Keywords: trastuzumab; neoadjuvant therapy; pathologic complete response; adjuvant therapy; survival

Effect of adjuvant trastuzumab among patients treated with anti-HER2-based neoadjuvant therapy

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Purpose: To study the impact of adjuvant trastuzumab among patients achieving a pathologic complete response (pCR) after trastuzumab-based neoadjuvant systemic therapy (NST).

Patients and methods: Patients with primary HER2-positive breast cancer treated with trastuzumab-based NST were categorised according to adjuvant trastuzumab administration and pCR status. Adjuvant trastuzumab became standard of care in 2006, this was the main reason patients in our cohort did not receive adjuvant trastuzumab. Kaplan–Meier was used to estimate survival. A test for interaction between adjuvant trastuzumab and pCR was completed.

Findings: Of 589 patients, 203 (34.5%) achieved a pCR. After surgery, 109 (18.5%) patients in the entire cohort did not receive adjuvant trastuzumab. Among patients achieving a pCR, 31.3% received adjuvant trastuzumab compared with 68.8% among those who did not achieve a pCR ($P=0.0006$). Among patients achieving pCR, adjuvant trastuzumab did not further improve overall survival (OS) or relapse-free survival (RFS) ($P=0.35$ and $P=0.93$, respectively). Any benefit of adjuvant trastuzumab in OS and RFS among patients without a pCR did not achieve statistical significance ($P=0.3$ and $P=0.44$, respectively).

Conclusions: In this cohort, patients treated with trastuzumab-based NST who achieved a pCR have excellent outcome regardless of whether they received adjuvant trastuzumab.

Neoadjuvant systemic therapy (NST) is commonly used to downstage the primary tumour and regional lymph nodes preoperatively, in order to increase operability and enable breast-conserving surgery in patients with large primary tumours or locally advanced disease (Fisher *et al*, 1998; Galow *et al*, 2008). NST also allows the assessment of the effectiveness of the systemic treatment by pathologic evaluation of the breast and nodes removed at surgery (Galow *et al*, 2008; Cortazar *et al*, 2014).

A pathologic complete response (pCR) in the breast and nodes is associated with favourable survival outcomes. However, this association is stronger among patients with highly proliferative, HER2-positive breast cancers (Untch *et al*, 2011; Kim *et al*, 2013; Cortazar *et al*, 2014).

HER2 is overexpressed in approximately 15–25% of primary breast cancers (Wolff *et al*, 2013). In the neoadjuvant setting, randomised trials have shown that the use of trastuzumab-based

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NST increases pCR rates compared with chemotherapy alone (Buzdar *et al*, 2005; Gianni *et al*, 2014), and recent data demonstrated that dual anti-HER2 therapy combined with chemotherapy further increases pCR rates as compared with trastuzumab-based chemotherapy (Baselga *et al*, 2012; Gianni *et al*, 2012).

Although 1 year of trastuzumab therapy is considered the standard of care today, several studies have been designed to look at shorter or longer treatment times (Goldhirsch *et al*, 2013; Pivot *et al*, 2013). A recent randomised trial comparing 6 months of adjuvant trastuzumab therapy vs 1 year failed to show that 6 months of adjuvant trastuzumab treatment was non-inferior to 12 months (Pivot *et al*, 2013). The impact of adjuvant trastuzumab among patients achieving a pCR after trastuzumab-based NST is unknown. We therefore, aimed to evaluate the impact of completion of adjuvant trastuzumab according to pCR status.

PATIENTS AND METHODS

A retrospective review of the Breast Medical Oncology Institutional database at The University of Texas MD Anderson Cancer Center was performed. Women with HER2-positive primary invasive breast cancer who received trastuzumab-based NST from 2001 to 2012 were identified. Adjuvant trastuzumab became standard of care in 2006; this was the main reason patients in our cohort did not receive adjuvant trastuzumab in earlier years. Patients were classified according to whether they had received adjuvant trastuzumab or not. Data were extracted on relevant prognostic factors including year of diagnosis, age, menopausal status, race, histology, grade, lymphovascular invasion (LVI), oestrogen receptor status, progesterone receptor status, adjuvant radiation, and adjuvant endocrine therapy. pCR was defined as no evidence of invasive cancer in the breast and lymph nodes (yT0/is,N0).

