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Oestrogen receptor co-activator AIB1 is a marker of tamoxifen benefit in postmenopausal breast cancer

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Background: The oestrogen receptor (ER) co-activator amplified in breast cancer 1 (AIB1) has been suggested as a treatment predictive and prognostic marker in breast cancer. Studies have however not been unanimous.

Patients and methods: AIB1 protein expression was analysed by immunohistochemistry on tissue micro-arrays with tumour samples from 910 postmenopausal women randomised to tamoxifen treatment or no adjuvant treatment. Associations between AIB1 expression, clinical outcome in the two arms and other clinicopathological variables were examined.

Results: In patients with ER-positive breast cancer expressing low tumour levels of AIB1 (<75%), we found no significant difference in recurrence-free survival (RFS) or breast cancer-specific survival (BCS) between tamoxifen treated and untreated patients. In patients with high AIB1 expression (>75%), there was a significant decrease in recurrence rate (HR 0.40, 95% CI 0.26–0.61, $P < 0.001$) and breast cancer mortality rate (HR 0.38, 95% CI 0.21–0.69, $P = 0.0015$) with tamoxifen treatment. In the untreated arm, we found high expression of AIB1 to be significantly associated with lower RFS (HR 1.74, 95% CI 1.20–2.53, $P = 0.0038$).

Conclusion: Our results suggest that high AIB1 is a predictive marker of good response to tamoxifen treatment in postmenopausal women and a prognostic marker of decreased RFS in systemically untreated patients.

Key words: AIB1, breast cancer, HER2, prognosis, SRC-3, treatment prediction

Introduction

About two-thirds of all breast cancers are oestrogen receptor (ER) positive and proliferate in response to oestrogenic stimulation [1]. The anti-oestrogen tamoxifen has been the first-line endocrine therapy for both pre- and post-menopausal women for many years. However, some tumours are *de novo* resistant, and a substantial fraction will eventually develop resistance to tamoxifen over time [2].

Tamoxifen competes with endogenous oestrogens for binding to the ER, but the effect of the binding is dependent on the recruitment of co-activators and co-repressors that modulate ER transcriptional activity [3]. Oestrogen binding normally favours the recruitment of co-activators, while tamoxifen binding leads to recruitment of co-repressors and inhibited transcription of genes involved in cell proliferation [2]. Thus, it has been hypothesised that tamoxifen resistance is associated with an increase in the amount of co-activators, leading to an agonistic activity of ER-bound tamoxifen [4].

Amplified in breast cancer 1 (AIB1) has been suggested in the development of breast cancer and tamoxifen resistance. AIB1 is a member of the SRC family of nuclear receptor co-activators. The gene is amplified in 10% and the mRNA was found over-expressed in 64% of breast cancers [5]. AIB1 interacts with the ER and enhances oestrogen-dependent gene transcription [6]. In addition, AIB1 interacts with several signalling molecules mediating proliferation, survival and migration of cells, including human epidermal growth factor receptor 2 (HER2) [7]. Over-expression of AIB1 in breast cancer cell lines enhances both oestrogen-stimulated and hormone-independent cell proliferation and renders the cells resistant to anti-oestrogens [8]. In mouse models, AIB1 has been shown to be important for both normal mammary development and mammary tumour formation [9, 10].

Some previous studies have shown that high expression of AIB1 is associated with shorter survival, although others have found no such association or an association to increased survival [11–16]. Our aim was to investigate the role of AIB1 as a tamoxifen treatment predictive and prognostic marker by assessing the expression of AIB1 in tumours from women randomised to either adjuvant tamoxifen or no adjuvant therapy.

