The Oncologist®

Breast Cancer

First-Line Palliative HER2-Targeted Therapy in HER2-Positive Metastatic Breast Cancer Is Less Effective After Previous Adjuvant Trastuzumab-Based Therapy

Hanah N. Rier,[a,b] Mark-David Levin,[a] Joost van Rosmalen,[c] Monique M. E. M. Bos,[d] Jan C. Drooger,[b,e] Paul de Jong,[f] Johanneke E. A. Portielje,[g] Elisabeth M. P. Elsten,[h] Albert-Jan ten Tije,[h] Stefan Sleijfer,[b] Agnes Jager[b]

[a]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands; [b]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [c]Department of Biostatistics, Erasmus MC, Rotterdam, The Netherlands; [d]Department of Internal Medicine, Reinier de Graaf Hospital, Delft, The Netherlands; [e]Department of Medical Oncology, Ikazia Hospital, Rotterdam, The Netherlands; [f]Department of Internal Medicine, Sint Antonius Hospital, Utrecht, The Netherlands; [g]Department of Internal Medicine, Haga Hospital, The Hague, The Netherlands; [h]Department of Internal Medicine, Amphia Hospital, Breda, The Netherlands

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. . Metastatic breast cancer • Human epidermal growth receptor 2 positive • Trastuzumab • Overall survival

Abstract

Background. Survival of patients with human epidermal growth receptor 2 (HER2)-positive metastatic breast cancer (MBC) has improved dramatically since trastuzumab has become available, although the disease eventually progresses in most patients. This study investigates the outcome (overall survival [OS] and time to next treatment [TNT]) in MBC patients pretreated with trastuzumab in the adjuvant setting (TP-group) compared with trastuzumab-naïve patients (TN-group) in order to investigate the possibility of trastuzumab resistance.

Patients and Methods. Patients treated with first-line HER2-targeted-containing chemotherapy were eligible for the study. A power analysis was performed to estimate the minimum size of the TP-group. OS and TNT were estimated using Kaplan-Meier curves and multivariable Cox proportional hazards models.

Results. Between January 1, 2000, and June 1, 2014, 469 patients were included, of whom 82 were in the TP-group and 387 were in the TN-group. Median OS and TNT were significantly worse in the TP-group compared with the TN-group (17 vs. 30 months, adjusted hazard ratio [HR] 1.84 [1.15–2.96], $p = .01$ and 7 vs. 13 months, adjusted HR 1.65 [1.06–2.58], $p = .03$) after adjustment for age, year of diagnosis, disease-free interval, hormone receptor status, metastatic site, and cytotoxic regimens.

Conclusion. First-line trastuzumab-containing treatment regimens are less effective in patients with failure of adjuvant trastuzumab compared with trastuzumab-naïve patients and might be due to trastuzumab resistance. The impact of trastuzumab resistance on the response on dual HER2 blockade with trastuzumab and pertuzumab and how resistance mechanisms can be used in the optimization of HER2-targeted treatment lines need further investigation. ***The Oncologist*** 2017;22:901–909

Implications for Practice: Evidence on the efficacy of palliative trastuzumab-based therapy after failure of trastuzumab in the adjuvant setting is limited because of a minority of patients treated with adjuvant trastuzumab in clinical trials. In this study, less clinical benefit of palliative trastuzumab-based therapy was observed in patients relapsing after adjuvant trastuzumab compared with no adjuvant trastuzumab treatment. Subgroup analyses and multivariable analyses revealed that this was independent of possible confounding factors, including adjuvant taxane-treatment. This might suggest a clinically meaningful impaired efficacy of trastuzumab after previous, in this case adjuvant, trastuzumab therapy. These results could have implications for treatment decision-making after short progression-free intervals on trastuzumab-containing regimens in the palliative setting.

