



A large proportion of breast cancers in older women have positive hormone receptors. Therefore, these women are eligible to receive adjuvant endocrine therapy to decrease their chance of cancer recurrence. Over the last few years, a new class of endocrine therapy, aromatase inhibitors (AIs), has challenged the place of tamoxifen as the gold standard adjuvant endocrine agent. We will discuss randomized clinical trials comparing tamoxifen to AIs in terms of efficacy and side effects.

Key words: breast cancer, tamoxifen, aromatase inhibitors, side effects, quality of life

Update on Endocrine Therapy for Postmenopausal Women with Early Breast Cancer

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Introduction

Age is a risk factor for breast cancer (BC). Therefore, it is not surprising that more than 50% of all women diagnosed with breast cancer in Canada are age 60 or older and nearly 30% are over 70 years old.¹ Among newly diagnosed women, older patients are more likely to have tumours expressing estrogen receptors²⁻⁴ and at a higher level than younger patients.³ Over 80% of tumours diagnosed in women older than 65 years of age express estrogen receptors;^{2,3} therefore, these patients are eligible to receive adjuvant hormonal therapy. We will discuss the indications, benefits, and side effects of hormonal therapy given in the adjuvant setting.

Indications

Until recently, tamoxifen was the standard adjuvant endocrine therapy for hormone-sensitive early breast cancer. The addition of five years of tamoxifen reduces recurrence and mortality risks by 47% and 26%, respectively.⁵ The optimal duration of treatment is usually five years, since longer therapy with tamoxifen does not seem to confer any extra benefits in terms of disease-free survival (DFS).⁶ The third-generation aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane are highly selective for

aromatase and inhibit 97–99% of estrogen synthesis. Their use is restricted to postmenopausal women. In the last few years, results of important trials have challenged the place of tamoxifen as the gold standard for adjuvant therapy in the early stage breast cancer population. Three different ways of using AIs in adjuvant treatment have been compared in randomized clinical trials (RCTs), the results of which are presented below and summarized in Table 1.

Initial therapy

Two RCTs have been conducted comparing upfront AIs to up-front tamoxifen (endocrine therapy was started soon after surgery or completion of chemotherapy, if given). The first published RCT, Arimidex, Tamoxifen, Alone or in Combination (ATAC),⁷ used three arms: anastrozole, tamoxifen, and a combination of both, and compared the effects of those three arms. As the combination arm showed no efficacy or tolerability benefits compared to the tamoxifen alone arm, this arm was discontinued after the initial analyses. The last analysis,⁸ completed after 68 months of median follow-up of the two monotherapy arms (6,186 patients) demonstrated a significant advantage of anastrozole over tamoxifen with a 13% improvement in DFS,

Table 1: Randomized Controlled Trials of Tamoxifen vs. Aromatase Inhibitors

Name of the trial	Experimental arm vs. control arm	Setting	Number of subjects	Median follow-up (months)	DFS (HR) P-value	OS (HR) P-value
ATAC ⁸	Anastrozole vs. tamoxifen	Up-front	6,241	68	0,87 P=0.01	0,97 P=0.7
BIG-98 ⁹	Letrozole vs. tamoxifen	Up-front	8,010	25.8	0,81 P=0.003	0,86 P=0.16
IES ¹⁰	Exemestane vs. tamoxifen	Sequential	4,742	30.6	0,68 P<0.001	0,88 P=0.37
ARNO ¹¹ ABCSG ¹¹	Anastrozole vs. tamoxifen	Sequential Sequential	962 2,262	28	0,60 P=0.0009	0,76 P=0.16
ITA ¹²	Anastrozole vs. tamoxifen	Sequential	448	36	0,35 P=0.003	Not available
MA-17 ^{14,15}	Letrozole x 5 years after tamoxifen x 5 years	Extended	5,187	30	0,58 P<0.001	0,82 P=0.04

DFS: Disease-free survival; OS: Overall survival.

corresponding to an absolute difference of 3.7% at six years (hazard ratio [HR] 0.87, $p=0.013$). Even though anastrozole decreased distant recurrences (HR 0.86, $p=0.04$), the difference in overall survival (OS) was not statistically significant ($p=0.7$). The second trial published in this setting is the Breast International Group (BIG) 1-98 trial⁹ comparing letrozole to tamoxifen. Over 8,000 postmenopausal patients were randomly assigned to four treatment arms: tamoxifen only for five years, letrozole only for five years, tamoxifen followed by letrozole or vice versa after two years of therapy for a total of five years. So far, data are only available for the two monotherapy arms and the first two years of sequential therapy. Results showed a statistically significant improvement of 19% in DFS (absolute benefit of 2.6%) in the letrozole sample (HR 0.81, $p=0.003$). As for the ATAC study, OS was not significantly different between treatments.⁸

