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Breast Cancer Res Treat (2009) 117:91–98
DOI 10.1007/s10549-008-0291-z

CLINICAL TRIAL

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Received: 9 December 2008 / Accepted: 10 December 2008 / Published online: 27 December 2008

Abstract Previous studies suggest that disease recurrence peaks at around 2 years in patients with early stage breast cancer (EBC), but provide no data regarding recurrence type. This retrospective analysis aimed to identify early recurrence types and risk factors in estrogen receptor-positive (ER+) EBC patients treated with adjuvant tamoxifen following breast cancer surgery. Postmenopausal women diagnosed with ER+ EBC from 1995 to 2004 were evaluated. Annual hazard ratios (HR) for recurrence at different sites were calculated. Time-dependent Cox regression analysis was used to identify predictors of recurrence within 2.5 years of diagnosis, including factors that were more strongly predictive of early than later recurrence. Of 3,614 patients evaluated, 476 developed recurrence during the 5-year median follow-up. Cumulative recurrence rates at 2.5 years (95% confidence interval) were: overall 6.3% (5.5–7.1), locoregional 1.1% (0.7–1.5), contralateral 0.5% (0.3–0.7), and distant 4.8% (4.0–5.6). The annual HR of overall recurrence peaked at 2 years (4.3% per annum). The majority of this peak represented distant recurrence (3.4% per annum). In Cox regression analysis, tumor size and grade, lymph node involvement, lymphovascular invasion, and symptomatic presentation were significant independent predictors of early recurrence. Age at diagnosis was independently predictive of recurrence within 2.5 years of diagnosis but not later recurrence. This study identified an early recurrence peak at 2 years, most of which were distant recurrences. Implementing an aromatase inhibitor after an initial 2–3 years of tamoxifen fails to address this early peak of distant recurrence and the potential breast cancer-associated mortality.

Keywords Distant metastases · Early breast cancer · Recurrence · Aromatase inhibitor · Tamoxifen

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Introduction

Postmenopausal women with estrogen receptor-positive (ER+) early breast cancer (EBC) who have successfully undergone surgical resection are candidates for adjuvant endocrine therapy to reduce the risk of disease recurrence at local and distant sites. Tamoxifen, a selective estrogen receptor modulator, was the standard of care for such patients for nearly 20 years; it can significantly reduce recurrence and breast cancer-related death in patients prescribed about 5 years of adjuvant treatment [1]. However, the third-generation aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane have proven more effective than tamoxifen at improving disease-free survival (DFS), whether given as upfront (initial) adjuvant therapy, as sequential or switch therapy following approximately 2–3 years of prior tamoxifen, or as extended adjuvant therapy following 5 years of tamoxifen treatment [2–8].

Consequently, AIs are now widely recommended as adjuvant endocrine treatment of postmenopausal women with EBC [9, 10].

Despite the results of major clinical trials proving the efficacy of AIs over tamoxifen, several issues remain unresolved regarding their use as adjuvant endocrine therapy. One of the primary unresolved considerations is whether these drugs should be used instead of tamoxifen as initial adjuvant treatment for postmenopausal women with successfully resected EBC, or whether 2–3 years of tamoxifen should precede the implementation of AI therapy. The latter strategy, using either exemestane [Intergroup Exemestane Study (IES)] or anastrozole (Arimidex Nolvadex [ARNO] 95 study and others) as endocrine therapy following 2–3 years of tamoxifen, potentially offers treatment cost savings relative to upfront AIs and significant improvements in DFS, event-free survival (EFS), and overall survival (OS) relative to tamoxifen alone [5–7, 11]. A significant caveat of the switching approach is that it effectively "misses" a sizable number of women who may relapse during the initial treatment period with tamoxifen; these patients have been excluded from AI switching trials such as the IES and ARNO 95 [5, 11]. Interestingly, in the Austrian Breast and Colorectal Study Group trial 8, the only reported sequencing trial that randomized patients at the time of surgery, the inclusion of recurrences during the tamoxifen period effectively negated the significant EFS benefit that was observed when these patients were not considered (hazard ratio [HR], 0.63; $P = 0.010$ compared with HR, 0.76; $P = 0.068$) [12]. Evidence from an earlier study further suggests a peak of breast cancer recurrence occurring between 1 and 2 years after surgery, and this was observed regardless of prognostic indicators such as tumor size and the degree of lymph node involvement [13]. The type of recurrence events occurring at this peak (i.e., local or contralateral recurrence or distant metastasis) was not reported. Furthermore this historical study used data from randomized trials were patients in the control arms did not receive adjuvant therapy as would be standard treatment protocol today.

