Published in final edited form as:
Breast Cancer Res Treat. 2013 January ; 137(2): . doi:10.1007/s10549-012-2336-6.

Adding hormonal therapy to chemotherapy and trastuzumab improves prognosis in patients with hormone receptor-positive and human epidermal growth factor receptor 2-positive primary breast cancer

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Abstract

Adjuvant hormonal therapy for hormone receptor (HR)-positive primary breast cancer patients and a human epidermal growth factor receptor 2 (HER2)-targeted agent for HER2-positive primary breast cancer patients are standard treatment. However, it is not well known whether adding hormonal therapy to the combination of preoperative or postoperative chemotherapy and HER2-targeted agent contributes any additional clinical benefit in patients with HR-positive/HER2-positive primary breast cancer regardless of cross-talk between HR and HER2. We retrospectively reviewed records from 897 patients with HR-positive/ HER2-positive primary breast cancer with clinical stage I–III disease who underwent surgery between 1988 and 2009. We determined the overall survival (OS) and disease-free survival (DFS) rates according to whether they received hormonal therapy or not and according to the type of hormonal therapy, tamoxifen and aromatase inhibitor, they received. The median followup time was 52.8 months (range 1–294.6 months).

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Conflict of interest The authors have declared no conflict of interest.

Patients who received hormonal therapy with chemotherapy and trastuzumab (n = 128) had significantly higher OS and DFS rates than did those who received only chemotherapy and trastuzumab (n = 46) in log-rank analysis (OS 96.1 vs. 87.0 %, p = 0.023, DFS 86.7 vs. 78.3 %, p = 0.029). There was no statistical difference in OS or DFS between those given an aromatase inhibitor and those given tamoxifen. In multivariate analysis, receiving hormonal therapy in addition to the combination of chemotherapy and trastuzumab was the sole independent prognostic factor for DFS (hazard ratio 0.446; 95 % CI 0.200–0.992; p = 0.048), and there was a similar trend in OS. Our study supported that hormonal therapy, whether in the form of an aromatase inhibitor or tamoxifen, confers a survival benefit when added to chemotherapy and trastuzumab in patients with HR-positive/HER2-positive primary breast cancer. Adjuvant treatment without hormonal therapy is inferior for this patient population.

Keywords

Hormonal therapy; Hormone receptor; Human epidermal growth factor receptor 2; Breast neoplasm; Chemotherapy

Introduction

In primary breast cancer, the status of hormone receptors (HR), including estrogen receptor (ER) and progesterone receptor (PR), has long been recognized as a prognostic factor; it is also a predictive factor for the efficacy of hormonal therapy [1]. Adjuvant hormonal therapies, aromatase inhibitors (AIs) and tamoxifen are both used in therapies for ER-positive tumors, but they suppress the activity of estrogen using different mechanisms. Tamoxifen, a selective ER modulator, binds directly to ER and prevents estrogen from binding to the receptor. AIs, on the other hand, block aromatase activity and thus decrease the levels of ER ligands to suppress tumor activity. In postmenopausal women with ER-positive breast cancer who were treated in the adjuvant setting or for metastatic cancer, AI decreased mortality rates and decreased the risk of recurrence more than tamoxifen did [2, 3].

The other important marker, HER2, is overexpressed and/or amplified in approximately 15–25 % of breast cancers [4, 5]. Patients with HER2-positive breast cancer are usually given standard chemotherapy in combination with a monoclonal antibody targeting HER2, trastuzumab; trastuzumab prolongs progression-free survival and overall survival (OS) durations relative to those seen with standard chemotherapy alone [6, 7].

Whereas treatments for patients with either HR- or HER2-positive breast cancers are clear-cut, those for the coexpression of HR and HER2 are not. The implications of this uncertainty may be profound since the coexistence of these features is notable: tumors in 36–53 % of patients with HER2-positive breast cancer are also positive for ER and/or PR [7–10]. The National Comprehensive Cancer Network guidelines recommend adjuvant hormonal therapy for HR-positive breast cancer regardless of HER2 status [11]. However, some preclinical studies have found that when HR is coexpressed with HER2, there may be cross-talk between the HR and HER2 signaling pathways [5, 9, 12–14] and that this cross-talk may cause resistance to both AIs and tamoxifen [12, 15–19].

