original article

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Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial

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Background: Aromatase inhibitors are considered standard adjuvant endocrine treatment of postmenopausal women with hormone receptor-positive breast cancer, but it remains uncertain whether aromatase inhibitors should be given upfront or sequentially with tamoxifen. Awaiting results from ongoing randomized trials, we examined prognostic factors of an early relapse among patients in the BIG 1-98 trial to aid in treatment choices.

Patients and methods: Analyses included all 7707 eligible patients treated on BIG 1-98. The median follow-up was 2 years, and the primary end point was breast cancer relapse. Cox proportional hazards regression was used to identify prognostic factors.

Results: Two hundred and eighty-five patients (3.7%) had an early relapse (3.1% on letrozole, 4.4% on tamoxifen). Predictive factors for early relapse were node positivity ($P < 0.001$), absence of both receptors being positive ($P < 0.001$), high tumor grade ($P < 0.001$), HER-2 overexpression/amplification ($P < 0.001$), large tumor size ($P = 0.001$), treatment with tamoxifen ($P = 0.002$), and vascular invasion ($P = 0.02$). There were no significant interactions between treatment and the covariates, though letrozole appeared to provide a greater than average reduction in the risk of early relapse in patients with many involved lymph nodes, large tumors, and vascular invasion present.

Conclusion: Upfront letrozole resulted in significantly fewer early relapses than tamoxifen, even after adjusting for significant prognostic factors.

Key words: adjuvant endocrine therapy, aromatase inhibitor, breast cancer, early relapse, letrozole, prognostic factors

introduction

The primary core analysis of the BIG 1-98 trial, coordinated by the International Breast Cancer Study Group, compared letrozole to tamoxifen given for 5 years alone or in sequence, in postmenopausal women with estrogen and/or progesterone receptor (ER/PgR)-positive breast cancer. Patients were randomized from 1998 to 2003 to tamoxifen for 5 years, letrozole for 5 years, tamoxifen for 2 years followed by letrozole for 3 years or letrozole for 2 years followed by tamoxifen for 3 years. A significant benefit of letrozole (19% risk reduction) on disease-free survival was seen, particularly for distant metastasis, at a median follow-up of 25.8 months [1].

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A total of five trials have shown that aromatase inhibitors improve disease-free survival compared with tamoxifen alone. ATAC (anastrozole) [2] and BIG 1-98 (letrozole) [1] compared upfront aromatase inhibitor for 5 years to tamoxifen for 5 years. The other three trials, IES (exemestane) [3], ITA (anastrozole) [4], and ABCSG 8-ARNO 95 (anastrozole) [5], compared tamoxifen alone for 5 years to sequential treatment with tamoxifen for 2–3 years and aromatase inhibitor for 2–3 years. While waiting for the definitive results of BIG 1-98 comparing upfront letrozole to sequential treatment, we conducted an exploratory analysis to determine which patients could benefit most from the best treatment to prevent early relapse.

The focus of the present analysis was to retrospectively identify patients who might most benefit from the initial selection of letrozole versus tamoxifen, on the basis of clinical and pathological prognostic factors of early relapse.

patients and methods

The analysis population was comprised of eligible patients randomized to BIG 1-98 and excluded patients who withdrew consent to participate in the trial before initiating treatment. Patients were included according to the treatment to which they were randomized.

The primary end point was breast cancer relapse, defined as the first proven invasive local, contralateral breast, regional, or distant recurrence in any site. Secondly, nonbreast malignancies were ignored and deaths without proven recurrence were censored. Analyses were based on treatment with tamoxifen or letrozole alone; follow-up and events were censored if they occurred beyond 2 years after randomization for patients in the two monotherapy arms, and beyond the date of treatment switch or 2 years after randomization (whichever was earlier) for patients in the sequential treatment arms. The analysis thus focused exclusively on early relapse.

Prognostic factors tested included age at randomization (<55, 55–64, ≥65 years), pathological tumor size (≤2, >2 cm), tumor grade (1, 2, 3, missing), mitotic grade (1, 2, 3, missing), locally assessed ER/PgR status (ER+/PgR+, ER+/PgR−, ER+/PgR unknown, ER−/PgR+), centrally assessed HER-2 status (overexpressed/amplified, normal, missing), axillary node positivity (zero, one to three, four or more positive nodes), and vascular invasion (yes, no, not assessable). All covariates were modeled categorically using indicator variables. Significance for HER-2 status was on the basis of the pairwise comparison of overexpressed versus normal, and significance for vascular invasion was on the basis of the pairwise comparison of yes versus no. Covariates with >5% of values missing were modeled with an indicator for missing values; covariates with ≤5% values were not modeled with an indicator, and patients with missing values for these covariates were excluded from the models.