From a surgical standpoint, it is important to determine the type of recurrence, in that if local or regional recurrences predominate, the use of more effective surgical interventions and/or adjuvant chemo- or radiotherapy can be advocated. The primary objective of this analysis was to determine the pattern of overall recurrence and the individual types of recurrence during the first 5 years of diagnosis in postmenopausal women with hormone receptor-positive EBC undergoing treatment with tamoxifen. A secondary objective was to identify predictors of recurrences developing within the early period to facilitate informed clinical decisions regarding the type of adjuvant endocrine therapy (i.e., AIs vs. tamoxifen) and the treatment strategy best suited to the patient (i.e., upfront AI vs. switch therapy).

Methods

Study population

Data were obtained from local breast cancer databases at five UK centres. All postmenopausal patients with ER+ EBC diagnosed between 1995 and 2004 with no previous history of breast cancer and who received adjuvant hormone therapy were considered for analysis. From this cohort patients known to have either received adjuvant endocrine therapy other than tamoxifen or participated in any randomised controlled trial involving AIs were excluded.

Follow up, definition of recurrence and prognostic factors

In each individual unit patients were reviewed as per the unit protocol. This involved outpatient clinic review for a minimum of two and a maximum of four visits per year. Mammographic surveillance was routinely performed every 12–24 months over the first five years of follow-up. Invasive recurrence was recorded as the endpoint for this study. The site of recurrence was classified as locoregional (ipsilateral breast, axilla or supraclavicular fossa), contralateral breast, or distant (any other site). Patients with concurrent locoregional and distant recurrence were recorded as reaching both end points for the purpose of site specific survival analysis. Patients who died with breast cancer as a recorded cause of death, but with no previous record of recurrence, were deemed to have had distant recurrence detected on the date of death. The prognostic factors for recurrence that were considered included age, tumor grade, tumor size, histological type, the number of lymph nodes involved, lymphovascular invasion, and screen detection. Treatment variables were also considered in the analysis, including type of surgery and use of chemotherapy and radiotherapy.

Statistical analysis

Time to recurrence was measured from the date of diagnosis to the earliest date of detection of recurrence at any site. Follow-up times were censored on the date of last follow-up or the date of non-breast cancer death. Cumulative recurrence was calculated by the Kaplan–Meier method, and univariate comparisons between patient groups were performed using the log rank test. Smoothed recurrence rates were calculated by summing the reciprocal

of the number of patients at risk for each recurrence event within a 6-month interval centered on the time point in question, and dividing by the length of that interval. Multivariate analysis was performed using time-dependent Cox regression stratified by center. The time-dependent term was a binary variable that distinguished between follow-up times of <2.5 years and later times. This time point was selected because previous studies [13, 14] had demonstrated a peak of recurrence around this time, and because switching studies have generally used the switch to an AI after 2–3 years of tamoxifen. All prognostic variables and their interactions with the time-dependent covariate were considered for inclusion in the final model, which was constructed by a stepwise variable selection procedure. Significance testing was based on a likelihood ratio statistic. SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for analysis, and P values <0.05 were considered significant.

Results

Patient and treatment characteristics

A total of 3,614 women were eligible for analysis. The demographic, pathologic, and treatment data of the study group are summarized in Table 1. The median age at diagnosis in the study group was 62 years. The majority of women in the study group had tumors <2 cm (62.0%), grade II disease (58.9%), no nodal involvement (60.5%), and no lymphovascular invasion (67.5%). A total of 2083 (57.6%) patients received radiotherapy and 713 (19.7%) received chemotherapy.