Conversely, the large randomized Arimidex, Tamoxifen Alone or in Combination (ATAC) trials showed that patients with ER-positive/HER2-positive breast cancer had a shorter time to recurrence than did those with ER-positive/HER2-negative breast cancer, regardless of whether patients received an AI or tamoxifen [20]. Also, Daly et al. [21] demonstrated that

there was no difference between the AI Letrozole and tamoxifen in terms of overall response rate in a preclinical model of HR-positive/HER2-positive primary breast cancer.

The joint analysis of data from the North Central Cancer Treatment Group (NCCTG) N9831 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 showed that the trastuzumab-containing chemotherapy arm had a better prognosis than did the control arm without trastuzumab in patients with HER2-positive primary breast cancer [22]. The combined data also showed the prognostic impact of hormone receptor status on disease-free survival (DFS) and OS in a multivariate analysis. These results contributed to the establishment of a standard treatment consisting of trastuzumab and hormonal therapy in addition to chemotherapy for HER2-positive patients. However, the effects of adding hormonal therapy only in patients with HR-positive/HER2-positive breast cancer have not been determined directly because most of the HR-positive patients in these studies had received hormonal therapy. Therefore, we still needed to determine whether adjuvant hormonal therapy contributes any additional benefit when added to chemotherapy and trastuzumab in the treatment of HR-positive/HER2-positive primary breast cancer. Hence, we set out to retrospectively analyze the clinicopathologic features and outcomes in a large group of patients. Specifically, we tested the hypothesis that receiving hormonal therapy in addition to the combination of preoperative or postoperative chemotherapy and trastuzumab contributes to a better prognosis than does not receiving hormonal therapy in patients with HR-positive/HER2-positive primary breast cancer. To evaluate this hypothesis and establish a baseline for comparison, we first assessed the prognostic impact of trastuzumab in our population. Next, we determined the OS and DFS rates in the groups of patients who did and did not receive hormonal therapy. Finally, to determine whether the type of hormonal therapy had an effect on prognosis, we looked for differential effects between tamoxifen and AI in this population.

Materials and methods

Patients

All clinical data for this study were collected from the Breast Cancer Management System database at The University of Texas MD Anderson Cancer Center in a protocol approved by our Institutional Review Board, which waived the need for written informed consent. We retrospectively reviewed data from patients with HR-positive/HER2-positive invasive primary breast cancer who were initially diagnosed as having clinical stage I–III disease and who underwent surgery between 1988 and 2009. Patients with a diagnosis of ductal carcinoma in situ or metaplastic carcinoma were excluded.

We identified 897 patients who had been diagnosed with HR-positive/HER2-positive primary breast cancer and had undergone surgery and who met the eligibility criteria for this study during this time period. We then extracted clinical and histologic information about the cases which had been copied from the patient medical records and entered prospectively into the above-mentioned database. Hormonal therapy had been administered sequentially after chemotherapy. In our review of the patients' medical records, we found that patients who had not received hormonal therapy regardless of receiving information on the benefit of receiving this therapy. We also found no records in which the prescribing oncologist had stated that hormonal therapy would be withheld because ER was expressed in less than 10 % of the tumor cells or because the therapy was contraindicated for other reasons.

Pathologic analyses

Samples from primary tumors were considered positive for ER or PR if ≥10 % of the cells had nuclear staining for the receptor on immunohistochemical analysis or if the status had

been coded “positive” in the medical records from hospitals where patients had been diagnosed as having HR-positive disease. *HR-positive disease* was defined as disease that was positive for ER and/or PR. HER2 status was evaluated by immunohistochemical analysis or fluorescence in situ hybridization. *HER2 positivity* was defined as a receptor overexpression staining score of 3+ on immunohistochemical analysis or gene amplification on fluorescence in situ hybridization such that the gene copy:CEP-17 ratio was greater than 2.0 [23].