Introduction

Survival of patients with human epidermal growth receptor 2 (HER2)-positive breast cancer has dramatically improved since trastuzumab has become available in both the (neo)adjuvant and palliative settings [1–3]. In the advanced setting, trastuzumab-based therapy is the cornerstone of antitumor treatment. Although significant improvement of survival has been reached with this strategy, most metastatic breast cancer (MBC) patients will eventually develop progressive disease. This might be due to

Correspondence: Hánah N. Rier, M.D., Department of Internal Medicine, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT Dordrecht, The Netherlands. Telephone: 31-78-6550549; e-mail: rier@asz.nl Received November 11, 2016; accepted for publication March 9, 2017; published Online First on May 22, 2017. ©AlphaMed Press 1083-7159/2017/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2016-0448

resistance against chemotherapy but might also be partly explained by resistance against trastuzumab, for example, due to previous exposure to trastuzumab in the adjuvant setting. Recognizing patients with (acquired) trastuzumab resistance could be of value to prevent unnecessary trastuzumab administrations, thus reducing costs and further stressing the need for developing new anti-HER2 treatment strategies.

In case acquired resistance to trastuzumab after previous exposure plays a role, it could be hypothesized that patients with prior exposure to adjuvant trastuzumab will have less clinical benefit from first-line palliative trastuzumab-treatment compared with trastuzumab-naïve patients. A possible way to study this might be comparing long-term outcome between patients pretreated with trastuzumab and patients without previous trastuzumab. However, studies investigating this issue have shown conflicting results [4–7], possibly due to small numbers of patients [4, 5], low numbers of events [6, 7], or short duration of follow-up [7]. We have therefore performed a retrospective study to compare the efficacy of first-line HER2-targeted-containing chemotherapy between patients who did or did not undergo adjuvant trastuzumab-based treatment in a large number of patients, determined by a power analysis calculated prior to the start of the study, thereby guaranteeing a sufficient number of events (deaths). Detailed information on previous systemic treatment was collected, and the influence of clinical prognostic parameters on the efficacy of retreatment with HER2-targeted-containing treatment schedules/therapy in palliative setting was determined.

Materials and Methods

Study Design

Consecutive patients who had received at least one dose of first-line HER2-targeted-containing chemotherapy because of HER2-positive MBC from January 1, 2000, to June 1, 2014, at seven hospitals in The Netherlands were eligible for the present study and retrospectively identified. Any first-line HER2-targeted-containing chemotherapy was allowed, irrespective of the anti-HER2 agent. Patients were excluded in case of pathologically proven HER2-negative MBC, incomplete clinical data in the patient record, or a second active malignancy in the 5 years prior to the initial breast cancer diagnosis. Only patients with combined chemotherapy and HER2-targeted therapy as first-line regimen were included because of two reasons. First, the beneficial effect of trastuzumab addition to first-line chemotherapy has been more pronounced than the beneficial effect of trastuzumab addition to palliative endocrine therapy. Second, the combination of an anti-HER2 agent with chemotherapy is independent of the hormone receptor status and thus allows a larger population to be investigated.

Patients were divided into two groups: the trastuzumab pretreated (TP)-group, consisting of patients who were treated with adjuvant trastuzumab in the past and the trastuzumab-naïve (TN)-group, consisting of patients who were not treated with trastuzumab before the diagnosis of MBC. Patients in the TN-group had either relapsed after stage I–III primary breast cancer or presented with de novo stage IV disease. Because previous studies reported that the presentation with primary metastatic disease does not affect long-term outcomes, these patients were pooled [4, 6]. The retrospective review of electronic patient records for the purpose of this study was approved by the central ethical review board (METC 15-046) in addition to the permission of omitting written informed consent.

Data Collection

Trained investigators searched electronic medical records for patient and tumor characteristics, treatment patterns, and location of metastases. The end of follow-up was January 1, 2015. HER2 receptor status was locally determined using immunohistochemistry (IHC) on the primary tumor or on a metastatic lesion if available. Tumors were classified as HER2-positive if there was 3+ staining on IHC or 2+ staining confirmed with gene amplification by CISH/FISH in at least 10% of the tumor cells. Hormone receptors were locally tested, and estrogen receptor (ER)-/progesterone receptor (PR)-positive MBC was defined as $\geq$10% of the primary breast tumor cells showing positive nuclear staining of estrogen and/or progesterone receptor. In case a biopsy had been performed from a metastatic lesion, the hormone receptor status was based on this material obtained by the biopsy. Tumor grade was determined on the primary breast tumor using the Bloom-Richardson grading system [8]. Tumor stage at initial presentation was scored using the seventh edition of the TNM classification for breast cancer [9]. At start of first-line HER2-targeted-containing chemotherapy, all radiological detectable sites of distant metastases per patient were described, that is, bone, visceral (liver, lung, and other intestinal sites), central nervous system, skin, or lymph nodes.