Pattern of recurrence

Recurrence occurred in 476 (13.2%) of the 3,614 women included in the analysis during follow-up, which was for a median of 5 years. The first recorded site of recurrence was locoregional in 94 patients, contralateral in 38 patients, distant in 335 patients, and a combination of locoregional and distant in nine patients. Kaplan-Meier estimates of cumulative recurrence at 2.5 years (with 95% confidence intervals [CIs]) were: overall 6.3% (5.5–7.1), locoregional 1.1% (0.7–1.5), contralateral 0.5% (0.3–0.7), and distant 4.8% (4.0–5.6). At 5 years, the corresponding results were: overall 13.9% (12.5–15.3), locoregional 3.0% (2.2–3.8), contralateral 1.2% (0.8–1.6), and distant 10.5% (9.3–11.7).

Figure 1 shows smoothed annual recurrence rates by site of recurrence as a function of time from diagnosis. Overall recurrence rates showed peaks at 2 years and at 3.5–4 years (4.3 and 4.5% per annum, respectively), and these primarily represented peaks of distant recurrence (3.4 and 3.5% per annum). In contrast, the annual recurrence rates for locoregional and contralateral recurrences never exceeded 1% over the 5 years following diagnosis, and no initial peak at 2 years was evident.

Analysis of predictors

The Kaplan–Meier estimates of overall recurrence at 2.5 and 5 years in various subgroups of patients are shown in Table 1. In univariate analysis, all variables listed in Table 1 were significantly associated with recurrence-free survival ($P < 0.001$; except radiotherapy, $P = 0.009$). Age > 75 years; tumor size >2 cm; grade 3 tumors, >3 involved nodes; and lymphovascular invasion were each associated with >10% cumulative recurrence at 2.5 years (Table 1).

In the time-dependent multivariate Cox regression analysis, the only significant interaction was between the time-dependent term and age ($P = 0.01$), indicating that age was a stronger predictor of early, rather than late, recurrence. The final model, including this interaction, is shown in Table 2. Age was a significant predictor of early recurrence after adjustment for the clinico-pathological factors in the model, with higher risk being associated with age ≥75 ($P = 0.008$). For recurrence >2.5 years after diagnosis, age had no significant independent predictive power. Tumor size, grade, nodal status, lymphovascular invasion, and mode of detection were all highly significant independent predictors of recurrence (Table 2). As they had no significant interaction with the time-dependent covariate, they were equally strong predictors of early and later recurrence. The highest categories of tumor size, grade, and nodal status were each independently associated with an approximately threefold increase in risk relative to their respective reference categories. No treatment variables or their interactions with clinico-pathological variables were independently significant predictors of recurrence in this analysis.

Discussion

In this retrospective analysis of postmenopausal women with ER+ EBC overall recurrence and distant recurrence peaked at approximately 2 years post diagnosis and then again peaked between 3.5 and 4 years post diagnosis (Fig. 1). These results support previous data from Saphner et al. who identified a peak of recurrences at 2 years in a large cohort of patients ($n = 3,585$) enrolled in 7 Eastern Cooperative Oncology Group studies of postoperative adjuvant therapy [13]. Likewise, Houghton and colleagues reported a similar peak of early recurrence in the Arimidex, Tamoxifen, Alone or in Combination (ATAC)

Table 1 Patient characteristics and Kaplan-Meier estimated 2.5- and 5-year overall recurrence rates