Statistical methods

We assessed OS and DFS for patients who received chemotherapy and hormonal therapy with trastuzumab (n = 128) and without trastuzumab (n = 422) and for patients who received chemotherapy and trastuzumab with hormonal therapy (n = 128) and without hormonal therapy (n = 46). We further assessed the correlation between prognosis and type of hormonal therapy (AI or tamoxifen) in the 128 patients who received chemotherapy and hormonal therapy with trastuzumab and in the 481 patients who received chemotherapy and hormonal therapy (n = 422) or hormonal therapy only (n = 59). The clinicopathologic factors were also correlated with OS and DFS.

DFS was measured from the date of diagnosis to the date of first recurrence, distant metastasis, or last followup. OS was measured from the date of diagnosis to the date of death or last followup. DFS and OS rates were estimated by the Kaplan–Meier method and were compared between groups using the log-rank test. Cox proportional hazards models were used to determine the association between type of treatment and risk of recurrence after adjustment for other patient and disease characteristics. All statistical analyses were done by means of SPSS software, version 17 (SPSS Inc., Chicago, IL); p values less than 0.05 were considered statistically significant.

Results

Baseline clinicopathologic features and treatment details of the cases are summarized in Table 1. The median followup time was 52.8 months (range 1–294.6 months). Of the 897 patients, 310 (34.6 %) had recurrences during the followup period. Of the 796 patients who received chemotherapy, 729 (91.6 %) received anthracycline-based and 591 (74.2 %) received taxane-based chemotherapy; 557 (70.0 %) received both an anthracycline and a taxane. Of these 796 patients, 387 (48.6 %) received chemotherapy before surgery and 578 (72.6 %) received chemotherapy after surgery; 169 (21.2 %) received chemotherapy both before and after surgery. Of the 609 patients who received hormonal therapy, 417 (68.5 %) were given tamoxifen and 190 (31.2 %) were given an AI. Two patients (0.3 %) who were first given tamoxifen and then an AI were included in the AI group in this analysis. The median durations of tamoxifen and AI treatment were 26.2 months (range 1–182.6 months) and 26.1 months (range 1–67.4 months), respectively. A sizeable proportion of patients (n = 288, or 32.1 %) did not receive hormonal therapy. Of the 174 patients who received trastuzumab, 97 (55.7 %) did so in a neoadjuvant setting and 136 (78.2 %) in an adjuvant setting.

Trastuzumab added to chemotherapy and hormonal therapy

First, we assessed the effect of adding trastuzumab to hormonal therapy and chemotherapy. Patients who received trastuzumab with chemotherapy and hormonal therapy had significantly higher DFS rates than did patients who received only chemotherapy and hormonal therapy (86.7 vs. 61.1 % at the median followup time, p = 0.005, Fig. 1a). Also, patients who received chemotherapy and hormonal therapy with trastuzumab had

significantly higher OS rates than did patients who received chemotherapy and hormonal therapy without trastuzumab (96.1 vs. 73.2 %, $p = 0.038$, Fig. 1b).

Hormonal therapy added to chemotherapy and trastuzumab

Second, we assessed the effect of adding hormonal therapy to chemotherapy and trastuzumab. Some of the patients who received chemotherapy and trastuzumab refused to receive hormonal therapy regardless of the explanation of benefit. Patients who received hormonal therapy in addition to chemotherapy and trastuzumab had significantly higher DFS rates than did those who did not receive hormonal therapy with chemotherapy and trastuzumab (86.7 vs. 78.3 %, $p = 0.029$, Fig. 1c). Patients who received hormonal therapy with chemotherapy and trastuzumab also had significantly higher OS rates than did those who received only chemotherapy and trastuzumab (96.1 vs. 87.0 %, $p = 0.023$, Fig. 1d).

Comparison of/effects of AI and tamoxifen

Finally, we compared the effects of adding the two hormonal therapies (tamoxifen and AI) to chemotherapy to determine whether they had differential effects on DFS and/or OS. In the group of 128 patients who received chemotherapy and hormonal therapy with trastuzumab, 65 patients received tamoxifen and 63 patients received AI. There was no statistical difference between these two subgroups in terms of DFS or OS (DFS 85.7 vs. 87.7 %, $p = 0.819$, and OS 95.2 vs. 96.9 %, $p = 0.881$; Fig. 2a, b).