Statistical Analyses

A power analysis was performed to determine the required number of patients to detect a clinically relevant difference in survival between the TP-group and the TN-group, assuming that this difference is present. A hazard ratio (HR) of 1.47 for overall survival (OS) was assumed based on a study that reported impaired OS for patients in the TP-group compared with the TN-group [4]. This study was chosen for the power analysis because other studies investigating this subject were not available at the start of this study. With a power of 80%, a two-sided significance level of 5%, and a survival rate of 40% at the end of follow-up in the TP group (based on the median duration of follow up in our study), approximately 100 patients in the TP-group were needed to detect an HR of 1.47 for OS in the TP-group compared with the TN group. Based on the incidence of MBC, the patients of seven regional hospitals were included in this study.

Continuous variables were described using medians and interquartile ranges. Categorical variables were described using percentages. Patient characteristics were compared between the TP-group and the TN-group using Mann-Whitney tests for continuous variables, Fisher's exact tests for categorical variables with two categories, and chi-square tests for categorical variables with more than 2 categories. The primary study endpoint was OS after start of first-line chemotherapy. OS was defined as the time between start of first-line HER2-targeted-containing chemotherapy and death of any cause. Patients were censored on January 1, 2015. The secondary study endpoint was time to next treatment (TNT), which was defined as the time between the start of first-line HER2-targeted-containing chemotherapy and the

Table 1. Patient characteristics

Characteristics, *n* (%)	TN-group (*n* = 387)	TP-group (*n* = 82)	*p* value
Age in years (range)	51.5 (25–84)	48.3 (24–72)	.02
Diagnosis before 2006	241 (62.3)	21 (25.6)	<.001
Hormone receptor status			
Positive	223 (57.6)	45 (54.9)	.72
Negative	163 (42.1)	37 (44.6)	
Unknown	1 (0.3)	0	
Tumor stage			<.001
I	53 (13.7)	3 (3.7)	
II	120 (31.0)	40 (48.8)	
III	80 (20.7)	39 (47.6)	
IV	119 (30.7)	0	
Unknown	15 (3.9)	0	
Nuclear grade			.31
I or II	95 (24.5)	19 (23.2)	
III	160 (41.3)	44 (53.7)	
Unknown	132 (34.1)	19 (23.2)	
Adjuvant chemotherapy			<.001
None	228 (58.9)	0	
Anthracyclines only	125 (32.3)	10 (12.2)	
Taxanes only	1 (0.3)	3 (3.7)	
Anthracyclines + taxanes	14 (3.6)	69 (84.1)	
Other	19 (4.9)	0	
Previous palliative endocrine therapy	82 (21.2)	17 (20.7)	1.00
First metastatic site			<.001[b]
Bone	67 (17.3)	17 (20.7)	
Visceral[a]	79 (20.4)	11 (13.4)	
CNS	2 (0.5)	9 (11.0)	
Other	41 (10.6)	10 (12.2)	
Multiple sites	198 (51.2)	35 (42.7)	
Number of metastatic sites			.47
1	189 (48.8)	47 (57.3)	
2	122 (31.5)	20 (24.4)	
3	52 (13.4)	9 (11.0)	
>3	24 (6.2)	6 (7.3)	
Disease-free interval[c] (IQR) (months)	42 (20–78)	33.5 (21–46)	.03
First-line HER2-targeted agent(s)			<.001
Trastuzumab monotherapy	366 (94.6)	66 (80.5)	
Lapatinib	10 (2.6)	9 (11.0)	
Trastuzumab + pertuzumab	11 (2.8)	7 (8.5)	
First line chemotherapy used in combination with HER2 targeted agent			<.001
Anthracyclines	7 (1.8)	0	
Taxanes	317 (81.9)	51 (62.2)	
Capecitabine	14 (3.6)	17 (20.7)	
Vinorelbine	29 (7.5)	11 (13.4)	
Other	9 (2.3)	2 (2.4)	
Unknown	11 (2.8)	1 (1.2)	
Overall duration of palliative trastuzumab (IQR) (months)	16 (8–32)	9.4 (4–19)	<.001
Unknown	16	4	

[a]Visceral: Liver, lung, pleural, peritoneal, pericardial, intestinal.
[b]When removing the patients with CNS-located metastases from this analysis, the first metastatic site did not differ between the groups ($p = .43$).
[c]Disease-free interval: time from initial breast cancer diagnosis until the diagnosis of distant metastases.
Abbreviations: CNS, central nervous system; HER2, human epidermal growth receptor 2; IQR, interquartile range; TP, trastuzumab pretreated, i.e. relapsed after adjuvant trastuzumab-treatment; TN, trastuzumab-naïve.