	Number	(%)	2.5-Year cumulative recurrence (%) (95% CI)	5-Year cumulative recurrence (%) (95% CI)
All patients	3,614	100.0	6.3 (5.5–7.1)	13.9 (12.5–15.3)
Age at diagnosis				
<55	787	21.8	4.5 (2.9–6.1)	13.2 (10.5–15.9)
55–64	1,348	37.3	4.7 (3.5–5.9)	10.7 (8.7–12.7)
65–74	857	23.7	7.1 (5.3–8.9)	16.7 (13.8–19.6)
>75	622	17.2	13.3 (8.6–14.0)	18.2 (14.5–21.9)
Tumor size				
<2 cm	2,242	62.0	3.0 (2.2–3.8)	8.1 (6.7–9.5)
2–5 cm	1,202	33.3	10.5 (8.7–12.3)	22.7 (20.0–25.4)
>5 cm	118	3.3	28.6 (19.2–38.0)	42.6 (31.0–54.2)
Unknown	52	1.4		
Grade				
I	717	19.8	1.5 (0.5–2.5)	4.4 (2.6–6.2)
II	2,130	58.9	5.4 (4.4–6.4)	12.8 (11.0–14.6)
III	700	19.4	13.6 (10.9–16.3)	27.7 (23.8–31.6)
Unknown	67	1.9		
Nodes involved				
0	2,186	60.5	2.9 (2.1–3.7)	7.2 (5.8–8.6)
1–3	820	22.7	7.3 (5.3–9.3)	16.0 (13.1–18.9)
>3	455	12.6	19.2 (15.5–22.9)	39.3 (34.2–34.4)
Unknown	153	4.2		
Lymphovascular invasion				
Positive	865	23.9	12.9 (10.5–15.3)	26.9 (23.4–30.)
Negative	2,438	67.5	4.1 (3.3–4.9)	9.6 (8.2–11.0)
Unknown	311	8.6		
Histological type				
Ductal	2,755	76.2	6.4 (5.4–7.4)	14.4 (12.8–16.0)
Lobular	494	13.7	8.1 (5.6–10.6)	17.0 (13.1–20.9)
Other	350	9.7	2.5 (0.7–4.3)	6.4 (3.5–9.3)
Unknown	15	0.4		
Screen detected				
Yes	1,369	37.9	2.1 (1.3–2.9)	7.1 (5.5–8.7)
No	2,026	56.1	9.5 (8.1–10.9)	19.2 (17.2–21.2)
Unknown	219	6.1		
Operation				
BCS	1,898	52.5	2.8 (2.0–3.6)	9.1 (7.5–10.7)
Mastectomy	1,715	47.5	9.9 (8.3–11.5)	19.1 (18.9–19.3)
Unknown	1	<0.1		
Radiotherapy				
Yes	2,083	57.6	6.5 (5.3–7.7)	14.8 (13.0–16.6)
No	1,385	38.3	5.9 (4.5–7.3)	12.8 (10.8–14.8)
Unknown	146	4.0		
Chemotherapy				
Yes	713	19.7	9.7 (7.3–12.1)	23.1 (19.4–26.8)
No	2,541	70.3	5.3 (4.3–6.3)	11.6 (10.2–13.0)
Unknown	360	10.0		

