effects such as skin rashes and neurologic manifestations such as somnolence and, in addition, required the concomitant administration of corticosteroids [4]. Its use has been abandoned with the advent of newer, second- and third-generation aromatase inhibitors now in routine clinical use [Table 1].

Newer aromatase inhibitors are of two classes: reversible non-steroidal inhibitors, including anastrozole (Arimidex®) and letrozole (Femara®), and irreversible steroidal inactivators of the enzyme, such as exemestane (Aromasin®) [5]. Aromatase inhibitors are typically given orally on a daily basis and are usually well tolerated. Most commonly described side effects include hot flashes, fatigue, musculoskeletal pain; long-term use may result in or aggravate osteoporosis due to chronic estrogen deprivation [Table 2].

The clinical development of aromatase inhibitors, summarized in Table 3, initially established their role as second-line hormone therapy in postmenopausal patients with advanced, hormone receptor-positive breast cancer whose disease had progressed following treatment with tamoxifen. In this setting, aromatase inhibitors were shown to be superior to progestins such as megestrol acetate, prompting the design and performance of clinical trials that compared aromatase inhibitors with tamoxifen as first-line hormone therapy in metastatic breast cancer.

Table 1. Third-generation aromatase inhibitors

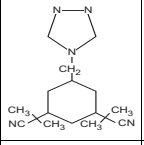
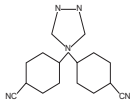
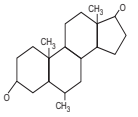
Name (generic)	Structure	Type	Daily dose	Mode of action
Anastrozole (Arimidex®)		Non-steroidal	1 mg	Ionic binding to aromatase with temporary inactivation
Letrozole (Femara®)		Non-steroidal	2.5 mg	Ionic binding to aromatase with temporary inactivation
Exemestane (Aromasin®)		Steroidal	25 mg	Covalent, irreversible binding to aromatase

Table 2. Side effects of aromatase inhibitors as reported in adjuvant trials

Side effects	Anastrozole	Letrozole		Exemestane	
	Any grade*	Any grade	Grade III-IV	Any grade	Grade III-IV
Hot flashes	35%	47%	0%	42%	10.3%
Fatigue	17%	30%	1.7%	24%	5.7%
Nausea	11%	–	–	11%	5.6%
Mood disturbance	17%	–	–	5%	1.7%
Headache	–	18%	3.6%	19%	6.3%
Weight gain	–	17%	0.8%	–	–
Vaginal bleeding	5%	4%	2.2%	4%	1.8%
Arthralgia	30%	21%	4.6%	5%	–
Osteoporosis	–	6%	–	7%	–
Deep vein thrombosis	1%	–	–	1%	–

* Grade III-IV toxicity not reported separately

Table 3. Clinical developmental milestones of aromatase inhibitors in postmenopausal patients with hormone receptor-positive breast cancer

Late 1970s	Aminoglutethimide
1990s	Second- and third-generation AIs
1996	AIs superior to megestrol acetate as second-line hormone therapy in metastatic breast cancer
2000	AIs better than tamoxifen as first-line therapy in advanced breast cancer
2002	Anastrozole better than tamoxifen in adjuvant setting
2003–2004	Sequential use of tamoxifen and either letrozole or exemestane more effective than tamoxifen alone as adjuvant therapy

AI = aromatase inhibitors

I shall briefly review these trials of aromatase inhibitors in advanced disease and describe their expanding use in the adjuvant setting in patients with primary breast cancer.

Aromatase inhibitors in advanced breast cancer

Use as second line

For many years tamoxifen has been in use as first-line hormonal therapy in patients with receptor-positive advanced breast cancer, with progestins given following failure of tamoxifen. The efficacy of the newer aromatase inhibitors, as shown in their earlier clinical development, prompted the performance of phase III clinical trials comparing both anastrozole and exemestane with megestrol acetate in postmenopausal patients with advanced breast cancer following progression of disease with tamoxifen.

In 1996 Buzdar et al. [6] for the Arimidex Study Group reported an analysis of two parallel trials of similar design where anastrozole was given at a dose of either 1 mg or 10 mg daily and compared with megestrol acetate 160 mg orally every day. In the 764 study patients the clinical benefit rates of about 33% were similar for all three treatment arms. While gastrointestinal disturbances occurred more frequently in patients receiving the aromatase inhibitor, weight gain was more prominent in the megestrol acetate group.