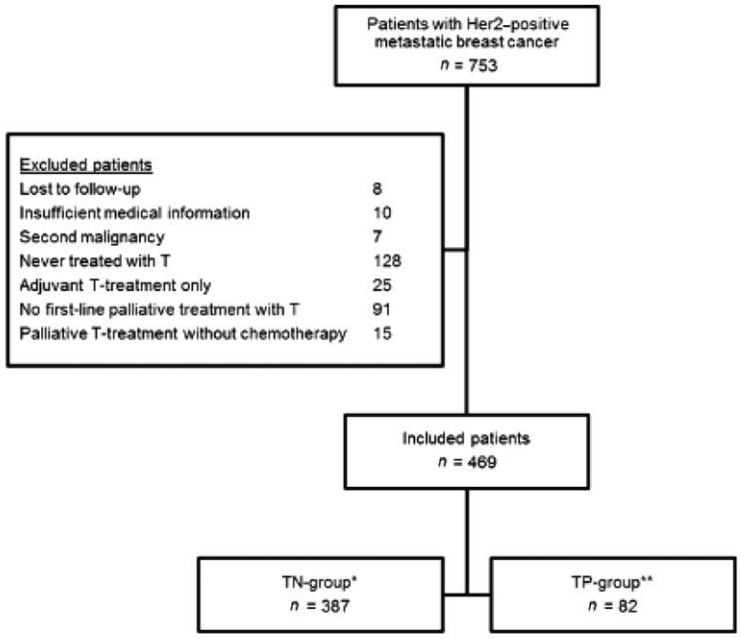

Figure 1. Flow chart patient inclusion.

Table 2. Univariable and multivariable Cox proportional hazard models for overall survival

	Univariable			Multivariable		
Patient characteristics	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age[a] (range) (y)	1.01	1.00–1.02	.33	1.01	1.00–1.02	.15
Diagnosis after 01.01.2006 vs. before 01.01.2006	1.21	0.97–1.51	.09	0.99	0.75–1.30	.94
DFI[b]	1.00	1.00–1.00	.20	1.00	1.00–1.00	.48
Hormone receptor status: positive vs. negative	0.86	0.69–1.06	.15	0.88	0.70–1.10	.88
Brain metastases vs. no brain metastases	**1.02**	**1.01–1.54**	**.04**	0.88	0.61–1.25	.88
Interaction between brain metastases and follow-up time (months)	—	—	—	**1.02**	**1.00–1.03**	**.01**
Visceral metastases vs. no visceral metastases	**1.25**	**1.01–1.56**	**.04**	**1.36**	**1.08–1.90**	**.01**
First line lapatinib vs. trastzumab	1.62	0.99–2.64	.05	1.36	0.82–2.28	.24
Adjuvant taxane treatment vs. no previous taxane treatment	**1.75**	**1.34–2.28**	**<.001**	1.16	0.74–1.83	.52
Adjuvant trastuzumab vs. no adjuvant trastuzumab[c]	**2.00**	**1.51–2.63**	**<.001**	**1.84**	**1.15–2.96**	**.01**

Bolded values indicate statistically significant results, i.e., $p < .05$.
[a]Age at initial breast cancer diagnosis.
[b]Time from initial breast cancer diagnosis until the first diagnosis of distant metastases.
[c]TP-group versus TN-group.
Abbreviations: —, no data; CI, confidence interval; CNS, central nervous system; DFI, disease-free interval; HR, hazard ratio; TN, trastuzumab pretreated, i.e. relapsed after adjuvant trastuzumab-treatment; TN, trastuzumab-naïve.