Cox proportional hazards regression analyses were used to identify significant prognostic factors, and all models included randomized treatment assignment (letrozole, tamoxifen). Only covariates that were significant 'univariately' (in a model that also included treatment) were considered in multivariate models. A full multivariate model was then fitted, and a manual backwards selection was conducted. To ensure noncollinearity in multivariate analyses, Spearman rank correlations were examined and Akaike's Information Criterion (AIC) was used to select between covariates with a correlation >0.50. After the significant main effects were identified, interactions between the main effects and treatment were tested to determine whether the effect of the covariate on the risk of relapse differed according to the treatment the patient initially received; interactions were tested individually to conserve power.

A significance level of $\alpha = 0.05$ was applied throughout without adjustment for multiple comparisons. Verification of the Cox proportional hazards assumption was done through visual inspection of the $\log(-\log(S(t)))$ plot, where $S(t)$ is the survivor function.

results

A total of 7707 of the 8028 patients were included (18 patients withdrew consent to participate before initiating treatment, 133 patients were ineligible, and another 170 had missing covariate values). At a median follow-up of 2 years (range 0.01–2 years), 285 patients (3.7%) had a relapse. Early relapse rates are 3.0% for the letrozole group and 4.4% for the tamoxifen group. The dominant sites of relapse are presented in Table 1 by treatment.

Table 2 gives the breakdown of the covariates by relapse status and also includes information on treatments received (radiotherapy, surgery, and chemotherapy). In 'univariate' models (including treatment), age was the only nonsignificant covariate ($P = 0.67$). Tumor grade and mitotic grade had a correlation of 0.60 and virtually identical AIC values; since tumor grade is a more commonly reported characteristic, it was kept in the full multivariate mode and mitotic grade was dropped. Node positivity and tumor size had a moderate correlation of 0.26; all other correlations were <16% in magnitude.

The significant prognostic factors in a multivariate analysis were node positivity ($P < 0.001$), lack of both receptors being positive ($P < 0.001$), tumor grade ($P < 0.001$), HER-2 expression/amplification ($P < 0.001$), tumor size ($P = 0.001$), endocrine treatment ($P = 0.002$), and vascular invasion ($P = 0.02$). The results from the final multivariate Cox regression model are presented in Table 3. Increasing tumor grade resulted in an increased risk of relapse. Risk of relapse by combined receptor status ranked as follows: ER−/PgR+ > ER+/PgR− > ER+/PgR unknown > ER+/PgR+. Patients with vascular invasion had a greater risk of relapse than those without; tumor with no assessable vascular invasion had an intermediate risk. Risk of relapse was greatest for patients with a high number of involved nodes, those with larger tumors, and those with HER-2 overexpressed/amplified tumors. There were no major violations of the proportional hazards assumption.

Letrozole resulted in a significant reduction in early relapse, even after adjusting for significant prognostic factors. Figure 1 shows average semiannual hazards of early relapse by treatment.

Table 1. Sites of early relapse by treatment

Site of early relapse	Treatment			
	Letrozole ($N = 3863$)		Tamoxifen ($N = 3844$)	
	N	%	*N*	%
Local	12	0.3	23	0.6
Contralateral breast	11	0.3	15	0.4
Regional	7	0.2	5	0.1
Distant	87	2.3	125	3.3
Soft tissue	3	<0.1	7	0.2
Bone	39	1.0	57	1.5
Viscera	45	1.2	61	1.6