A further analysis by the same group of investigators – focusing on survival results of these trials – revealed an advantage for anastrozole with a median survival of 27 months for the 1 mg dose and 25 months for the 10 mg dose, as compared to a median of 22 months for patients receiving megestrol acetate. The 1 mg daily dose of anastrozole thus resulted in a 5 month median survival advantage over the progestin [7]. The 2 year survival rate reached 55% for both anastrozole dosages and 46% for megestrol acetate, thus establishing the superiority of anastrozole over megestrol acetate as second-line hormonal therapy in patients failing tamoxifen.

In a further phase III trial that included over 250 patients, exemestane 25 mg/day orally was compared with megestrol acetate; clinical benefit favored the former – 37% vs. 34%, lasting a median of 14 and 11 months, respectively. The median survival had not been reached in the exemestane group at the time of analysis as compared to a median of 28 months in the megestrol acetate arm [8]. Quality of life assessment also favored the aromatase inhibitor in terms of global well-being and physical functioning. Hot flashes, nausea and fatigue were the most frequent side effects of exemestane, reported by 10% or less of the patients and consistent with estrogen deprivation as a result of this therapy. Serum levels of estradiol were determined over time in about 60 patients in each arm; suppression was more pronounced and prolonged in patients receiving exemestane. Results of this trial point to exemestane as a treatment option in patients failing tamoxifen.

First-line clinical trials

Both anastrozole and letrozole were shown in phase III trials to be superior to tamoxifen as a first-line hormone therapy in postmenopausal patients with advanced breast cancer. Boneterre et al. in Europe, Australia and South America [9], and Nabholtz and collaborators for the Arimidex Study Group in North America [10], reported simultaneously on two identically designed clinical trials in which over 1,000 patients who fulfilled the eligibility criteria – namely, advanced breast cancer with either positive hormone receptors in their tumor or an unknown receptor status – were randomized to receive either anastrozole 1 mg daily or tamoxifen 20 mg daily. In both studies the therapeutic index favored the aromatase inhibitor. In both trials anastrozole was better tolerated and was associated with fewer thromboembolic events, 4%, as compared to 7–8% with tamoxifen, and with a lower incidence of vaginal bleeding, 1% vs. 3–4% in the tamoxifen subgroup. The incidence of other side effects such as hot flashes, nausea and weight gain were similarly distributed among both study arms. Clinical benefit, including a complete or partial remission and stabilization of disease for 6 months or longer, favored anastrozole, 59% vs. 46% for tamoxifen, for a median duration of response of 16 and 14 months respectively in the North American trial and was equally achieved (55%) in the European trial for a median of 15 months in both arms.

Novel aromatase inhibitors are superior to tamoxifen in postmenopausal patients with hormone receptor-positive advanced breast cancer

Their identical design notwithstanding, the two trials were not homogeneous with regard to several characteristics of the participating patients. Two differences need to be particularly emphasized: in the North American trial a higher proportion of patients, 48%, presented with visceral disease when entering the trial as compared to less than 40% of patients in the European trial. In the latter trial, in as many as 55% of the patients the estrogen receptor status in their tumors was unknown, which is rather surprising since the trial was conducted in the latter part of the 1990s. Indeed, in the North American trial of Nabholtz et al. [10], the proportion of patients with unknown hormone receptor status was 11%. When clinical benefit parameters were analyzed for patients with known estrogen receptor status in the European trial of Bonaterre's group, excluding those patients with unavailable

information on estrogen receptors in their tumors, an advantage was observed for anastrozole in terms of time to progression, resembling the findings in the American trial where, as described, hormone receptor status was known for the majority of patients.

A combined analysis of these two trials was undertaken by the Arimidex Committee members and published in 2001 [11]. The combined analysis of the 1,021 total study population confirmed results of the individual trials, showing an advantage for anastrozole over tamoxifen with regard to the overall objective response rate (29% vs. 27%), clinical benefit (57% vs. 51%), and time to progression (8 vs. 7 months for all patients and 10 vs. 6 months for those with positive hormone receptors), leading the investigators to conclude that anastrozole is at least as effective as tamoxifen as first-line hormonal therapy in postmenopausal patients with advanced breast cancer. For patients with known positive hormone receptor status, anastrozole may be superior to tamoxifen and is, in fact, better tolerated. It should therefore be considered as standard first-line therapy in these patients.