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materials and methods

patients

A cohort of 1780 postmenopausal women with breast cancer was randomised between adjuvant tamoxifen and no adjuvant therapy during 1976 through 1990. The patients had a tumour size < 30 mm and negative lymph node status (N0). The trial has been described in detail previously [17]. For the present study, it was possible to retrieve archived tumour tissue from 910 patients. The clinicopathological characteristics in this subset were similar to those in the complete cohort. The tumours were graded retrospectively according to the Nottingham system (NHG) by one pathologist blinded to clinical outcome. The mean follow-up period was 17 years. The study was approved by the local ethical committee at the Karolinska Institute, Stockholm, Sweden.

breast cancer tissue micro-array and immunohistochemistry for AIB1

Tissue micro-arrays (TMA) were constructed as previously described [18]. TMA sections were deparaffinised in xylene and rehydrated in a series of ethanol of decreasing concentration. Antigen retrieval was carried out by cooking in Tris-EDTA, pH 9. A mouse monoclonal antibody recognising the amino acids 376–389 was used as the primary antibody in a 1 : 100 dilution (clone 34, BD BioScience, San José, CA) and incubation was done overnight at 4°C. This antibody has been used previously [15], and it has been shown to be specific for AIB1 [19]. Further validation of the antibody is presented in supplementary Figure S1, available at *Annals of Oncology* online. For detection, the secondary antibody DAKO Envision+ System-HRP Labelled Polymer, was used (Dako North America, Inc., Carpinteria, CA).

staining evaluation

AIB1 immunostaining was evaluated by light microscopy by two independent observers blinded to clinicopathological information. In cases of discrepant scoring, a consensus score was reached after re-evaluation. A proportion score, representing the estimated proportion of stained cell nuclei (0: <1%; 1: 1%–25%; 2: 26%–75%; 3: 76%–100%) and an intensity score (0: no staining; 1: weak staining; 2: moderate staining; 3: strong staining) was assigned. The proportion and intensity scores were added to obtain a total score, ranging from 0 to 6. We considered a proportion score of 3 (>75%) as high frequency and an intensity score of ≥ 2 as high intensity. A total score of 0–3, 4 and 5–6 were considered as low, intermediate and high expression, respectively, dividing the patients into three groups of approximately equal size.

immunohistochemistry for ER, PgR and HER2

Retrospective immunohistochemical evaluation of the expression of ER and progesterone receptor (PgR) was previously described [18]. Positivity was defined as >25% stained nuclei. High ER expression was defined as $\geq 90\%$ positive cells. If immunohistochemical data were missing, ER positivity was defined as >0.05 fmol/ μ g DNA, based on biochemical assays carried out at the time of diagnosis [17]. Immunohistochemical staining for HER2 was carried out and scored (0, 1+, 2+, 3+) as described elsewhere [20].

statistical analysis

Recurrence-free survival (RFS) and breast cancer-specific survival (BCS) were chosen as primary end points. Correlation between AIB1 and other clinicopathological factors was evaluated using χ^2 -test or χ^2 -test for trend. Survival curves and probabilities of RFS and BCS were estimated using the Kaplan–Meier method. Hazard ratios were calculated using Cox hazard regression analysis. To test for the interaction between AIB1 and treatment

effect, a Cox model including AIB1, treatment and the interaction term treatment \times AIB1 was carried out. The pattern of the treatment effect of tamoxifen for different AIB1 levels was studied using subpopulation treatment effect pattern plots (STEPP) analysis [21]. The method used was the tailored version with $g = 11$. All statistical calculations were done with the statistical software STATISTICA 8.0 (StatSoft, Inc., Tulsa, OK). *P*-values <0.05 in two-sided tests were considered significant.

results

After excluding TMA cores that were missing or consisting of mainly stroma or non-malignant cells, 814 tumours (89.4%) were evaluated for AIB1 expression. The characteristics of the excluded tumours were similar to the ones included (data not shown). The flow of patients through the study is described in supplementary Figure S2, available at *Annals of Oncology* online.

AIB1 expression and association with clinicopathological factors

The expression of AIB1 was almost exclusively nuclear and therefore only staining of the nuclei was analysed. Different staining patterns of AIB1 are shown in supplementary Figure S1, available at *Annals of Oncology* online. AIB1 expression was found in 89.2% of the tumour samples. High staining frequency was found in 58.6% of the tumours and high staining intensity in 40.2%. When considering the total score, 31.7% were classified as having high expression of AIB1.