Sequential Therapy

Three RCTs of sequential therapy (two or three years of tamoxifen followed by AI for a total of five years) have been published. Although the authors used the

same treatment plan, the studies differ in many ways. The Intergroup Exemestane Study (IES)¹⁰ randomized patients after two years of tamoxifen to continue tamoxifen for a total of five years or switched them to exemestane for a total of five years of endocrine therapy. It is important to note that at the time of randomization, patients had to show no evidence of recurrence. The HR for exemestane was 0.68, $p<0.001$, representing a 32% decrease in recurrence risk (absolute difference of 4.7%). The second study combined the results of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 and the Arimidex/Nolvadex (ARNO) 95 trial¹¹ comparing anastrozole with tamoxifen. In this trial, for almost one-third of patients considered for the combined analysis (962/3,224) the two years of tamoxifen treatment were not part of the study and, consequently, analyses were done using two years postsurgery as the starting point. The results showed a 40% decrease in the risk for an event (local recurrence, distant metastasis, or contralateral breast cancer) in the anastrozole group compared to the tamoxifen group ($p=0.0009$). Lastly, the Italian Tamoxifen Anastrozole

trial (ITA), an RCT of 448 patients randomized to anastrozole or tamoxifen to complete five years of endocrine therapy after two to three years of tamoxifen, also showed a benefit in DFS with anastrozole.¹² For the last two studies, a meta-analysis showed a benefit in overall survival for anastrozole.¹³

Extended Therapy

Stopping adjuvant tamoxifen treatment after five years, particularly for the node-positive patients, often makes both doctors and patients anxious. Although five years of tamoxifen results in decreased recurrence and mortality, 39% of recurrences occur between five and 10 years after BC is diagnosed.⁵ Based on this observation, Mammary 17 (MA.17) randomized women to five years of letrozole vs. five years of placebo after five years of adjuvant tamoxifen.¹⁴ The trial was stopped early because a benefit was found in the letrozole arm after a median follow-up of 2.4 years (HR 0.57 for DFS [$p\leq 0.001$]; absolute benefit 6%). In addition, a significant survival advantage was observed for letrozole in the node-positive subgroup.¹⁵

The optimal approach remains

unclear at this time. All approaches described above are recommended by the American Society of Clinical Oncology guidelines.¹⁶

Although thousands of women participated in these trials, each study differed slightly in its design. Consequently, making an unbiased comparison between studies becomes difficult. Is it better to start endocrine therapy up-front, sequentially, or should one opt for extended therapy? Although it seems that the sequential approach yields greater benefits, clinicians argue that the up-front approach with AIs prevents the recurrences that may occur early in the first two years of tamoxifen in a sequential approach. Firmer answers are expected from results on the two-arms/sequential therapy of BIG 1-98. The best AI in the up-front adjuvant setting is still controversial. The answer will come from two RCTs that are still in their recruitment phase: the MA²⁷ comparing anastrozole with exemestane, and FACE (Femara vs. Anastrozole Clinical Evaluation) comparing letrozole to anastrozole. Until data are available from these trials, definitive recommendations on the best approach cannot be made. In daily practice, choice of AI is based on published data specific to the individual clinical setting and the different alternatives are discussed with patients.

Side Effects of Endocrine Therapy Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, has been available for more than 30 years and its side effects are well-documented. Thromboembolic disease and endometrial cancer are the two most serious complications.