In the 481 patients who did not receive trastuzumab but did receive either chemotherapy and hormonal therapy or hormonal therapy alone, 352 patients received tamoxifen and 129 patients received AI. Again, there was no statistical difference between these groups in terms of DFS or OS (DFS 69.0 vs. 58.8 %, $p = 0.561$, and OS 84.5 vs. 68.8 %, $p = 0.479$; Fig. 2c, d).

Univariate and multivariate analysis of prognostic factors

Our final assessment looked at the prognostic impact of hormonal therapy and other clinicopathologic factors for the 174 patients who received chemotherapy and trastuzumab with hormonal therapy ($n = 128$) or without it ($n = 46$). On univariate analysis of the clinicopathologic factors, we found that the presence of metastasis to four or more lymph nodes [hazard ratio (HR) 2.735; 95 % CI 1.259–5.939; $p = 0.011$) was associated with increased risk of disease progression during the followup period and that lymphatic invasion in the surgical specimen (HR 1.989; 95 % CI 0.910–4.344; $p = 0.085$) showed a trend toward an increased risk of progression (Table 2). In multivariate analysis, receiving hormonal therapy in addition to chemotherapy and trastuzumab was the sole independent favorable prognostic factor in terms of DFS (HR 0.446; 95 % CI 0.200–0.992; $p = 0.048$).

Turning to OS, vascular invasion (HR 0.389; 95 % CI 1.115–13.146; $p = 0.033$) and lymphatic invasion (HR 3.777; 95 % CI 1.100–12.970; $p = 0.035$) in the surgical specimen were associated with higher risk of death during the followup period in univariate analysis (Table 3). Similar to the analysis of DFS, in multivariate analysis there was a trend of longer OS for those who received hormonal therapy in addition to chemotherapy and trastuzumab versus those who did not (HR 2.940; 95 % CI 0.858–10.072; $p = 0.086$); however, no factor had independent prognostic significance.

Discussion

We showed that adding hormonal therapy to the combination of preoperative and/or postoperative chemotherapy and trastuzumab confers a survival benefit to patients with HR-

positive/HER2-positive primary breast cancer. A noteworthy fact is that both AI and tamoxifen had an equivalent effect on prognosis for this patient population.

Since the U.S. Food and Drug Administration approved the use of trastuzumab in the adjuvant setting in November 2006, patients with HR-positive/HER2-positive primary breast cancer have received three-pronged treatments of the type examined here in clinical practice. However, no previous study has shown that adding adjuvant hormonal therapy to the combination of chemotherapy and anti-HER2 agents yields quantifiable advantages, and it is not possible to perform a randomized prospective study of this question because it is unethical to randomize someone out of the current standard of care. Therefore, we had to retrospectively assess the possible benefits of adding hormonal therapy in this patient population. In both univariate and multivariate analysis, we found that the three-pronged treatment provided significant improvement in DFS rates and a similar trend in OS rates, compared with chemotherapy and trastuzumab therapy without hormonal therapy.

Our results also indicate that any cross-talk that occurs between ER and HER2 is insufficient to degrade the effects of adding hormonal therapy to the chemotherapy-trastuzumab combination. Furthermore, we found that the specific hormonal agent used did not affect this finding. This result is in contrast to some previous results. For instance, others have asserted that the cross-talk between ER and HER2 is bidirectional and may cause resistance to both AI and tamoxifen in patients with HR-positive/HER2-positive breast cancer [15–17]. Dowsett et al. [24] found no significant benefit from adding tamoxifen to chemotherapy and trastuzumab for patients with HR-positive/HER2-positive breast cancer. However, as they noted, the number of patients ($n = 75$) was small and tamoxifen was administered for only 2 years. Furthermore, that study used a unique definition of HR positivity (H-score), making it difficult to compare those findings with others. Therefore, our results will provide a different perspective to this area of study.