High staining frequency was correlated with expression of ER, PgR and HER2. Increasing total score was correlated with high tumour grade, PgR and expression of HER2 (supplementary Table S3, available at *Annals of Oncology* online). The association between AIB1 frequency score and ER

Table 1. Cox regression analysis of recurrence-free survival among patients with ER-positive tumours

	Recurrence-free survival		
	Tamoxifen versus no tamoxifen		
	Hazard ratio (95% CI)	<i>P</i> -value	^a <i>P</i> _{Interaction}
All ER+			
AIB1 frequency			
AIB1 $\leq 75\%$	0.77 (0.45–1.34)	0.36	0.023
AIB1 >75%	0.40 (0.26–0.61)	<0.001	
AIB1 total score			
0–3	0.66 (0.36–1.22)	0.18	0.46
4	0.47 (0.26–0.86)	0.015	
5–6	0.47 (0.28–0.81)	0.006	
Highly ER+ ($\geq 90\%$)			
AIB1 frequency			
AIB1 $\leq 75\%$	1.52 (0.57–4.1)	0.40	0.0036
AIB1 >75%	0.28 (0.15–0.52)	<0.001	
AIB1 total score			
0–3	1.07 (0.35–3.3)	0.91	0.079
4	0.52 (0.22–1.23)	0.14	
5–6	0.29 (0.13–0.63)	0.002	

Tamoxifen benefit in relation to AIB1 expression.

AIB1 amplified in breast cancer 1.

^aAdjusted for tumour size, NHG, PgR and HER2.

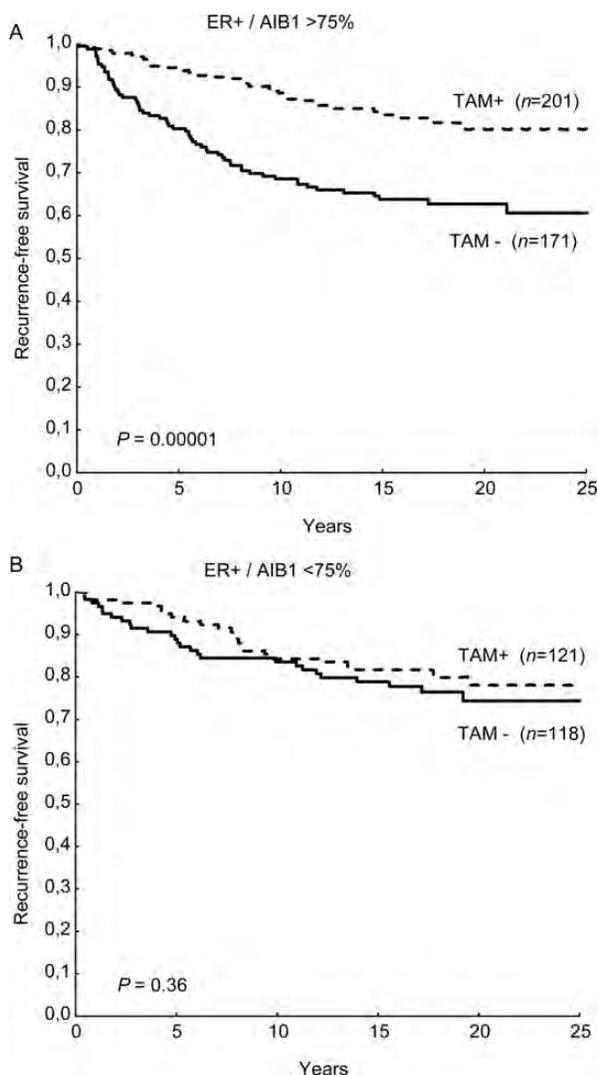


Figure 1. Kaplan–Meier estimates of recurrence-free survival (RFS) in tamoxifen-treated and -untreated patients in relation to AIB1 expression; AIB1 >75% (A) and AIB1 ≤75% (B).

became stronger when taking into account different levels of ER expression (<25%, 25%–89%, ≥90%) ($P < 0.001$).