Preliminary data show a disease-free survival advantage and a decreased incidence of contralateral primary breast cancers for anastrozole as compared to tamoxifen and for the sequential use of tamoxifen and letrozole or exemestane vs. tamoxifen alone in the adjuvant setting

A further phase III trial comparing tamoxifen with a third-generation aromatase inhibitor, letrozole, as first-line treatment for postmenopausal patients with metastatic breast cancer was reported in 2001, 6 months after the tamoxifen vs. anastrozole trials were published. In the letrozole-tamoxifen study – also a multi-institutional, international study (29 participating centers, including Israel) – just over 900 patients were accrued between 1996 and 1999 and randomized to receive either letrozole 2.5 mg a day or tamoxifen 20 mg daily, both orally [12]. Hormone receptor status was known in two-thirds of the patients; a similar proportion of patients had evidence of soft tissue involvement, in 25% as the only site of disease activity. Clinical benefit was achieved in 49% of the patients in the letrozole group and in 38% of the patients who received tamoxifen ($P = 0.001$). The median time to progression was prolonged in the letrozole arm (41 weeks) as compared to the tamoxifen group (26 weeks). An analysis of objective response (complete and partial remission) by baseline characteristics revealed that for patients who had received endocrine therapy in the adjuvant setting, letrozole was clearly superior with a response rate of 29% while only 8% responded in the tamoxifen group ($P = 0.002$). The objective response rates were 31% and 21% for letrozole and tamoxifen respectively in patients with known hormone receptor status ($P = 0.003$) and 48% and 34% for patients with soft-tissue disease only, respectively ($P = 0.04$), decreasing to 26% and 16% ($P = 0.02$) for patients who also had visceral involvement. Best results were therefore achieved with letrozole in patients with no prior adjuvant hormone therapy who were hormone receptor-positive and had soft-tissue disease only. Both agents resulted in a similar incidence and type of side effects, the most frequently reported being hot flashes (15%) and nausea (5%); 2% of patients in the tamoxifen arm experienced thromboembolic phenomena as compared to 1% in the letrozole arm.

Of note, the results of this study were analyzed by geographic area of participating institutions (Europe, North America, and the rest of the world), and in all three, letrozole was better than tamoxifen in terms of time to progression, supporting the superior efficacy of the new-generation aromatase inhibitor, letrozole, over tamoxifen, as was also the case for anastrozole.

Aromatase inhibitors in the adjuvant treatment of primary breast cancer

Until recently tamoxifen was the indisputable agent of choice in use in the adjuvant setting for patients with hormone-dependent primary breast cancer following locoregional treatment, given as sole systemic therapy or in conjunction with chemotherapy. A meta-analysis undertaken by the Early Breast Cancer Collaborators Group [13] confirmed the significant contribution of adjuvant tamoxifen in decreasing the odds of both recurrence and death from breast cancer. Results of recent clinical investigations, however, challenge the hegemony of tamoxifen as hormonal therapy in the adjuvant setting [Table 4].The first of these studies, referred to as the ATAC trial, was designed as a three-arm randomized study to compare the efficacy of anastrozole with that of tamoxifen, or to both drugs given in combination (ATAC: Anastrozole, Tamoxifen, Anastrozole in Combination) [14]. The design of this trial was prompted, among other reasons, by results of an earlier Italian investigation that used the first-generation aromatase inhibitor, aminoglutethimide, as adjuvant therapy following treatment with tamoxifen [15]. At a median follow-up of 5 years a disease-free survival advantage was

Table 4. Summary of trials including aromatase inhibitors in the adjuvant setting

Trial	Ref	No. of patients	Median follow-up (months)	Disease-free survival	*P*	Reduction in contralateral breast cancer in AI arm
ATAC	16	9,366	47	86.9% (anastrozole) 84.5% (tamoxifen)	0.03	43%
Tamoxifen alone vs. tamoxifen & exemestane	19	4,742	30	86.8% 91.5%	<0.001	50%
Tamoxifen & placebo vs. tamoxifen & letrozole	17	5,187	29	87% 93%	<0.001	46%

shown for the cohort of patients receiving both drugs, tamoxifen and aminoglutethimide, in sequence.

The ATAC trial is undoubtedly one of the largest ever undertaken in clinical oncology, with an accrual of over 9,000 postmenopausal patients with primary breast cancer following local therapy; 84% of the patients were known to harbor estrogen receptor-positive tumors and 21% had received adjuvant chemotherapy prior to the onset of therapy with either anastrozole 1 mg, tamoxifen 20 mg, or anastrozole 1 mg concomitantly with tamoxifen 20 mg – all given daily by mouth for a total treatment period of 5 years [14]. An initial analysis of the preliminary results published in 2002 after a median follow-up of 33 months revealed an advantage in terms of disease-free survival and in the incidence of a second primary tumor in the contralateral breast for patients randomized to the anastrozole arm. The results for patients receiving anastrozole and tamoxifen in combination did not differ from those observed with tamoxifen as a single agent. For the smaller subgroup of patients previously treated with adjuvant chemotherapy, no significant difference in outcome was observed between treatment arms. Treatment in all three arms was usually well tolerated. Anastrozole resulted in side effects such as hot flashes, fatigue, arthralgias and myalgias, which were mild to moderate in the vast majority of patients [14].