CI confidence interval, *BCS* breast-conserving surgery

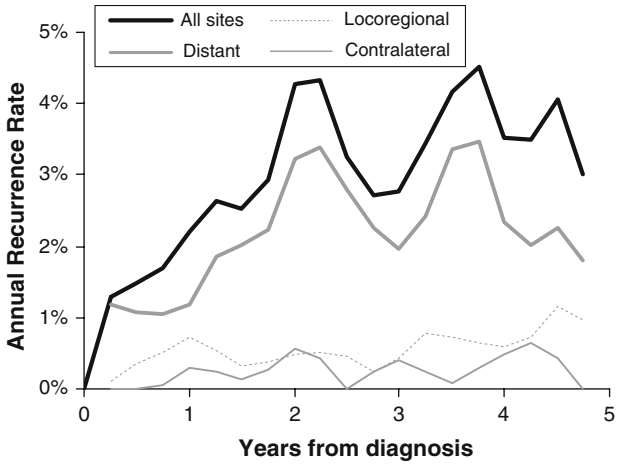

Fig. 1 Annual recurrence rates by site of recurrence

Table 2 Time-dependent Cox regression analysis for recurrence

	Hazard ratio (95% CI)	*P* value
Age at diagnosis (<2.5 years follow-up)[a]		
<55	1.00	
55–64	1.20 (0.75–1.93)	0.45
65–74	1.49 (0.93–2.39)	0.10
≥75	1.89 (1.17–3.05)	0.009
Age at diagnosis (≥2.5 years follow-up)		
<55	1.00	
55–64	0.82 (0.59–1.15)	0.26
65–74	0.89 (0.62–1.27)	0.52
≥75	0.72 (0.47–1.12)	0.14
Tumor size		
<2 cm	1.00	
2–5 cm	1.39 (1.10–1.74)	0.005
>5 cm	2.82 (1.92–4.14)	<0.001
Grade		
I	1.00	
II	1.66 (1.13–2.44)	0.01
III	3.16 (2.10–4.75)	<0.001
Nodes involved		
0	1.00	
1–3	1.43 (1.10–1.85)	0.007
>3	3.03 (2.34–3.94)	<0.001
Lymphovascular invasion		
Negative	1.00	<0.001
Positive	1.53 (1.23–1.92)	
Screen detected		
Yes	1.00	0.003
No	1.51 (1.15–1.99)	

[a] Hazard ratios different from those for follow-up time ≥2.5 years with the following significance levels: overall $P = 0.03$; age 55–64 years, $P = 0.20$; age 65–74 years, $P = 0.08$; age ≥75 years, $P = 0.003$, *CI* confidence interval

trial [14, 15]. Interestingly, the overlap in overall and distant recurrence rates observed in the current analysis (Fig. 1) suggests that distant recurrences predominate as the primary type of recurrence at both time points. These findings of a peak in both overall and distant recurrences at 2 years is corroborated by data from two recent investigations of recurrences in the ATAC and Breast International Group (BIG) 1–98 early adjuvant trials, which demonstrated a predominance of distant recurrences at 2.5 years. In the ATAC trial, there were 195 and 236 total recurrences in the anastrozole and tamoxifen monotherapy arms, respectively; 133 (68.2%) and 143 (60.6%) were distant recurrences [14]. Similarly, in the BIG 1–98 trial, early recurrences occurred in 117 and 168 patients at 2 years in the letrozole and tamoxifen groups, respectively, and 87 (74.4%) and 125 (74.4%) were distant recurrences [16]. Results of these two major trials and the current analysis thus identify distant recurrence as the primary type of early recurrence event for postmenopausal women with ER-positive EBC. Of note, a potential bias could have affected the time dependence of recurrence rates in this retrospective study: an increased likelihood of detecting recurrences during scheduled follow-up visits and investigations. For example, an annual cycle in detection of recurrence in the contralateral breast is clearly visible in Fig. 1; this could be synchronous with the performance of follow-up mammography. By comparison, locoregional and distant recurrence show no such periodic variations that would be linked to follow-up procedures (Fig. 1). Therefore, it is likely that the peak in distant recurrence at 2 years is genuine, and consistent with the existence of a subgroup of patients with a relatively high risk of early relapse.

Evidence that distant disease recurrence predominates among all first recurrences is important when trying to determine which adjuvant AI strategy (i.e., upfront AI therapy versus switching to an AI after 2–3 years of tamoxifen) offers the greatest potential benefit, especially in reducing distant disease recurrence, during this early treatment period. In terms of its impact on survival, it has been widely accepted that distant recurrence is a major predictor of death; thus, distant disease-free survival (DDFS) is a key efficacy endpoint in major clinical trials of adjuvant endocrine therapy [17]. Indeed, data from a number of large, well-controlled, adjuvant trials show that early improvements in DDFS often precede later improvements in OS [18]. Retrospective cohort studies also distinguish distant recurrences from locoregional or contralateral recurrences as a significant predictor of death. In a study of 1,616 patients in a large integrated healthcare system (median 44.5-month follow-up), distant recurrence events were more predictive of death and had the lowest 5-year OS probability (HR, 13.6; $P < 0.001$; 41.3%) compared with locoregional recurrences (HR, 4.5;