Conversely, Elledge et al. [25] showed that HER2 expression in ER-positive metastatic breast cancer was not significantly associated with a poorer response to tamoxifen in terms of response rate, time to treatment failure, or survival time in 205 patients in the Southwest Oncology Group 8228 study who had not received any prior therapy for metastatic disease. The researchers suggested that other studies' data showing resistance to tamoxifen in this population might be due to those studies' inclusion of "ER-negative" tumors (that is, with <10 % of cells expressing ER); such tumors are known to be less likely to respond to tamoxifen than are those expressing higher levels of ER. In the group of postmenopausal women with HR-positive primary breast cancer in the ATAC trial [20], those treated with an AI had a longer time to recurrence than did those treated with tamoxifen. However, there was no difference in recurrence rates between the patients who received AI and tamoxifen at 5 years; this result is not conclusive because the number of late recurrences in the study was small. The investigators concluded that low expression of ER or PR or high expression of HER2 was associated with a high risk of recurrence. Indeed, in a subset analysis, HER2-positive patients had a higher recurrence rate than HER2-negative patients at 5 years ($p = 0.018$) [20].

The first randomized phase III study, the TAnDEM trial [26], revealed that the combination of trastuzumab and anastrozole resulted in a significantly longer median progression-free survival time (4.8 vs. 2.4 months, $p = 0.0016$) and a higher overall response rate (20.3 vs. 6.8 %) than did anastrozole alone in patients with HR-positive/HER2-positive metastatic breast cancer [26].

Our results showed that the triple combination of hormonal therapy, an anti-HER2 agent, and chemotherapy is the most effective treatment in HR-positive/HER2-positive primary

breast cancer in the adjuvant setting. This treatment appears to effectively block tumor cell proliferation and growth and improve prognosis over that conferred by monotherapy or the combination of any two of the agents, even if cross-talk does exist between the ER- and HER2-signaling pathways. Recently, Montemurro et al. [27] demonstrated a progression-free survival benefit was gained by adding hormonal therapy to chemotherapy and trastuzumab in patients with metastatic breast cancer ($p = 0.007$). In that study, trastuzumab was given not in a neoadjuvant or adjuvant setting but in a metastatic setting. We could show similar benefit of adding hormonal therapy in an adjuvant setting. Furthermore, we demonstrated the benefit of receiving hormonal therapy whether in the form of an AI or tamoxifen. Taken together, our findings and theirs suggest that adding hormonal therapy confer benefits regardless of the extent of disease.

There were some limitations to this retrospective study. First, the prescription of AIs is limited to postmenopausal women, but our study included both premenopausal and postmenopausal women. However, because age and menopausal status had no significant effect in terms of DFS and OS rates, we believe this limitation did not affect our results. This is also supported by the fact that the AI and tamoxifen groups did not differ. Second, we could not assess the association between quantitative expression levels of ER or PR and prognosis. We used a cutoff value of 10 % to define ER or PR positivity because all patients' disease was were diagnosed before the American Society for Clinical Oncology's revisions to the definition, and treatment had been performed accordingly. Our population also included patients from hospitals that did not include a quantitative expression level in the patients' medical records. However, we believe our results can be applied in clinical practice even without those quantitative assessments because of the very low revised cutoff values from the American Society of Clinical Oncology and the College of American Pathologists, which recommend that ER and PR assays be considered positive if even 1 % of tumor nuclei in a sample are positive [28]. Third, many patients did not receive hormonal therapy in this study. Although we could not find records describing whether low HR expression had influenced the prescription of hormone therapy or patients' refusal, not receiving hormone therapy as well as the level of HR expression might have affected the prognosis in this population.

Because there are signaling pathways influenced by both ER and HER2, additional molecules could be targeted to overcome more cross-talk and further boost response. ER regulates cellular proliferation and survival through genomic and nongenomic signaling pathways [5, 29]. Phosphorylation of HER2 activates downstream signaling pathways, including the PI3K/Akt/mTOR and mitogen-activated protein pathways [30]. Cross-talk thus exists not only between ER and HER2 but also among other epidermal growth factor families [5]. To further block interaction between ER and HER2 signaling pathways, one could combine novel agents targeting these signaling pathways, e.g., mTOR inhibitors, with hormonal therapy; this approach has great potential to further benefit patients with HR-positive/HER2-positive breast cancer.