Table 2. Covariates according to whether or not an early relapse occurred

	Early relapse			
	No (N = 7422)		Yes (N = 285)	
	N	%	N	%
Treatment				
Letrozole	3746	97.0	117	3.0
Tamoxifen	3676	95.6	168	4.4
Age at randomization				
<55 years	1399	96.3	53	3.7
55–64 years	3392	96.5	124	3.5
≥65 years	2631	96.1	108	3.9
Tumor size				
≤2cm	4711	97.8	108	2.2
>2cm	2711	93.9	177	6.1
Tumor grade				
Grade 1	2015	98.2	36	1.8
Grade 2	3650	96.6	127	3.4
Grade 3	1092	92.8	85	7.2
Missing	665	94.7	37	5.3
Mitotic grade				
Grade 0	3	100.0	0	0.0
Grade 1	3297	97.8	74	2.2
Grade 2	1616	95.8	71	4.2
Grade 3	695	92.2	59	7.8
Missing	1811	95.7	81	4.3
ER/PgR receptor status				
ER+/PgR+	4762	97.5	122	2.5
ER+/PgR−	1498	94.5	87	5.5
ER+/PgR unknown	1039	94.2	64	5.8
ER−/PgR+	123	91.1	12	8.9
HER-2 expression				
Normal	3865	97.5	101	2.5
Overexpressed	239	90.2	26	9.8
Missing	3318	95.5	158	4.5
Axillary node positivity				
0 positive	4411	98.2	81	1.8
1–3 positive	2157	96.4	81	3.6
≥4 positive	854	87.4	123	12.6
Vascular invasion				
No	5605	97.2	161	2.8
Yes	1247	92.7	98	7.3
Not assessable	419	96.1	17	3.9
Missing	151	94.4	9	5.6
Radiotherapy given				
No	2059	95.7	93	4.3
Yes	5355	96.5	192	3.5
Missing	8	100.0	0	0.0
Primary surgery				
Breast-conserving procedure	4303	98.1	84	1.9
Mastectomy	3114	93.9	201	6.1
Other	5	100.0	0	0.0
Chemotherapy use				
None	5564	96.7	192	3.3
Adjuvant only	1723	95.6	79	4.4
Neo-adjuvant with/without adjuvant	134	90.5	14	9.5
Missing	1	100.0	0	0.0

ER, estrogen receptor; PgR, progesterone receptor.

The difference in hazards appears to emerge around 1 year following randomization.

Figure 2 shows Cox model hazard ratios and confidence intervals (CIs) within subgroups of the significant prognostic factors. For all of the subgroups examined, with the exception of the grade 3 cohort, fewer early relapses were observed for the letrozole group compared with the tamoxifen group. The 95% CI for the hazard ratio of risk of early relapse for letrozole compared with tamoxifen did not cross the solid vertical line at 1.0 for patients with tumors that were bigger than 2 cm, grade 1 or 2, ER+ and PgR+/unknown, with four or more positive nodes, and with vascular invasion.

Within each subgroup in Figure 2, boxes located to the left of the dashed vertical line indicate that the observed effect of letrozole in that subgroup was greater than the effect of letrozole in the overall population. Though the observed effect of letrozole was greatest in patients with tumors that were grade 1, ER+/PgR unknown, or HER-2 over-expressing/amplified, these results were on the basis of little data (small boxes for hazard ratios and wide CIs). The data indicating a larger benefit from letrozole were statistically more robust for patients with four or more positive nodes, those with tumors >2 cm in diameter, or those with vascular invasion.

A comparison of the hazard ratios across the subgroup levels of each covariate (e.g. between tumors ≤2 cm and >2 cm) in Figure 2 shows that none of the prognostic factors is significantly predictive for the specific efficacy of letrozole. None of the interaction terms was statistically significant, as seen by the fact that, for each covariate, the CIs across levels of that covariate overlap. For example, the benefit of letrozole in patients with four or more positive nodes did not significantly differ from the benefit seen in patients with one to three or zero positive nodes.

Thus, the results of this multivariate analysis show that (i) letrozole significantly reduced the risk of early relapse compared with tamoxifen overall; (ii) within many but not all subgroups letrozole was significantly better than tamoxifen in preventing early relapse; and (iii) statistically there was no difference in the effect of letrozole across subgroup levels of any of the covariates examined, but letrozole was qualitatively more effective than tamoxifen within some subgroups (patients with four or more positive nodes, tumors > 2cm, or with vascular invasion).

discussion

Though a number of trials have shown superiority of aromatase inhibitors compared with standard tamoxifen therapy or placebo, it remains unclear whether an aromatase inhibitor should be given in sequence with tamoxifen or in place of it. Use of mathematical models with data from the aforementioned aromatase inhibitor trials led Cuzick et al. [6] to assert that early treatment with an aromatase inhibitor is superior to sequencing after 2 years of tamoxifen. Punglia et al. [7] reached the opposite conclusion when applying simulations on the basis of data from the aforementioned trials, namely that sequential therapy is preferable to an aromatase inhibitor alone.