Patient characteristics were tabulated and compared between the adjuvant trastuzumab vs no adjuvant trastuzumab groups using Chi-square test. Overall survival (OS) was measured from the date of diagnosis to the date of death or lost to follow-up. Relapse-free survival (RFS) was measured from the date of diagnosis to the date of first documented local or distant recurrence. Patients who died before experiencing the relevant events were considered censored for RFS at their dates of last follow-up. The Kaplan–Meier product limit method was used to estimate the 5-year OS and RFS with 95% confidence intervals (CIs) of all patients, and compared using the log-rank statistic. Cox proportional hazards models were fit to determine the association of patient and clinical characteristics with survival outcomes. Initially, a Cox proportional hazard model that included pCR, adjuvant trastuzumab and the interaction between both covariates was tested. Because of rare events in one of the groups defined by the two variables, Firth's penalised likelihood approach was applied to obtain a finite estimate for the coefficient (Firth, 1993). The profile-likelihood confidence limits for the hazard ratios (HR) are presented. Variables were included in the final Cox multivariate model based on both statistical significance and clinical relevance including adjuvant trastuzumab, pCR, race, clinical stage at presentation, hormone receptor status, and LVI, year of diagnosis and adjuvant endocrine therapy. Results are expressed in HR and 95% CIs. *P* values less than 0.05 were considered statistically significant; all tests were two-sided. Statistical analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC, USA) and S-Plus 8.2 (TIBCO Software Inc., Houston, TX, USA).

RESULTS

A total of 589 women with HER2-positive breast cancer diagnosed between 2001 and 2012 were identified. Patients received NST with

either PH-FECH (paclitaxel 80 mg m⁻² intravenously weekly for 12 weeks or paclitaxel 225 mg m⁻² intravenously over 24 h every 3 weeks, followed by 4 cycles of FEC-75 (5-fluorouracil 500 mg m⁻², epirubicin 75 mg m⁻², and cyclophosphamide 500 mg m⁻²) intravenously on day 1, every 3 weeks. A loading dose of 4 mg kg⁻¹ intravenously trastuzumab was given on day 1 followed by 2 mg kg⁻¹ weekly, during the 24 weeks of NST). After surgery, 109 (18.5%) patients did not receive adjuvant trastuzumab, and 480 (81.5%) patients received adjuvant trastuzumab for 6 months to complete 1 year of therapy. Patient characteristics by adjuvant trastuzumab therapy are presented in Table 1. There were no significant differences amongst clinical and pathologic factors. A total of 203 patients (34.5%) achieved a pCR. Among them, 73.9% of the patients received adjuvant trastuzumab compared with 85.5% of patients not achieving a pCR (*P* = 0.0006).

At a median follow-up of 45 months, (range, 9–144 months), 38 patients (6.5%) had died, and 61 (10.4%) had experienced a recurrence. Table 2 summarises the 5-year OS and RFS estimates by patient and tumour characteristics. For the overall cohort, 5-year OS and RFS were 93% and 87%, respectively. The 5-year OS estimates were 91% and 93% for patients who did not or did receive adjuvant trastuzumab (*P* = 0.97); and the 5-year RFS estimates were 92% and 85% for patients who did not or did receive adjuvant trastuzumab (*P* = 0.33), respectively. When comparing patients who did not or did achieve a pCR after NST, the 5-year OS estimates were 90% and 98% (*P* = 0.002), respectively; and the 5-year RFS estimates were 83% and 95% (*P* < 0.0001), respectively. The Kaplan–Meier estimates of OS and RFS stratified by adjuvant trastuzumab and pCR status are presented in Figure 1.