$P < 0.001$; 59.3%) or contralateral recurrences (HR, 3.0, $P = 0.01$; 83.4%) [19]. In addition, there was a significantly higher risk of breast cancer-related death for women with distant compared with locoregional recurrences (HR, 3.6, $P < 0.001$). Distant recurrence events are also associated with substantially higher healthcare costs compared with locoregional or contralateral recurrences [20]. Adjuvant therapies that reduce the risk for distant, compared with locoregional or contralateral recurrences, are therefore likely to offer the most benefit in terms of survival. In this regard, results from the ATAC trial at 2.5 years demonstrated that anastrozole reduced distant recurrences by 7% over tamoxifen (143 vs. 133 events), whereas the reduction of locoregional, and especially contralateral, recurrences by anastrozole was considerably greater (17 and 74% reductions, respectively) [14]; the relative reduction in time to distant recurrence at 100 months' follow-up was 16% ($P = 0.022$) [21]. By comparison, results from a retrospective analysis of early predictors in BIG 1–98 at 2 years of follow-up demonstrated that letrozole reduced distant recurrences by 30% compared with tamoxifen (87 vs. 125 events) [16]; the relative reduction in time to distant recurrence at 25.8 months' median follow-up in the primary core analysis was 27% ($P = 0.001$) [4]. Most importantly, had the AI, in either case, been introduced after 2–3 years of tamoxifen therapy had elapsed, the reductions in these early distant events would not have been possible. Given the predominance of distant recurrence as a first event at this time point, the results of the present analysis strongly argue for the use of an AI rather than tamoxifen as upfront adjuvant endocrine therapy.

There are limited data to identify subgroups of postmenopausal women with EBC who would be most likely to benefit from initial adjuvant AI therapy compared with tamoxifen. In the absence of such information, the most pragmatic approach is to identify patients at the greatest risk for early recurrence and thus those who, in light of the efficacy of AIs compared with tamoxifen, would be likely to derive the greatest benefit of early AI therapy. In this current study we have shown that large tumour size, high grade, involvement of more than 3 axillary nodes and the presence of lymhovascular invasion are highly significant independent predictors of recurrence within 2.5 years ($P < 0.001$) (Table 2). Time-dependent Cox regression analysis allows the identification of factors whose influence on the risk of recurrence changes with time. Using this analysis technique we additionally identified age >75 years as a group greater risk of earlier recurrence compared with later recurrence (>2.5 years) (Table 2). Women aged over 75 years were significantly less likely to receive adjuvant chemotherapy (5 vs. 25% $P < 0.001$) or radiotherapy (41 vs. 64% $P < 0.001$) compared with women below the age of 75 years. This may be due to increased co-morbidity in patients older than 75 or the lack of robust evidence of a benefit of chemotherapy in addition to endocrine therapy in this age group. However, in the multivariate analysis, adjusting for the effects of radiotherapy and chemotherapy did not alter the conclusion that women in this age group were at a significantly higher risk of recurrence within the first 2.5 years than at later times. Women over 75 were also more likely than younger patients to be recorded as dying from breast cancer without a separate record of recurrence. This could potentially cause an overattribution of death related to breast cancer in elderly patients and subsequently increase the early recurrence rate. However, there was no evidence that such inferred recurrences occurred earlier than explicitly recorded recurrences in elderly patients or in the cohort as a whole.

Three other studies undertaken to identify prognostic factors for early recurrence have shown similar findings [16, 22, 23]. Additional factors found to be independent predictors of early recurrence include low ER positivity and human epidermal growth factor receptor 2 (HER2) overexpression/amplification [16, 23]. In ER-positive patients progesterone receptor negativity (PR-) has also been shown to be associated with increased early recurrence compared with PR positivity [16]. Unfortunately PR and HER2 status was not performed routinely in ER + EBC patients in any of the centres during the study period. Kennecke and coworkers identified grade 3 status (odds ratio [OR] vs. grade 1 or 2, 2.53; $P < 0.001$), low ER positivity (OR vs. moderate/high ER positivity, 2.27; $P < 0.001$), and number of positive lymph nodes (1–3 vs. 0, OR, 2.27; 4–9 vs. 0, OR, 4.49; $P < 0.001$) as significant predictors of early (within 2.5 years) recurrence [23]. Debled and coworkers found that approximately 16% of patients with modified Scarff-Bloom-Richardson grade 3, node-positive tumors developed recurrences within the first 3 years of tamoxifen therapy [22]. In the BIG 1–98 trial, significant predictors of early recurrence in multivariate analysis also included tumor size and grade and node positivity; however, even after adjusting for significant prognostic factors, letrozole was associated with a significant reduction in early relapses relative to tamoxifen (letrozole vs. tamoxifen: HR, 0.69; $P = 0.002$), with the difference in hazards occurring at about 1 year post randomization [16]. Fewer early relapses also were observed with letrozole relative to tamoxifen in all subgroups examined, with the exception of the grade 3 cohort; these findings highlight the potential benefits of implementing an AI therapy earlier rather than later [16].