Treatment choices on the basis of prognostic factors of relapse, without focusing on early relapses, have been previously studied. Among patients with small tumors without axillary

Table 3. Final multivariate Cox model results

Variable	Comparison	Hazard ratio	95% CI lower limit	95% CI upper limit	*P* value
Treatment	Letrozole versus tamoxifen	0.69	0.5	0.9	0.002
Tumor size	>2 versus ≤2 cm	1.54	1.2	2.0	0.001
Tumor grade	Grade 3 versus 1	2.43	1.6	3.6	<0.001
	Grade 2 versus 1	1.55	1.1	2.3	0.02
	Grade 3 versus 2	1.57	1.2	2.1	0.002
	Grade missing versus 1	1.96	1.2	3.1	0.005
ER/PgR status	ER+/PgR− versus ER+/PgR+	2.04	1.5	2.7	<0.001
	ER+/PgR unknown versus ER+/PgR+	1.59	1.1	2.2	0.005
	ER+/PgR− versus ER+/PgR unknown	1.28	0.9	1.8	0.16
	ER−/PgR+ versus ER+/PgR+	3.10	1.7	5.6	<0.001
	ER−/PgR+ versus ER+/PgR−	1.52	0.8	2.8	0.17
	ER−/PgR+ versus ER+/PgR unknown	1.95	1.0	3.7	0.04
HER-2	Overexpressed versus normal	2.48	1.6	3.8	<0.001
	Missing versus normal	0.79	0.5	1.2	0.29
Node positivity	≥4 versus 0 positive	4.81	3.5	6.6	<0.001
	1–3 versus 0 positive	1.73	1.3	2.4	<0.001
	≥4 versus 1–3 positive	2.79	2.1	3.7	<0.001
Vascular invasion	Yes versus no	1.39	1.1	1.8	0.02
	Not assessable versus no	1.26	0.8	1.9	0.29

CI, confidence interval; ER, estrogen receptor; PgR, progesterone receptor.

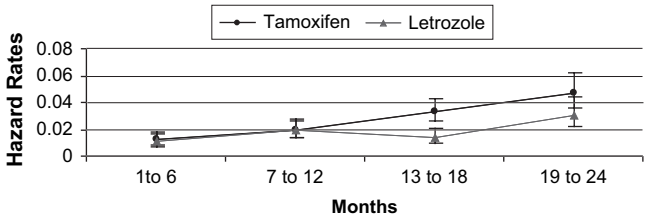

Figure 1. Semiannualized hazards of early relapse by treatment. Tamoxifen is represented in black by circles; letrozole is represented by gray triangles.

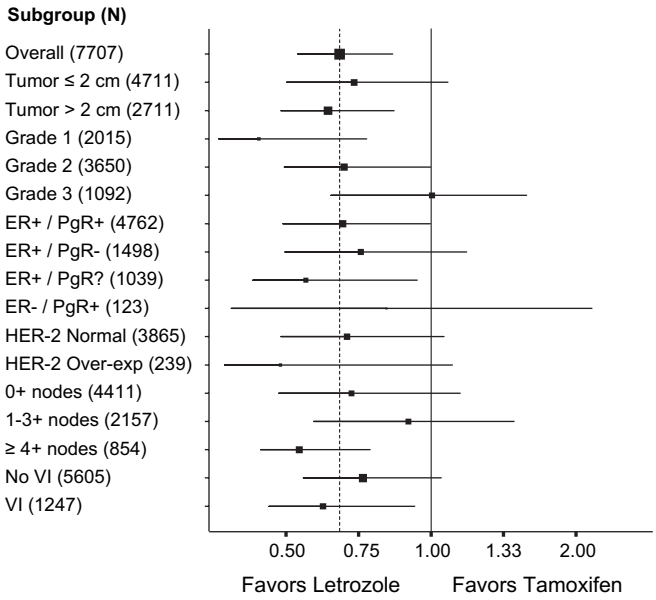

Figure 2. Cox model results for subgroup analyses of time to early relapse. Results were adjusted by all covariates present in the final multivariate model. Boxes represent hazard ratios (letrozole : tamoxifen) and lines represent 95% confidence intervals. Values <1.0 favor letrozole. The size of the boxes is inversely proportional to the standard error of the hazard ratio. The dashed vertical line at 0.69 gives the overall hazard ratio estimate for endocrine treatment in the final multivariate Cox model.