In summary, we report that hormonal therapy, whether with an AI or tamoxifen, added to the combination of preoperative or postoperative chemotherapy and trastuzumab improves the prognosis of patients with HR-positive/HER2-positive primary breast cancer. Preoperative and/or postoperative chemotherapy and trastuzumab without adjuvant hormonal therapy is an inferior treatment for this patient group.

Acknowledgments

We thank Kathryn B. Carnes and Maude Veech from the Department of Scientific Publications at The University of Texas MD Anderson Cancer Center for the editorial review. This research was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant CA016672, by the Nellie B. Connally

Breast Cancer Research Fund, by NIH Grant R01 CA123318, by the Morgan Welch Inflammatory Breast Cancer Research Program, and by the State of Texas Rare and Aggressive Breast Cancer Research Program Grant.

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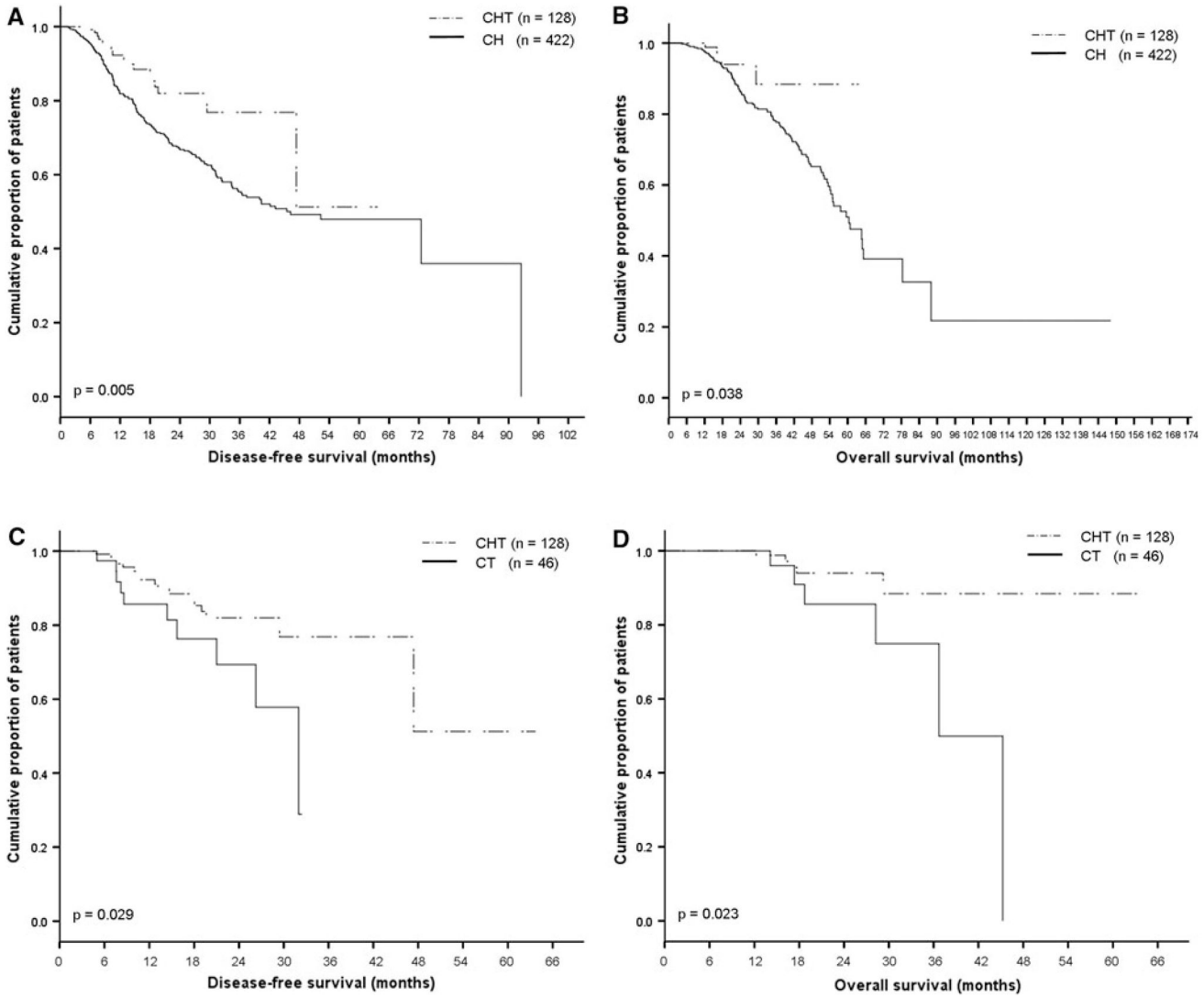