Results from two groups have used mathematical models to evaluate the benefit of initial versus sequential use of AIs. One analysis predicted that the upfront strategy was superior to the sequencing strategy, while the other analysis favored the use of a sequential strategy (2.5 years of

tamoxifen followed by an AI) [24, 25]. These studies are limited by the use of results from switching trials to promote a sequential treatment strategy. Results from the sequential arms of BIG 1–98, expected in the near future, will be a key determinant in resolving this issue. These study arms have evaluated the efficacy of 2 years of tamoxifen followed by 3 years of letrozole, and 2 years of letrozole followed by 3 years of tamoxifen, in a directly comparative manner [4].

Clinical guidelines from the St. Gallen Consensus Conference and the American Society of Clinical Oncology acknowledge the efficacy of AIs over tamoxifen based on the major clinical trials, but they do not clearly distinguish among treatment strategies (upfront or sequential use) [9, 10]. In particular, a majority of the 2007 St. Gallen panel suggested the use of an AI sequentially (i.e., after 2–3 years of tamoxifen), while reserving upfront use for higher risk patients, defined as those with 1–3 or more involved nodes and HER-2/neu amplification or patients with 4 or more involved nodes [9]. Importantly, the risk categories of St. Gallen include as intermediate risk those with tumors > 2 cm and grade 2–3 tumors. The present findings suggest that the use of a sequential approach in these patients could place a substantial number at risk for recurrence while on tamoxifen, as patients in these categories have a significant risk of early recurrence.. Until results of the BIG 1–98 and TEAM trials, which compare upfront versus sequencing AI therapy, are available all postmenopausal women with ER + EBC should be considered for an upfront AI apart from those with small, grade 1 or 2, node-negative tumors. All patients live with the risk that their cancer will return. The greatest protection should be provided to prevent recurrence, particularly early fatal distant recurrence.

Acknowledgments We thank Sharon Thomas, PhD, of Phase Five Communications Inc. for editorial assistance with this manuscript. Financial support for editorial assistance was provided by Novartis Oncology.

Financial disclosures Astra Zeneca provided an educational grant for this study. IJ Monypenny has received honoraria from Astra Zeneca. JC Doughty has received honoraria from Astra Zeneca, Novartis, Pfizer and Roche. R Carpenter has received honoraria from Astra Zeneca, Novartis, Pfizer and Roche. W Angerson has received lecture fees from Astra Zeneca.