In a more recent update of the ATAC trial [16], at a median follow-up of 47 months, anastrozole as a single agent continues to show a statistically significant advantage in disease-free survival over tamoxifen, with an absolute difference of 2.4% (86.9% vs. 84.5%, respectively) for all patients, increasing to 2.9% for the subgroup of patients with hormone-receptor positive tumors.

While the ATAC trial compared a SERM and a new-generation aromatase inhibitor, more recent trials have focused on investigating the potential advantage of the sequential use of an aromatase inhibitor once the established 5 year treatment period of tamoxifen therapy has elapsed or, in an alternative design, discontinuing tamoxifen after 2–3 years and substituting tamoxifen by an aromatase inhibitor until completion of 5 years of treatment. In the first of these trials, Goss and associates randomized close to 5,200 postmenopausal patients with early-stage breast cancer to receive 5 years of adjuvant tamoxifen followed by a placebo, or to continue therapy with letrozole 2.5 mg daily for an additional 5 years. Interim results were published in November 2003, at a median follow-up of 2.4 years [17]. First breast cancer-related events, defined as either a local or distant recurrence or a new primary in the contralateral breast, occurred more frequently in the tamoxifen-only group (n=132), as compared to 75 events recorded in the subgroup of patients treated with letrozole, for an estimated 4 year disease-free survival of 87% and 93%, respectively ($P = 0.001$). Treatment with letrozole resulted in a relative reduction of 46% in the incidence of contralateral breast cancer. In view of these differences in the rates of events observed at the first interim analysis, the monitoring committee of the trial recommended its early termination, and patients in the placebo arm were allowed to cross over to letrozole. Letrozole was usually well tolerated, with mild to moderate arthralgias and myalgias, hot flashes and fatigue being the most frequently reported side effects. Long-term administration of letrozole and other aromatase inhibitors can be associated with osteoporosis; patients should therefore be monitored for bone density, and treatment with calcium supplements, vitamin D and bisphosphonates should be considered accordingly [18].

The early termination of the trial with crossover from placebo to letrozole confounds a possible survival advantage with the latter. Five years of therapy with letrozole cannot be recommended on the basis of this study since none of the participants have been followed that long at publication of the initial analysis, which in fact evaluated 2–3 years of treatment with this agent.

Other ongoing trials, one in the U.S. and two in Europe (Austria, Spain), are exploring the possible benefit of adding an aromatase inhibitor after 5 years of adjuvant tamoxifen (unpublished results). In a trial by Coombes and co-workers [19] for the Intergroup Exemestane Study, 4,742 postmenopausal patients with early breast cancer were randomized after 2 or 3 years of adjuvant tamoxifen to either complete 5 years of therapy with this agent or to switch to exemestane, 25 mg a day until the completion of 5 years of adjuvant hormone therapy. At a median follow-up of 2.5 years after randomization, exemestane resulted in a 32% reduction in the risk of relapse, corresponding to a 5% absolute benefit in disease-free survival (92% vs. 87% respectively with or without exemestane). Moreover, a decreased incidence of contralateral breast cancer was also observed in the exemestane arm, 9 cases, as compared to 20 contralateral cancers in the group receiving tamoxifen alone. No difference in overall survival between the two treatment arms is apparent at present. Exemestane resulted in a higher incidence of arthralgias (5%) and diarrhea (4%) than tamoxifen, and in an increased incidence of osteoporosis; thromboembolic events occurred more frequently with tamoxifen, 2.4% vs. 1.2% with exemestane.

The trials described above challenge the widely accepted treatment strategy of adjuvant therapy with single-agent tamoxifen in patients with hormone receptor-positive breast cancer, since switching to an aromatase inhibitor has resulted in improved disease-free survival; however, follow-up has been short and mature data on the possible impact on survival are still lacking.

The sequential use of an aromatase inhibitor and tamoxifen provides additional options for improving the outcome of adjuvant endocrine therapy for postmenopausal patients with hormone receptor-positive early breast cancer. Five years of tamoxifen monotherapy might be suboptimal in many of these patients. However, the optimal sequencing and duration of combined endocrine therapy with tamoxifen and an aromatase inhibitor in the adjuvant setting remains unsettled and is being investigated.