AIB1 as a treatment predictive factor

In patients with ER-positive tumours with low AIB1 expression (total score 0–3 or proportion score <3) we found no significant difference in RFS between the group of patients receiving and those not receiving tamoxifen. In the group with intermediate (total score 4) or high AIB1 expression (total score 5–6), there was a significant increase in RFS with tamoxifen treatment. This was also true for patients with high proportion score (Table 1, Figure 1). High AIB1 expression was also associated with good benefit from tamoxifen in terms of BCS (HR = 0.38 95% CI 0.21–0.69 $P = 0.0015$). A test for interaction between AIB1 and tamoxifen benefit reached borderline significance ($P = 0.064$). However, when adjusting for tumour size, NHG, PgR and HER2, the interaction was

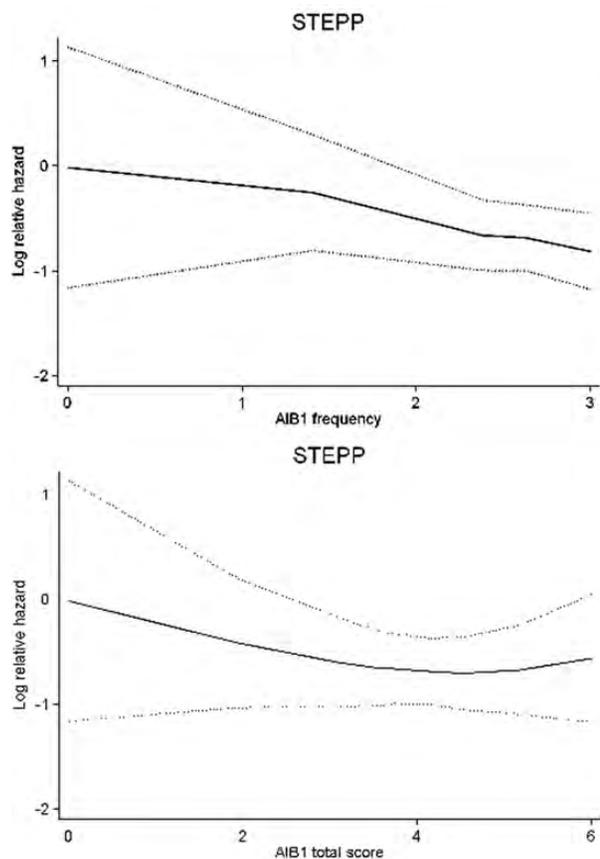


Figure 2. Sub-population treatment effect pattern plots (STEPP) showing the effect of tamoxifen for AIB1 frequency and AIB1 total score. Log-relative hazard for recurrence-free survival (RFS) with the corresponding 95% confidence interval (dotted lines) is plotted against the mean AIB1 for overlapping subgroups.

significant ($P = 0.023$) (Table 1). The intensity score alone was not significantly associated with differences in tamoxifen benefit (data not shown).

To further illustrate the trends in tamoxifen treatment effect in relation to AIB1 expression, we carried out STEPP analysis (Figure 2). The STEPP curves indicated that the benefit from tamoxifen was absent for low levels of AIB1 and increased with higher levels. As AIB1 and ER expression levels were correlated, we investigated whether AIB1 could predict the efficacy of tamoxifen also when restricting the analysis to patients with highly ER-positive tumours (ER > 90%). The significance of the interaction between AIB1 and treatment benefit was increased for this group of patients, showing that AIB1 is predictive in addition to ER (Table 1).