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717. doi:10.1016/S0140-6736(05)66544-0
2. Howell A, ATAC Trialists' Group (2004) ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen [abstract 1]. Presented at the 27th Annual San Antonio breast cancer symposium; San Antonio, TX, 8–11 December
3. Howell A, Cuzick J, Baum M, ATAC Trialists' Group et al (2005) Results of the ATAC (Arimidex, Tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60–62. doi:10.1016/S0140-6736(05)74803-0
4. Thürlimann B, Keshaviah A, Coates AS et al (2005) A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 353:2747–2757. doi:10.1056/NEJMoa052258
5. Coombes RC, Kilburn LS, Snowdon CF, Intergroup Exemestane Study et al (2007) Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 369:559–570. doi:10.1016/S0140-6736(07)60200-1 (Erratum in: Lancet 2007; 369:906)
6. Jakesz R, Jonat W, Gnant M, ABCSG, The GABG et al (2005) 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 366:455–462. doi:10.1016/S0140-6736(05)67059-6
7. Jonat W, Gnant M, Boccardo F et al (2006) Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol 7:991–996. doi:10.1016/S1470-2045(06)70948-2 Erratum in: Lancet Oncol 2007;8:6
8. Goss PE, Ingle JN, Martino S et al (2005) 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 97:1262–1271
9. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ (2007) Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007 10th St. Gallen conference. Ann Oncol 18:1133–1144. doi:10.1093/annonc/mdm271 (Erratum in: Ann Oncol 2007; 18:1917)
10. Winer EP, Hudis C, Burstein HJ et al (2005) 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 23:619–629. doi:10.1200/JCO.2005.09.121
11. Kaufmann M, Jonat W, Hilfrich J et al (2007) Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. J Clin Oncol 25:2664–2670. doi:10.1200/JCO.2006.08.8054
12. Jakesz R, Gnant M, Greil R et al (2005) The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of ABCSG Trial 8. Breast Cancer Res Treat 94(Suppl. 2):S10 (abstract 13)
13. Saphner T, Tormey DC, Gray R (1996) Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 14:2738–2746
14. Houghton J, ATAC Trialists' Group (2006) Initial adjuvant therapy with anastrozole (S) reduced rates of early breast cancer recurrent and adverse events compared with tamoxifen (T)—data reported on behalf of the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) Trialists' group. Ann Oncol 17(Suppl. 9):ix94 (abstract 243PD)

15. Houghton J, ATAC Trialists' Group (2005) Using anastrozole as initial adjuvant treatment prevents early and reduces adverse events: updated data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial. J Clin Oncol 23(16S):24s (abstract 582)
16. Mauriac L, Keshaviah A, Debled M, IG B, Collaborative Group; International Breast Cancer Study Group et al (2007) Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1–98 trial1–98. Ann Oncol 18:859–867. doi:10.1093/annonc/mdm001
17. Hudis CA, Barlow WE, Costantino JP et al (2007) Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 25:2127–2132. doi:10.1200/JCO.2006.10.3523
18. Melisko M, Lin A, Rugo H (2007) Adjuvant therapy for early stage breast cancer (EBC): Distant disease-free survival (DDFS) as a predictor of overall survival (OS). J Clin Oncol 25(18S):23s (abstract 583)
19. Lamerato L, Havstad S, Gandhi S, Jones D, Chlebowski R (2005) Breast cancer recurrence and related mortality in US pts with early breast cancer. J Clin Oncol 23(16S):62s (abstract 738)
20. Lamerato L, Havstad S, Gandhi S, Jones D, Nathanson D (2006) Economic burden associated with breast cancer recurrence: findings from a retrospective analysis of health system data. Cancer 106:1875–1882. doi:10.1002/cncr.21824
21. Arimidex Tamoxifen, Alone or in Combination (ATAC) Trialists' Group, Frbes JF, Cuzick J et al (2008) Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 9:45–53. doi:10.1016/S1470-2045(07)70385-6
22. Debled M, MacGrogan G, Brouste V, Mathoulin-Pelissier S, Durand M, Mauriac L (2007) Prognostic factors of early distant recurrence in hormone receptor-positive, postmenopausal breast cancer patients receiving adjuvant tamoxifen therapy: results of a retrospective analysis. Cancer 109:2197–2204. doi:10.1002/cncr.22667
23. Kennecke H, McArthur H, Olivotto IA et al (2008) Risk of early recurrence among postmenopausal women with estrogen receptor-positive early breast cancer treated with adjuvant tamoxifen. Cancer 112:1437–1444. doi:10.1002/cncr.23320
24. Punglia RS, Kuntz KM, Winer EP, Weeks JC, Burstein HJ (2005) Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: a decision analysis. J Clin Oncol 23:5178–5187. doi:10.1200/JCO.2005.02.964
25. Cuzick J, Sasieni P, Howell A (2006) Should aromatase inhibitors be used as initial adjuvant treatment or sequenced after tamoxifen? Br J Cancer 94:460–464. doi:10.1038/sj.bjc.6602964