The risk of developing uterine cancer with tamoxifen is about two- to four-fold compared to the general population.¹⁷⁻¹⁹ The majority of endometrial cancers that develop in women on tamoxifen are stage I¹⁷ and are curable with surgery.²⁰ The American Society of Clinical Oncology recommends regular gynecologic follow-up and pelvic examination.²⁰ Screening endometrial biopsy

or transvaginal ultrasound in women taking tamoxifen is not recommended.²¹⁻²⁴ However, women should be advised to report promptly any vaginal bleeding and be referred to a gynecologist for investigation.²⁰

Venous thromboses are more frequent events. RCTs of tamoxifen vs. placebo or observation report a relative risk (RR) of venous thromboembolic events (VTE) varying from 1.06 to 6.0.²⁵⁻²⁹ Inherited coagulation disorders do not seem to affect the risk of VTE.³⁰⁻³² As other factors such as immobilization increase the risk of thrombosis, some have recommended to discontinue tamoxifen one month before a major surgery and resume it when the patient recovers her mobility.³⁰ Meta-analyses show that strokes are slightly more common for women taking tamoxifen (RR 1.49) while death from myocardial infarction seems to be slightly decreased with the use of tamoxifen (RR 0.62).^{18,19}

Other side effects are not life-threatening but can be burdensome for women taking tamoxifen. Hot flashes are more common in women taking tamoxifen, although they are a frequent problem for many postmenopausal women who do not. For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial comparing tamoxifen to placebo in women with node-negative breast cancer and estrogen-receptor positive tumours, 64.1% of women randomized to tamoxifen reported hot flashes compared to 47.7% for those on placebo.²⁸ Numerous nonhormonal agents can be used to alleviate hot flashes and have been reviewed elsewhere.³³ It is important to remember that hormone replacement therapy (HRT) is contraindicated in women with a history of breast cancer. An interim analysis of RCTs of HRT in women with breast cancer led to early stopping of the trial because an increase in cancer relapse was found in the HRT arm; a second trial with similar design also closed due to anticipated difficulties in recruitment.³⁴

Women sometimes attribute weight gain to tamoxifen. However, data do not support a role for tamoxifen to explain

significant weight gain.³⁵⁻³⁷ Cataracts have been reported to be increased in a prevention trial using tamoxifen¹⁷ although it has not been confirmed in a case-control study.³⁸

In terms of quality of life (QOL), studies comparing tamoxifen to placebo for prevention³⁵ or treatment³⁹ of breast cancer showed no overall difference in QOL but vasomotor and gynecological symptoms were more frequent with tamoxifen.³⁵

Aromatase Inhibitors

Aromatase inhibitors (AIs) act by inhibiting or inactivating aromatase, the enzyme responsible for the conversion of androgens into estrogens; this leads to a suppression of estrogen levels.⁴⁰ In contrast to tamoxifen, it is unclear whether AIs are associated with an increased incidence of VTE. Even though the risk is lower than the one associated with tamoxifen, it seems to be higher than in the general population.^{25, 41} The MA.17 trial is the only randomized trial that compared an AI (letrozole) with a placebo; 0.4% of patients had a thromboembolic event on letrozole versus 0.2% on placebo.¹⁵ The safety of patients with past history of VTE is not well documented.

There seems to be a trend for AIs to be associated with a slightly higher number of coronary heart disease (CHD) events but numbers are very small, and the difference is often not statistically significant; as such, a definitive conclusion cannot be drawn. Moreover, since tamoxifen is associated with a small decrease in mortality from heart disease, it is possible that apparent differences might be due to the absence of protective effect from tamoxifen and reflect the baseline cardiovascular risk found in the general population. This is supported by the observation that in the MA.17 trial comparing letrozole to placebo, there was no significant difference in the number of vascular events (5.8% on letrozole and 5.6% on placebo; $p = 0.76$).¹⁵ Longer follow-up of recent trials is needed to better quantify this risk if it is present. Regarding lipid profile, a recent review found that AIs had variable effects on lipid

profile.⁴² In a substudy of MA.17 where lipids were measured at baseline and at six months, 12 months, and yearly thereafter, there was no difference in the proportion of patients exceeding the threshold of lipid parameters in letrozole vs. placebo.¹⁵ Given the uncertainty with regard to cardiovascular risk and lipids, it seems prudent to assess risk factors for CHD, but the optimal frequency of lipids measurement is not known, and no specific recommendations exist.¹⁶

The effects of AIs on the musculoskeletal system are twofold. First, from a symptomatic point of view, patients may experience arthralgias, myalgias, and diffuse pain. In trials comparing AI with tamoxifen or AI with placebo, there

was an increase in the proportion of women who experienced these symptoms (Table 2). In the only trial comparing an AI to placebo, 25% of women experienced arthralgia on letrozole vs. 21% on placebo and for myalgia, 15% vs. 12%, respectively; these differences were statistically significant.¹⁵ The QOL assessment in this trial showed that 43% of women on letrozole were at least “very bothered” by aching muscles compared to 39% with placebo ($p=0.02$). Most trials comparing AI to tamoxifen found an increase in musculoskeletal symptoms.