On multivariate analysis, there was no significant interaction between adjuvant trastuzumab and pCR on OS (*P* = 0.32) or RFS (*P* = 0.15). After adjustment for year of diagnosis, pCR, race, clinical stage at presentation, hormone receptor status, LVI and adjuvant endocrine therapy, adjuvant trastuzumab had no significant impact on OS (HR = 0.75; 95% CI = 0.31–1.78; *P* = 0.51) or RFS (HR = 1.10; 95% CI = 0.52–2.33; *P* = 0.81). As expected, patients who achieved a pCR had a decreased risk of death (HR = 0.23; 95% CI = 0.08–0.60; *P* = 0.003) and recurrence (HR = 0.22; 95% CI = 0.1–0.49; *P* = 0.0002). In addition, black race (HR = 2.07; 95% CI = 1.11–3.87; *P* = 0.022), clinical stage III disease at diagnosis (HR = 2.28; 95% CI = 1.3–3.99; *P* = 0.004), and the presence of LVI (HR = 2.28; 95% CI = 1.33–3.93; *P* = 0.003) were associated with an increased risk of recurrence (Table 3).

DISCUSSION

This study was undertaken to evaluate the impact of completion of adjuvant trastuzumab in patients with HER2-positive disease treated at our institution according to pCR status. In this cohort of patients treated with trastuzumab-based NST, those who achieved a pCR had an excellent outcome regardless of whether they received adjuvant trastuzumab or not.

In our initial trastuzumab-based neoadjuvant study, patients received trastuzumab for only 24 weeks during chemotherapy and did not receive adjuvant trastuzumab following local therapy because adjuvant trastuzumab was, at the time, not part of the standard of care (Buzdar *et al*, 2007). This practice was continued until trastuzumab was approved in the adjuvant setting with the recommended duration of 1 year of treatment. To our knowledge, this is the only cohort of patients available to evaluate the impact of adjuvant trastuzumab among patients who achieved a pCR. A recently published retrospective study evaluating the outcomes of patients with HER2-positive breast cancer reported that 65 (8.4%) of the 776 patients in the study did not receive adjuvant

Table 1. Patient and tumour characteristics

	All patients (N= 589)	No adjuvant trastuzumab (N= 109)		Adjuvant trastuzumab (N= 480)		P-value
	N (%)	N	%	N	%	
Year of diagnosis						
2001–2006	142 (24.1%)	80	73.4	62	12.9	<0.0001
2007–2012	447 (75.9%)	29	26.6	418	87.1	
Age (years)						
Age ≤50	293 (49.7%)	52	47.7	241	50.2	0.64
Age > 50	296 (50.3%)	57	52.3	239	49.8	
Race/ethnicity						
White	344 (58.4%)	66	60.6	278	57.9	0.78
Black	73 (12.4%)	15	13.8	58	12.1	
Hispanic	116 (19.7%)	20	18.3	96	20.0	
Other	56 (9.5%)	8	7.3	48	10.0	
Clinical stage						
I	8 (1.4%)	2	1.9	6	1.3	0.50
II	293 (50.3%)	59	54.6	234	49.3	
III	282 (48.4%)	47	43.5	235	49.5	
Histology						
Ductal	543 (92.2%)	102	93.6	441	91.9	0.55
Other	46 (7.8%)	7	6.4	39	8.1	
Nuclear grade						
1–2	123 (21.4%)	86	78.9	366	78.5	0.93
3	452 (78.6%)	23	21.1	100	21.5	
Lymphovascular invasion						
Negative	479 (81.3%)	92	84.4	387	80.6	0.36
Positive	110 (18.7%)	17	15.6	93	19.4	
Hormone receptor status						
Negative	236 (40.4%)	51	46.8	185	38.9	0.13
Positive	348 (59.6%)	58	53.2	290	61.1	
Pathologic complete response						
No	386 (65.5%)	56	51.4	330	68.8	0.0006
Yes	203 (34.5%)	53	48.6	150	31.3	
Adjuvant radiation						
No	125 (21.2%)	24	22.0	101	21.0	0.82
Yes	464 (78.8%)	85	78.0	379	79.0	
Adjuvant endocrine therapy						
No	301 (51.1%)	59	54.1	242	50.4	0.48
Yes	288 (48.9%)	50	45.9	238	49.6	

trastuzumab, however, outcomes in this group were not discussed (Takada *et al*, 2014).