Fig. 1.

Kaplan–Meier survival curves for **a** DFS for CHT versus CH, **b** OS for CHT versus CH, **c** DFS for CHT versus CT, and **d** OS for CHT versus CT

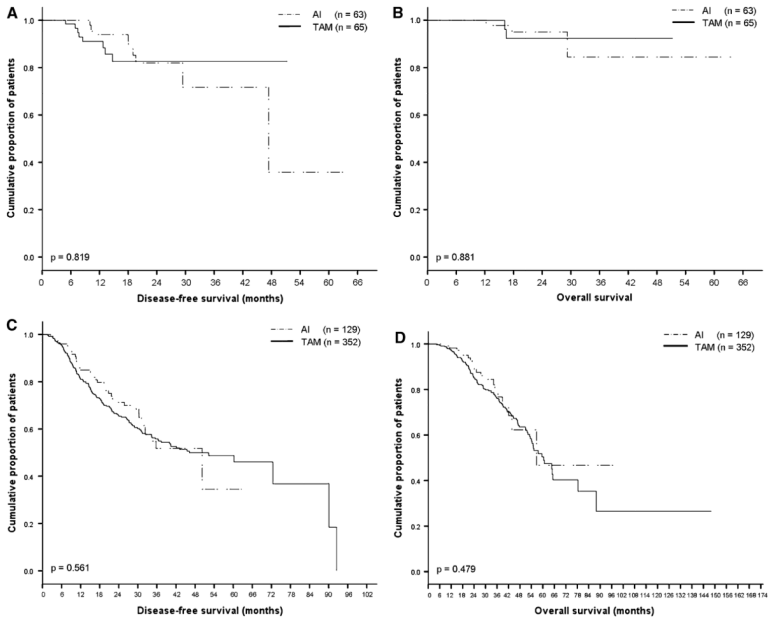

Fig. 2.

Kaplan–Meier survival curves for aromatase inhibitor vs tamoxifen: **a** DFS for CHT, **b** OS for CHT, **c** DFS for CH or hormonal therapy alone, and **d** OS for CH or hormonal therapy alone. *CHT* chemotherapy, hormonal therapy, and trastuzumab, *CH* chemotherapy and hormonal therapy, *CT* chemotherapy and trastuzumab, *DFS* disease-free survival, *OS* overall survival

Table 1

Patient and clinicopathologic characteristics

Characteristic	
Median age (range)	48 years (21–91)
Median followup time (range)	1,584 days (27–8892)
Menopausal status	
Premenopausal	416 (46.4 %)
Postmenopausal	474 (52.8 %)
N/A	7 (0.8 %)
Median tumor size (range)	2.3 cm (0–25 cm)
Tumor grade	
1 and 2	267 (29.8 %)
3	620 (69.1 %)
N/A	14 (1.6 %)
Lymph node metastasis status	
0	285 (31.8 %)
1–3	361 (40.2 %)
≥4	251 (28.0 %)
Pathologic stage	
0	75 (8.4 %)
I	80 (8.9 %)
II	585 (65.2 %)
III	157 (17.5 %)
Treatment	
Chemotherapy, trastuzumab, and hormonal therapy	128 (14.3 %) TAM: 65 (7.3 %), AI: 63 (7.0 %)
Chemotherapy and trastuzumab	46 (5.1 %)
Chemotherapy and hormonal therapy	422 (47.0 %) TAM: 318 (35.4 %), AI: 104 (11.6 %)
Chemotherapy alone	200 (22.3 %)
Hormonal therapy alone	59 (6.6 %) TAM: 34 (3.8 %), AI: 25 (2.8 %)
None	42 (4.7 %)
Survival status at last followup	
Alive	675 (75.3 %)
Dead	222 (24.7 %)
Recurrence at last followup	
Yes	310 (34.6 %)
No	587 (65.4 %)