AIB1 as a prognostic factor

The prognostic importance of AIB1 was analysed in the group of patients not treated with tamoxifen. A high AIB1 proportion score was significantly associated with lower RFS (HR 1.74, 95% CI 1.20–2.53, $P = 0.0038$), as was a high total score of AIB1 in the ER-positive group (HR 1.66, 95% CI 1.09–2.52, $P = 0.019$) (Figure 3). The proportion score was not significantly associated with BCS, but showed a similar trend as for RFS (HR 1.49, 95%

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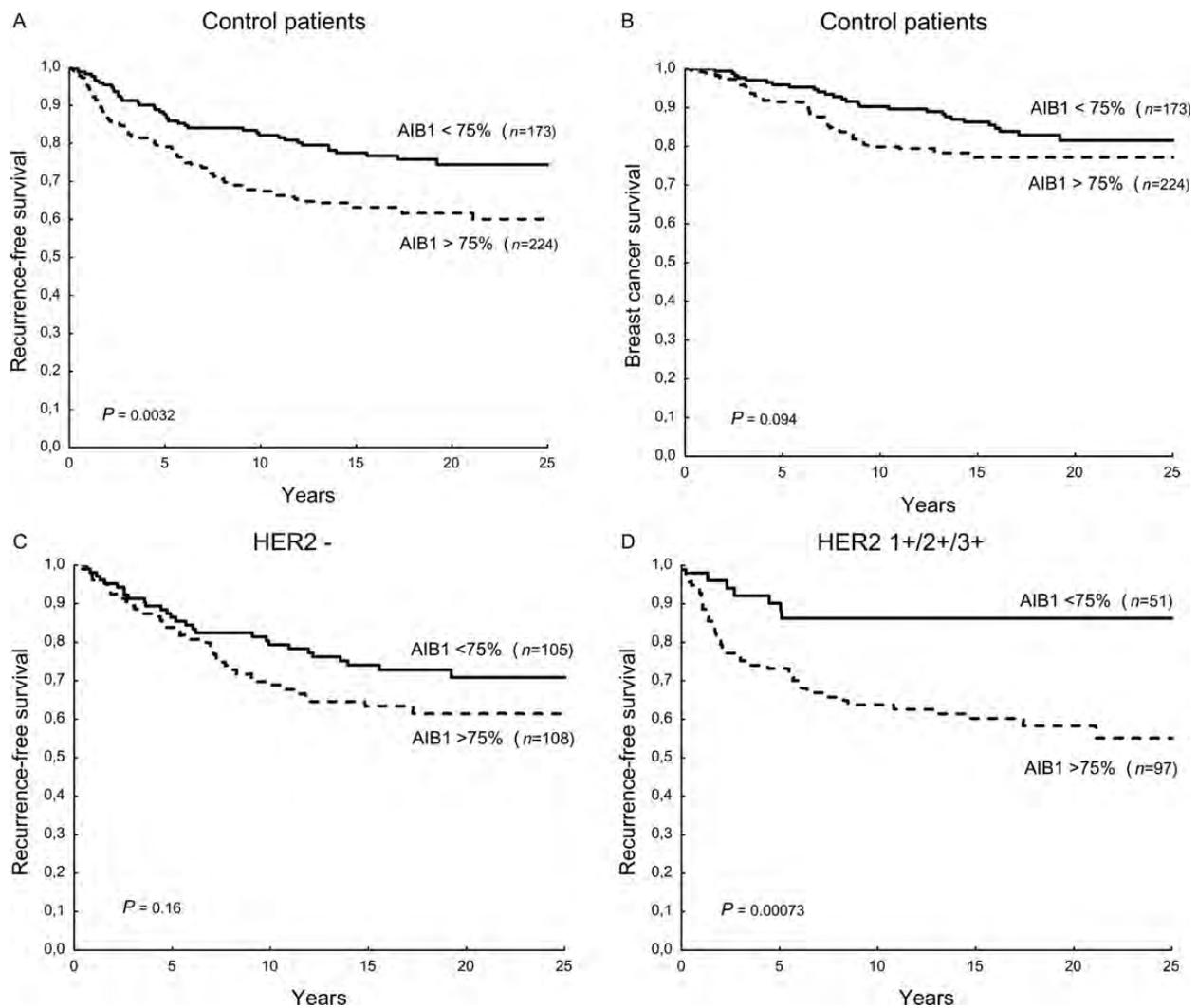