Finally, some data are now emerging from the use of an aromatase inhibitor as preoperative (neoadjuvant) therapy in postmenopausal patients with primary breast cancer. Ellis and colleagues [20] conducted a phase III endocrine therapy trial, comparing 4 months of preoperative therapy with either letrozole 2.5 mg a day or tamoxifen in postmenopausal patients with estrogen receptor-positive breast cancer not deemed eligible for breast-conserving surgery at diagnosis, in order to compare

SERM = selective estrogen receptor modulator

response rates and surgical outcome. Of the 324 patients participating in the trial, 60% of the patients in the letrozole arm achieved a clinical objective remission and 48% underwent breast-conserving surgery as compared with a 41% objective remission rate and a 36% rate of breast-conserving surgery in the tamoxifen arm. Of particular interest, the greatest difference in efficacy favoring letrozole was observed in patients with ErbB-1 and/or ErbB-2 positive tumors, with a remission rate of 88% as compared to only 21% with tamoxifen. Infrequent response to tamoxifen in these tumors is possibly due to a downstream mediator of ErbB 1-2 signaling MEKK1, which activates the estrogen receptor and may stimulate the agonist activity of tamoxifen.

Neoadjuvant letrozole offers a new clinical approach to improve surgical outcomes in older women with breast cancer. Molecular tumor characteristics other than positive estrogen receptor, such as over-expression of ErbB 1-2, can contribute to the decision-making process for selecting the optimal neoadjuvant endocrine treatment in these patients.

Summary

The clinical development of aromatase inhibitors in recent years represents a significant addition to our armamentarium for the treatment of postmenopausal patients with hormone receptor-positive breast cancer – both for metastatic disease and in the adjuvant setting. In patients with metastatic disease, third-generation aromatase inhibitors have shown significantly superior efficacy over tamoxifen as first-line hormone therapy. In the adjuvant setting, preliminary results with the use of aromatase inhibitors in ongoing large clinical trials indicate significant gains in disease-free survival rates and in the occurrence of contralateral breast cancer, either alone for 5 years or sequentially after tamoxifen for 2–3 or 5 years. While tamoxifen monotherapy continues to be standard adjuvant therapy for patients with low risk primary breast cancer, postmenopausal patients with higher risk hormone-positive primary breast cancer should also be offered an aromatase inhibitor. Aromatase inhibitors are also prescribed for patients with contraindications to tamoxifen. The optimal sequence and duration of aromatase inhibitor adjuvant therapy as well as its long-term impact on overall survival remain to be established. In general, aromatase inhibitors have a good toxicity profile. Long-term effects such as the risk of osteoporosis need to be better defined.

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References

1. Beatson GT. On the new treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet* 1896;ii:104–7.
2. James VH, McNeill JM, Lai LC, Newton CJ, Ghilchik MW, Reed MJ. Aromatase activity in normal breast tumor tissues: in vivo and in vitro studies. *Steroids* 1987;50:269–79.
3. Geisler J, Haynes B, Anker G, Dowsett M, Lonning PE. Influence of letrozole and anastrozole 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;751–7.
4. Stuart-Harris RC, Smith IE. Aminoglutethimide in the treatment of advanced breast cancer. *Cancer Treat Rev* 1984;11:189–204.
5. Goss PE, Strasser K. Aromatase inhibitors in the treatment and prevention of breast cancer. *J Clin Oncol* 2001;19:881–94.
6. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *J Clin Oncol* 1996;14:2000–11.
7. Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma. Results of a survival update based on a combined analysis of data from two mature phase III trials. *Cancer* 1998;83:1142–52.
8. 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 phase III randomized double-blind trial. *J Clin Oncol* 2000;18:1399–411.
9. Bonneterre J, Thurlimann B, Robertson JFR, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 post-menopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability Study. *J Clin Oncol* 2000;18:3748–57.
10. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in post-menopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000;18:3758–67.
11. Boneterre 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.
12. 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.
13. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomized trials. *Lancet* 1998;351: 1451–67.
14. ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trials. *Lancet* 2002;259:2131–9.
15. Boccardo F, Rubagotti A, Amoroso D. Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: results of an Italian cooperative study. *J Clin Oncol* 2001;119:4209–15.
16. Baum M, Buzdar A, Cuzick J, et al., for the ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer. Results of the ATAC trial efficacy and safety update analyses. *Cancer* 2003;98:1802–10.
17. 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;349:1793–802.
18. Eastell R, Adams J. Results of the ATAC trial: effects on bone mineral density and bone turnover (ATAC Trialists' Group). *Ann Oncol Suppl* 2002;5:32.
19. Coombes CR, 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.
20. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for Erb-2 positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001;19:3808–16.

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