The second effect on the musculoskeletal system is the decrease in bone mineral density (BMD).⁴³ Trials showed that AI are associated with an increase in

clinical fractures, although not all results were statistically significant.^{8–10,15} One trial showed no difference in fracture rates (ITA).⁴³ This association is supported by a large retrospective cohort study showing a RR of fracture of 1.4 (13.5% in the AI group vs. 10.3% in the controls; $p = 0.001$).⁴⁴ Longer follow-up is needed to quantify the long-term adverse profile of AIs on bones. In the meantime, it is recommended to follow-up bone mineral density and to treat as necessary. Whether patients with pre-existing osteoporosis should receive an aromatase inhibitor is unclear as most studies^{7,9,11,14} did not include the BMD in their eligibility criteria.

Hot flashes are increased compared

Table 2: Musculoskeletal Symptoms Associated with Aromatase Inhibitors

Trials	Arms: experimental vs. standard	Experimental	Standard	P value
ATAC⁸	Anastrozole vs. tamoxifen			
Muscle cramps		4.0%	8.0%	<0.0001
Arthralgia		35.6%	29.4%	<0.0001
Fractures		11.0%	7.7%	<0.0001
BIG-98	Letrozole vs. tamoxifen			
Arthralgia*		20.3%	12.3%	<0.001
Myalgia*		6.4%	6.1%	0.61
Fractures		5.7%	4%	<0.001
IES¹⁰	Exemestane vs. tamoxifen			
Pain or aches†		33.2%	29.4%	0.17
Arthralgia		5.4%	3.6%	0.01
Fractures		3.1%	2.3%	0.08
ABCSG trial 8 and ARNO 95 trial¹¹	Anastrozole vs. placebo			
Bone pain		19%	16%	0.05
Fractures		2%	1%	0.015
ITA¹²				
Musculoskeletal disorders		8.4%	12%	0.2
Bone fractures		1%	1.3%	0.6
MA.17¹⁵	Letrozole vs. placebo			
Arthralgia*		25%	21%	<0.001
Myalgia*		15%	12%	0.004
Fractures		5.3%	4.6%	0.025

* Grade 1-4 combined from the Common Toxicity Criteria Version 2.0

† Grade 1-4 combined from the Common Toxicity Criteria Version 1.0

Key Points

Breast cancer is common among older women, the majority of whom are candidates for adjuvant endocrine therapy (tamoxifen or aromatase inhibitors).

Adjuvant endocrine therapy is associated with a benefit in overall survival.

Adjuvant endocrine therapy is usually well tolerated with minimal adverse impact on quality of life.

Serious possible side effects with tamoxifen are venous thrombosis and uterine cancer.

Aromatase inhibitors are associated with an increased risk of fractures compared to tamoxifen, and patients receiving AIs should have their bone mineral density followed and appropriate treatment prescribed for osteopenia/osteoporosis.

to placebo¹⁵ but are less common^{8,9} or equivalent^{10, 11} to tamoxifen. Overall QOL is not or is only minimally impaired with AI.⁴⁵⁻⁴⁷

Conclusion

At present, the best adjuvant treatment for hormone-sensitive early breast cancer in postmenopausal women should include an aromatase inhibitor.¹⁶ Although there are some side effects, most of them are manageable. The safety profile of AIs makes them a very good choice for aging patients. Of course, clinicians should balance the risk of recurrence and the side effects of therapy, according to risk of cancer recurrence, comorbid conditions, and life expectancy.