nodal involvement, and who did not receive adjuvant systemic therapy, high grade and lymphovascular invasion are commonly considered prognostic factors for recurrence at 10 years of follow-up [8]. Data are somewhat conflicting regarding the prognostic value of steroid hormone receptor status. According to a retrospective study by Bardou et al. [9] in the absence of adjuvant tamoxifen, PgR negativity is not a poor prognostic factor. In patients treated with tamoxifen, ER+/PgR− tumors displayed more aggressive features compared with ER+/PgR+ tumors [9, 10]. However, in a retrospective study from two randomized trials of adjuvant tamoxifen versus no other treatment, Dowsett et al. [11] found that antiestrogen improves relapse-free survival in case of ER+ tumors, regardless of PgR status. Nevertheless, these results would be better analyzed taking into account expression level of PgR [12].

In patients treated with anastrozole in the ATAC trial, Dowsett et al. [13] found that those with ER+/PgR− tumors had the same prognosis as those with ER+/PgR+ tumors, and that anastrozole was more effective than tamoxifen in both groups. Analyses of early relapses are infrequently carried out, but can be used to inform treatment choices, particularly for high-risk patients. Our analysis showed that highest risk for early relapse is linked to tumor burden (tumor size, nodal involvement) and tumor aggressiveness (high grade, partial endocrine insensitivity, HER-2neu overexpression, vascular invasion). These findings are supported by three recent retrospective analyses carried out on patients treated with tamoxifen [14–16] or toremifene [16]. These studies identified grade 3 [14, 15],

lymph node involvement [14, 15], and low-positive ER status [14] as independent significant predictors of early relapse. Lymphovascular invasion, which was recognized as a poor prognostic factor in the St Gallen consensus conference [17], is an independent predictor of metastasis, particularly for patients with no nodal involvement [18, 19].

Even after controlling for predictors of high risk, we found that letrozole significantly reduced the risk of early relapse compared with tamoxifen. Despite the lack of significant interaction between endocrine treatment and the prognostic factors of early relapse, multivariate analyses indicated that the beneficial effect of letrozole versus tamoxifen may be qualitatively greater for patients with poor prognosis (four or more positive nodes, tumors >2 cm, or with vascular invasion) than for patients without poor prognosis (i.e. those with intermediate risk). For patients with intermediate risk of early relapse (less than four positive nodes, tumors ≤2 cm, and without vascular invasion), tamoxifen may be as effective as letrozole, and therefore sequential therapy may represent a good option, with toxicity profiles playing a greater role in therapy choice. Definitive evidence to support or refute this conjecture must await the results of ongoing randomized trials.

Curiously, letrozole appeared to be more effective than tamoxifen in patients with grade 1 tumors, though the number of recurrences in both treatment groups was low and almost 10% of patients did not have tumor grade available for analysis. Similarly, although HER-2 status was significant in the model, almost half of the patients did not have HER-2 measured and thus results and conclusions may change if all patients were assessed. Analysis of HER-2 as a predictive factor is important, considering that PgR expression and the HER-2 signaling pathway are linked [20, 21], and that among patients treated with adjuvant tamoxifen, ER+/PgR− tumors more frequently express HER-1 and HER-2, which are associated with poorer prognosis [10]. A similar analysis of early relapse would be useful once data from the BIG 1-98 second primary analysis on the role of switching become available.

In conclusion, letrozole resulted in a significant reduction in early relapse in BIG 1-98, even after adjusting for significant prognostic factors, which included node positivity, absence of both receptors being positive, high grade, HER-2 overexpression/amplification, large tumor size, and vascular invasion. Subgroup analyses of this large controlled randomized trial indicate that patients with high risk for early relapse may benefit most from upfront letrozole, while sequential therapy might be reserved for patients with intermediate risk, in whom tamoxifen did not differ significantly from letrozole. The second primary analysis of BIG 1-98, scheduled for 2008, will shed more light on this key question and will also address which sequence of tamoxifen and letrozole is best.

appendix

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