Figure 3. Kaplan-Meier estimates of recurrence-free survival (RFS) (A) and breast cancer survival (BCS) (B) in the control arm in relation to AIB1 expression. RFS was further analysed in relation to AIB1 and HER2 expression. RFS is shown for patients with tumours graded as HER2-negative (C) and HER2 1+/2+/3+ (D).

CI 0.93–2.39, $P = 0.098$), and tended to be associated with lower RFS also when restricting the analysis to ER-negative disease (HR 1.96, 95% CI 0.96–4.0, $P = 0.065$). Refining the analysis to more than two categories based on AIB1 frequency did not further improve the prognostic significance (data not shown). In multivariate analysis, AIB1 remained a significant prognostic factor (supplementary Table S4, available at *Annals of Oncology* online). The intensity of stained cells was not significantly associated with RFS (data not shown).

The prognostic significance of AIB1 frequency was clearly seen in patients with tumours expressing HER2 (HR 3.55, 95% CI 1.59–7.94, $P = 0.002$) as opposed to patients with tumours lacking HER2 (HR 1.41, 95% CI 0.87–2.29, $P = 0.16$) (Figure 3). A test for interaction between AIB1 and HER2 on the effect on RFS was significant ($P = 0.042$).

discussion

This cohort based on a randomised tamoxifen trial gave a unique opportunity to study AIB1 both as a treatment predictive and prognostic factor. High expression of AIB1

predicted a good response to tamoxifen treatment, but a poor prognosis among systemically untreated patients. Both results are consistent with the view of AIB1 being an important co-activator for ER signalling and as such a marker for oestrogen dependence. The association between AIB1 and tamoxifen efficacy was in particular evident when the tumours were highly ER positive.

The first study of AIB1 and clinical outcome by Osborne et al. [11] found high expression to be associated with lower survival in patients treated with tamoxifen. We found that there was no significant benefit from tamoxifen for patients with low AIB1 expression, in line with the findings reported by Alkner et al. [15], in which high expression of AIB1 was found to predict a good response to tamoxifen in premenopausal women. Our results suggest that high AIB1 could predict a good response to tamoxifen also for postmenopausal patients. In contrast to previous studies, the study by Alkner et al. [15] and the present were based on randomised, controlled trials.

Previous studies have used different cut-off values for positivity or high expression, and the results have varied from

10% to 75% [11–16]. When using the frequency score, we found over-expression in 59% of the tumours. This is similar to the finding that 64% of breast cancers over-express AIB1 mRNA [5]. The STEPP analysis suggests that the prediction of tamoxifen benefit may be favoured by a high cut-off value for the frequency score.

In patients not receiving tamoxifen, we found high expression of AIB1 to be associated with lower RFS and BCS, indicating that AIB1 could be a prognostic marker. The expression of AIB1 has been shown to increase when breast epithelium transforms from normal to malignant [22]. AIB1 may also increase the invasiveness of tumour cells [23]. This implicates that AIB1 could be important in tumour formation and subsequent spread of the cancer cells. Similar to our results, Alkner et al. [15] found that high AIB1 was associated with lower RFS in untreated patients. A recent report based on a large cohort confirmed that AIB1 has a negative impact on prognosis in ER-negative breast cancer [16], and our results suggest that this holds true also when confining the analysis to systemically untreated patients.

High expression of AIB1 was associated with expression of ER, PgR, HER2 and high tumour grade. The association between HER2 and AIB1 was stronger regarding the total score when compared with frequency score (supplementary Table S3, available at *Annals of Oncology* online), which indirectly reflects a strong association between HER2 and AIB1 intensity score. This in turn may explain why the ability to predict tamoxifen benefit was slightly different when applying the different AIB1 scores.