Although the test for interaction in the analysis of our patient cohort was negative, we applied a Firth's penalised likelihood approach to obtain a finite estimate for the coefficients and the profile-likelihood confidence limits for the HR in the multivariable analysis to compensate for our limited sample size before commit to our conclusions (Firth, 1993).

Currently, there is compelling evidence from large phase III randomised clinical trials including approximately 12 000 patients supporting the standard use of adjuvant trastuzumab for 1 year. On the basis of the results of the FinHER study (Joensuu *et al*, 2009), shorter adjuvant trastuzumab regimens are being evaluated (9 weeks, 3 months, and 6 months), but only one has been fully reported. Results from the PHARE trial failed to show that 6 months of trastuzumab is non-inferior to 12 months. Nevertheless, the cardiac safety profile was more favourable for the shorter treatment (Pivot *et al*, 2013). The results of other on-going or recently completed studies are not expected before 2015, at which time they might be less relevant given that dual anti-HER2 therapy with pertuzumab and trastuzumab is now part of the new standard of care.

As our treatment armamentarium increases, we continue to struggle to find biomarkers capable of identifying those patients with HER2-positive breast cancer who need less extensive or less complex therapies, and pCR after adequate NST may be a good surrogate. All anti-HER2-based NST studies have shown that patients who achieved a pCR at the time of surgery have an excellent prognosis and the majority are probably cured (Buzdar *et al*, 2007; Untch *et al*, 2011; Baselga *et al*, 2012; Bayraktar *et al*, 2012; Gianni *et al*, 2012; Buzdar *et al*, 2013; Cortazar *et al*, 2014; Gianni *et al*, 2014). The use of maintenance trastuzumab to complete a year of therapy is considered standard, and no data are available to support the use of pertuzumab, T-DM1, or lapatinib in the adjuvant setting; further, the neoadjuvant studies adding lapatinib and pertuzumab only used these targeted therapies in the pre-operative portion of the treatment (Baselga *et al*, 2012; Gianni *et al*, 2012). Our work is limited by its retrospective nature and limited sample size; despite including in the multivariable model important clinical variables, residual confounding cannot be excluded. Furthermore, selection bias is a potential concern because we do not have specific information on the reason a patient was prescribed further adjuvant trastuzumab or not. Our results are hypothesis-generating and need to be interpreted with