Data are number of patients (%) unless otherwise specified

E, estrogen receptor, *PR* progesterone receptor, *N/A* not available, *TAM* tamoxifen, *AI* aromatase inhibitor

Table 2

Predictors of DFS in univariate and multivariate Cox regression analysis

Characteristic	Univariate analysis				Multivariate analysis			
	p	HR	95 % CI		*p*	HR	95 % CI	
			Lower	Upper			Lower	Upper
Age, years (<50 vs. ≥50)	0.382	0.705	0.322	1.545	–	–	–	–
Menopausal status (pre- vs. post-)	0.690	1.168	0.545	2.499	–	–	–	–
Pathologic stage (0 vs. I)	0.660	0.293	0.079	1.087	–	–	–	–
Pathologic stage (0 vs. II)	0.079	0.246	0.051	1.174	–	–	–	–
Pathologic stage (0 vs. III)	0.230	0.590	0.249	1.397	–	–	–	–
Tumor size	0.176	1.081	0.966	1.209	–	–	–	–
Lymph node metastasis (0–3 vs. ≥4)	0.011	2.735	1.259	5.939	0.089	2.171	0.889	5.300
Tumor grade (1 and 2 vs. 3)	0.798	1.128	0.447	2.847	–	–	–	–
Lymphatic invasion (negative vs. positive)	0.085	1.989	0.910	4.344	1.451	0.590	3.568	1.451
Vascular invasion (negative vs. positive)	0.165	1.748	0.795	3.842	–	–	–	–
Expression of Ki-67	0.890	0.997	0.957	1.039	–	–	–	–
Postoperative local radiation therapy (received vs. not received)	0.744	1.148	0.502	2.625	–	–	–	–
Hormonal therapy (received vs. not received)	0.034	0.424	0.192	0.938	0.048	0.446	0.200	0.992

DFS disease-free survival, *CI* confidence interval, *HR* hazard ratio

Table 3

Predictors of OS in univariate and multivariate Cox regression analysis

Characteristic	Univariate analysis				Multivariate analysis			
	p	HR	95 % CI		*p*	HR	95 % CI	
			Lower	Upper			Lower	Upper
Age, years (<50 vs. ≥50)	0.604	0.722	0.211	2.468	–	–	–	–
Menopausal status (pre- vs. post-)	0.955	0.966	0.289	3.224	–	–	–	–
Pathologic stage (0 vs. I)	0.974	0.000	0.000	–	–	–	–	–
Pathologic stage (0 vs. II)	0.105	0.161	0.018	1.462	–	–	–	–
Pathologic stage (0 vs. III)	0.088	0.320	0.086	1.186	–	–	–	–
Tumor size	0.620	1.051	0.862	1.282	–	–	–	–
Lymph node metastasis (0–3 vs. ≥4)	0.125	2.552	0.772	8.434	–	–	–	–
Tumor grade (1 and 2 vs. 3)	0.803	0.844	0.224	3.189	–	–	–	–
Lymphatic invasion (negative vs. positive)	0.035	3.777	1.100	12.970	0.685	0.399	0.005	34.039
Vascular invasion (negative vs. positive)	0.033	3.829	1.115	13.146	0.919	0.793	0.009	70.007
Expression of Ki67	0.874	0.994	0.924	1.070	–	–	–	–
Postoperative local radiation therapy (received vs. not received)	0.972	1.024	0.272	3.862	–	–	–	–
Hormonal therapy (received vs. not received)	0.033	0.275	0.084	0.903	0.086	2.940	0.858	10.072

OS overall survival, *CI* confidence interval, *HR* hazard ratio