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References

1. Canadian Cancer Society/National Cancer Institute of Canada. Canadian Cancer Statistics 2006:112.
2. Nixon AJ, Neuberger D, Hayes DF, et al. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *J Clin Oncol* 1994;12:888-94.
3. Zavagno G, Meggiolaro F, Pluchinotta A, et al. Influence of age and menopausal status on pathologic and biologic features of breast cancer. *Breast* 2000;9:320-8.
4. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? *J Natl Cancer Inst Monogr* 1994;35-42.
5. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;351:1451-67.
6. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 1996;88:1529-42.
7. Baum M, Budzar AU, Cuzick J, et al. 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 randomised trial. *Lancet* 2002;359:2131-9.
8. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60-2.
9. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005;353:2747-57.
10. 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.
11. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;366:455-62.
12. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol* 2005;23:5138-47.
13. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006;7:991-6.
14. 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.
15. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97:1262-71.
16. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005;23:619-29.
17. 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.
18. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-717.
19. Braithwaite RS, Chlebowski RT, Lau J, et al. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *J Gen Intern Med* 2003;18:937-47.
20. Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 2006;24:5091-7.
21. Barakat RR, Gilewski TA, Almadrones L, et al. Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol* 2000;18:3459-63.
22. Love CD, Muir BB, Scrimgeour JB, et al. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. *J Clin Oncol* 1999;17:2050-4.
23. Gerber B, Krause A, Muller H, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 2000;18:3464-70.
24. Runowicz CD. Gynecologic surveillance of women on tamoxifen: first do no harm. *J Clin Oncol* 2000;18:3457-8.
25. Deitcher SR, Gomes MP. The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review. *Cancer* 2004;101:439-49.
26. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 1996;88:1529-42.

27. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intra-ductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999;353:1993–2000.
28. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 1989;320:479–84.
29. Rutqvist LE, Mattsson A. Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. The Stockholm Breast Cancer Study Group. *J Natl Cancer Inst* 1993;85:1398–406.
30. Duggan C, Marriott K, Edwards R, Cuzick J. Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. *J Clin Oncol* 2003;21:3588–93.
31. Abramson N, Costantino JP, Garber JE, et al. Effect of Factor V Leiden and prothrombin G20210→A mutations on thromboembolic risk in the national surgical adjuvant breast and bowel project breast cancer prevention trial. *J Natl Cancer Inst* 2006;98:904–10.
32. Abramson N, Aster RH. Retrospective assessment of hypercoagulability in breast cancer prevention trial. *J Clin Oncol* 2002;20:4133–4.
33. Gainford MC, Simmons C, Nguyen H, et al. A practical guide to the management of menopausal symptoms in breast cancer patients. *Support Care Cancer* 2005;13:573–8.
34. Holmberg L, Anderson H and HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet* 2004;363:453–5.
35. Day R, Ganz PA, Costantino JP, et al. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Clin Oncol* 1999;17:2659–69.
36. Kumar NB, Allen K and Cantor A, et al. Weight gain associated with adjuvant tamoxifen therapy in stage I and II breast cancer: fact or artifact? *Breast Cancer Res Treat* 1997;44:135–43.
37. Goodwin PJ, Ennis M and Pritchard KI, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. *J Clin Oncol* 1999;17:120–9.
38. Bradbury BD, Lash TL, Kaye JA and Jick SS. Tamoxifen and cataracts: a null association. *Breast Cancer Res Treat* 2004;87:189–96.
39. Love RR, Cameron L, Connell BL, et al. Symptoms associated with tamoxifen treatment in postmenopausal women. *Arch Intern Med* 1991;151:1842–7.
40. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med* 2003;348:2431–42.
41. Lycette JL, Luoh SW, Beer TM, et al. Acute bilateral pulmonary emboli occurring while on adjuvant aromatase inhibitor therapy with anastrozole: case report and review of the literature. *Breast Cancer Res Treat* 2006;99:249–55.
42. Esteva FJ, Hortobagyi GN. Comparative assessment of lipid effects of endocrine therapy for breast cancer: implications for cardiovascular disease prevention in postmenopausal women. *Breast* 2006;15:301–12.
43. Chien JA, Goss PE. Aromatase inhibitors and bone health in women with breast cancer. *J Clin Onc* 2006;24:5305–12.
44. Mincey BA, Duh MS, Thomas SK, et al. Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. *Clin Breast Cancer* 2006;7:127–32.
45. Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. *J Clin Oncol* 2005;23:6931–40.
46. Cella D, Fallowfield L, Barker P, et al. Quality of life of postmenopausal women in the ATAC (“Arimidex”, Tamoxifen, Alone or in Combination) trial after completion of 5 years’ adjuvant treatment for early breast cancer. *Breast Cancer Res Treat* 2006;100:273–84.
47. Fallowfield LJ, Bliss JM, Porter LS, et al. Quality of life in the intergroup exemestane study: a randomized trial of exemestane versus continued tamoxifen after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer. *J Clin Oncol* 2006;24:910–7.