There is a bidirectional cross-talk between the ER and growth factor receptors. This may be a way of overcoming the antiproliferative effects of anti-oestrogens that could lead to insensitivity to tamoxifen in breast cancer cells over-expressing both AIB1 and HER2 [24]. Patients with tumours expressing high levels of both proteins exhibited the worst clinical outcome [11]. Similarly, others have found an association between AIB1 and shorter survival only in the subgroup over-expressing HER2 [12, 14]. We found that high expression of AIB1 was significantly associated with HER2 expression and the prognostic importance of AIB1 was only seen when the tumours also expressed HER2. For patients with tumours over-expressing both proteins, RFS was not increased in the tamoxifen-treated group. However, this group consisted of only 18 patients, and the results should be interpreted with caution.

In conclusion, our results suggest that high AIB1 is a predictive marker of tamoxifen benefit among postmenopausal women with ER-positive breast cancer and a prognostic marker of worse survival in systemically untreated patients. AIB1 has been shown to enhance the effects of oestrogen, which may be in accordance with the view of AIB1 as a negative prognostic factor that at the same time predicts good benefit from tamoxifen. However, this study does not exclude that a minor subgroup of patients with ER-positive tumours simultaneously over-expressing AIB1 and HER2 exhibit resistance to tamoxifen.

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disclosure

The authors have declared no conflicts of interest.

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Pathologic complete response to neoadjuvant chemotherapy with trastuzumab predicts for improved survival in women with HER2-overexpressing breast cancer

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Background: We sought to determine the prognostic value of pathologic response to neoadjuvant chemotherapy with concurrent trastuzumab.

Patients and methods: Two hundred and twenty-nine women with HER2/neu (HER2)-overexpressing breast cancer were treated with neoadjuvant chemotherapy plus trastuzumab between 2001 and 2008. Patients were grouped based on pathologic complete response (pCR, $n = 114$) or less than pCR (<pCR, $n = 115$); as well as by pathologic stage. Locoregional recurrence-free (LRFS), distant metastasis-free (DMFS), recurrence-free (RFS), and overall survival (OS) rates were compared.

Results: The median follow-up was 63 (range 53–77) months. There was no difference in clinical stage between patients with pCR or <pCR. Compared with patients achieving <pCR, those with the pCR had higher 5-year rates of LRFS (100% versus 95%, $P = 0.011$), DMFS (96% versus 80%, $P < 0.001$), RFS (96% versus 79%, $P < 0.001$), and OS (95% versus 84%, $P = 0.006$). Improvements in RFS and OS were seen with decreasing post-treatment stage. Failure to achieve a pCR was the strongest independent predictor of recurrence (hazard ratio [HR] = 4.09, 95% confidence interval [CI]: 1.67–10.04, $P = 0.002$) and death (HR = 4.15, 95% CI: 1.39–12.38, $P = 0.011$).

Conclusions: pCR and lower pathologic stage after neoadjuvant chemotherapy with trastuzumab are the strongest predictors of recurrence and survival and are surrogates of the long-term outcome in patients with HER2-overexpressing disease.

Key words: breast cancer, HER2, neoadjuvant chemotherapy, pathologic complete response, trastuzumab

Introduction

Potential benefits of neoadjuvant chemotherapy include tumor downsizing allowing appropriately selected patients to undergo

breast-conserving therapy (BCT), assessment of response to therapy, and early treatment of micrometastatic disease [1, 2]. Response to neoadjuvant chemotherapy is an early surrogate of long-term prognosis, as pathologic complete response (pCR) has been shown to correlate with an improved outcome [3–5].

With the routine use of trastuzumab, improvements in survival among women with HER2/neu (HER2)-overexpressing tumors have been demonstrated in the metastatic and adjuvant settings [6–10]. More recently, the efficacy of trastuzumab

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