Table 2. Survival estimates by patient characteristics							
	N Patients	N Events	5-year overall survival estimate (95% CI)	P-value	N Events	5-year relapse-tree survival estimate (95% CI)	P-value
All patients	589	38	0.93 (0.9, 0.95)		61	0.87 (0.84, 0.9)	
Year of diagnosis							
2001–2006	142	14	0.92 (0.86, 0.96)	0.60	19	0.88 (0.82, 0.93)	0.64
2007–2012	447	24	0.93 (0.89, 0.95)		42	0.86 (0.8, 0.9)	
Age (years)							
Age ≤ 50	293	19	0.93 (0.88, 0.96)	0.78	30	0.87 (0.82, 0.91)	0.80
Age > 50	296	19	0.92 (0.88, 0.95)		31	0.87 (0.82, 0.91)	
Race/ethnicity							
White	344	23	0.92 (0.88, 0.95)	0.39	33	0.89 (0.85, 0.92)	0.03
Black	73	6	0.89 (0.77, 0.95)		13	0.72 (0.55, 0.84)	
Hispanic	116	4	0.98 (0.92, 0.99)		7	0.92 (0.83, 0.96)	
Other	56	5	0.87 (0.71, 0.95)		8	0.84 (0.71, 0.92)	
Clinical stage							
I–II	301	17	0.93 (0.89, 0.96)	0.42	22	0.9 (0.85, 0.94)	0.01
III	282	20	0.92 (0.87, 0.95)		38	0.84 (0.79, 0.88)	
Histology							
Ductal	543	34	0.93 (0.9, 0.95)	0.56	54	0.88 (0.84, 0.91)	0.26
Other	46	4	0.91 (0.74, 0.97)		7	0.82 (0.64, 0.92)	
Nuclear grade							
1–2	123	7	0.93 (0.84, 0.97)	0.57	14	0.86 (0.76, 0.92)	0.71
3	452	30	0.93 (0.89, 0.95)		45	0.88 (0.84, 0.91)	
Lymphovascular invasion							
Negative	479	24	0.94 (0.91, 0.96)	0.002	37	0.9 (0.87, 0.93)	<0.0001
Positive	110	14	0.86 (0.76, 0.92)		24	0.72 (0.6, 0.81)	
Hormone receptor status							
Negative	236	18	0.92 (0.86, 0.95)	0.53	24	0.88 (0.82, 0.92)	0.77
Positive	348	20	0.93 (0.89, 0.96)		36	0.87 (0.82, 0.91)	
Pathologic complete response							
No	386	33	0.9 (0.85, 0.93)	0.002	54	0.83 (0.78, 0.87)	<0.0001
Yes	203	5	0.98 (0.93, 0.99)		7	0.95 (0.9, 0.98)	
Adjuvant trastuzumab							
No	109	11	0.91 (0.84, 0.95)	0.97	12	0.92 (0.85, 0.96)	0.33
Yes	480	27	0.93 (0.9, 0.95)		49	0.85 (0.8, 0.89)	
Adjuvant radiation							
No	125	8	0.94 (0.86, 0.97)	0.69	10	0.89 (0.79, 0.95)	0.63
Yes	464	30	0.92 (0.89, 0.95)		51	0.87 (0.83, 0.9)	
Adjuvant endocrine therapy							
No	301	23	0.91 (0.87, 0.94)	0.17	31	0.87 (0.82, 0.91)	0.84
Yes	288	15	0.94 (0.89, 0.96)		30	0.87 (0.82, 0.91)	
Abbreviation: CI = confidence interval.

Figure 1. Kaplan–Meier OS estimates (A) and RFS estimates (B) according to adjuvant trastuzumab use and pCR status.

Table 3. Multivariable Cox proportional hazards models						
	Overall survival			Relapse-free survival		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Adjuvant trastuzumab vs no	0.75	0.31–1.78	0.51	1.1	0.52–2.33	0.81
Year of diagnosis: 2001–2006 vs 2007–2012	0.78	0.34–1.79	0.56	1.13	0.59–2.17	0.72
pCR vs no	0.23	0.08–0.6	0.003	0.22	0.1–0.49	0.0002
Black race vs other	1.37	0.56–3.33	0.49	2.07	1.11–3.87	0.022
Clinical stage III vs I and II	1.42	0.71–2.84	0.32	2.28	1.3–3.99	0.004
Hormone receptor positive vs negative.	1.48	0.54–4.05	0.45	1.45	0.63–3.33	0.38
Lymphovascular invasion vs no	2.17	1.06–4.45	0.034	2.28	1.33–3.93	0.003
Adjuvant endocrine therapy vs no	0.37	0.14–1.02	0.05	0.57	0.25–1.28	0.17
Abbreviation: CI = confidence interval.						

caution, but they support the concept that patients achieving a pCR may not receive further benefit from adjuvant anti-HER2 therapy and therefore, toxicities may be avoided. Furthermore, if patients achieving a pCR do not receive further benefit from adjuvant trastuzumab, this could have important implications associated with resource optimisation. This is particularly relevant as the use of double anti-HER2 blockade becomes standard in the neoadjuvant setting and we increase the rates of pCR. Further prospective studies are needed to evaluate the impact of continued HER2 therapy among patients with a pCR. In addition, ongoing prospective studies evaluating the benefit of adjuvant anti-HER2 therapies after a pCR would be ideal to answer this important question and an opportunity for comparative effectiveness research, particularly as we incorporate newer targeted therapies into the care of our patients (Pritchard, 2010).

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CONFLICT OF INTEREST

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