start of a second treatment line because of disease progression. A switch to another regimen because of toxicity or patient demand was not considered a switch to second-line treatment. In case no second treatment line was started, TNT was until the date of documented disease progression or death, whichever came first. In all other cases, patients were censored at January 1, 2015. In this study, TNT was chosen as marker of progression-free survival (PFS) to indicate the duration of clinical benefit, that is, the time until another treatment was deemed necessary by the treating physician to get disease control. The difference between TNT and the more commonly used time until documented disease progression (i.e., PFS) was minimal, with less than 1 month in 82.5% of the entire study population and less than 2 months in 92.5%. OS and TNT were assessed using Kaplan-Meier curves and further explored by univariable and multivariable Cox proportional hazard models. To assess the effects of selection bias, the survival analyses were repeated with the following subgroups: (a) exclusion of the patients treated with lapatinib, (b) exclusion of the patients presenting with brain metastases, (c) exclusion of the patients treated before 2006, and (d) exclusion of the patients without adjuvant treatment with taxanes. The independent variables in the Cox proportional hazard models were included based on their prognostic relevance and were age, year of diagnosis, the disease-free interval (time between the

initial breast cancer diagnosis and the occurrence of distant metastases), estrogen/progesterone receptor positivity, treatment with lapatinib, previous treatment with taxanes, the presence of brain metastases, and the presence of visceral metastases. The proportional hazards assumption was assessed by including interaction effects of covariates and follow-up time in a Cox proportional hazard model with time-dependent covariates. Variance inflation factors were calculated to assess the degree of multicollinearity among the independent variables in the Cox proportional hazard models. A two-sided p value of $p < .05$ was considered to be statistically significant. All analyses were conducted using SPSS version 24 (SPSS Inc., Chicago, IL, http://www.spss.com.hk/corpinfo/index.htm).

Results

Patient Characteristics

Between January 1, 2000, and June 1, 2014, 753 patients with HER2-positive MBC were identified. After excluding patients who did not receive first-line HER2-targeted-based chemotherapy ($n = 259$; see also below) and patients with incomplete clinical data ($n = 25$), 469 were included in the final analyses (Fig. 1), of which 82 were in the TP-group and 387 were in the TN-group. The median duration of follow-up was 30 months (range 0–165 months), starting at the diagnosis of distant metastases. The death rate in the entire cohort was 74%. No patients were lost to follow-up.

Patients in the TP-group were slightly younger than patients in the TN-group (48.3 vs. 51.5 years, $p = .02$). All patients in the TP-group had received adjuvant chemotherapy (as this was combined with trastuzumab) compared with 41.1% of the patients in the TN-group. Patients in the TP-group more often had brain metastases at presentation of metastatic disease (11.0% vs. 0.5%) and were more often treated with other first-line anti-HER2 agents (i.e. lapatinib and pertuzumab) than with trastuzumab monotherapy (19.5% vs. 5.4%, $p < .001$). Hormone receptor status, nuclear grade of the primary tumor, and localization of metastatic sites were equally distributed over the two groups (Table 1).

Selection of Patients Treated with Anti-HER2 Agents

The omission of first-line anti-HER2-based chemotherapy of the 259 excluded patients was mostly due to preferred anthracyclines without trastuzumab as first-line therapy (32.8%), poor clinical condition (19.7%), or no indication of chemotherapy yet (9.7%; supplemental online Table 1). To investigate potential selection bias of the excluded patients, these were also divided into (a) patients having received adjuvant trastuzumab or having an indication for adjuvant trastuzumab without receiving it and (b) patients without an indication for adjuvant trastuzumab. Patient characteristics for both groups were compared with the TP- and TN-groups of the included patients, respectively, showing no selection of patients with prognostic negative characteristics in the TP-group and no selection of patients with prognostic positive characteristics in the TN-group (supplemental online Table 2).

OS and TNT

Median OS was 17 months in the TP-group and 30 months in the TN-group (HR 2.00, 95% confidence interval [CI] 1.51–2.63, $p < .001$). Median TNT was 7 months in the TP-group and 13 months in the TN-group (HR 2.02, 95% CI 1.56–2.62, $p < .001$; Fig. 2A and 2B). Dividing the TN-group into patients relapsing after stage I–III breast cancer and patients presenting with de novo stage IV disease did not affect the results (supplemental online Fig. 1). Lapatinib instead of trastuzumab as first-line anti-HER2 therapy was administered in 19 patients (TP-group: $n = 9$, TN-group:

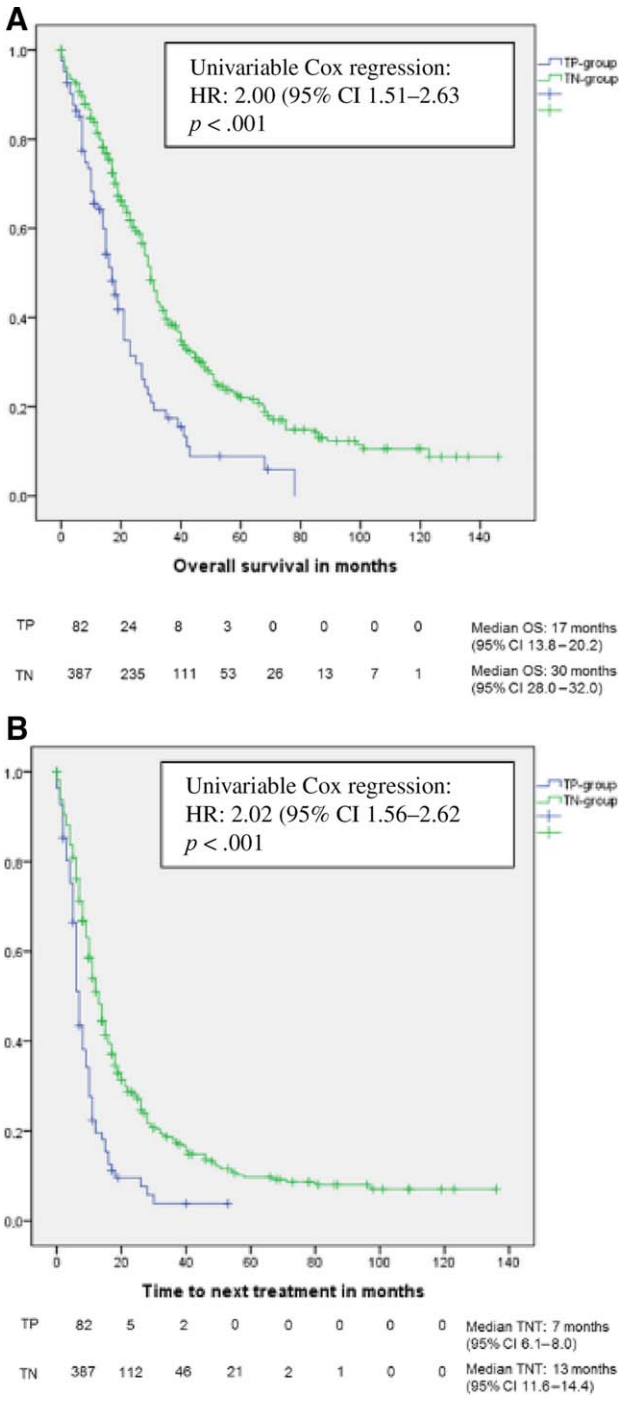

Figure 2. Overall survival **(A)** and time to next treatment **(B)** in patients treated with first-line palliative anti-human epidermal growth receptor 2 therapy.

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; TP, Trastuzumab pretreated, i.e. relapsed after adjuvant trastuzumab-treatment; TN, Trastuzumab-naïve.

Table 3. Univariable and multivariable Cox proportional hazard models for time to next treatment

	Univariable			Multivariable		
Patient characteristics	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age[a] (range) (y)	1.00	0.99–1.01	.79	1.01	1.00–1.02	.28
Diagnosis after 01.01.2006 vs. before 01.01.2006	1.08	0.89–1.32	.43	0.86	0.67–1.11	.25
DFI[b]	1.00	1.00–1.00	.13	1.00	1.00–1.00	.12
Hormone receptor status: positive vs negative	0.91	0.74–1.11	.33	0.91	0.73–1.12	.35
Brain metastases vs. no brain metastases	**1.33**	**1.09–1.63**	**.01**	0.78	0.58–1.05	.10
Interaction between brain metastases and follow-up time (months)	—	—	—	**1.04**	**1.03–1.06**	**<.001**
Visceral metastases vs. no visceral metastases	1.10	0.90–1.35	.36	**1.23**	**1.00–1.52**	**.048**
First-line lapatinib vs. trastzumab	1.59	0.97–2.58	.06	1.36	0.82–2.26	.23
Adjuvant taxane treatment vs. no previous taxane treatment	**1.93**	**1.50–2.48**	**<.001**	1.41	0.92–2.15	.11
Adjuvant trastuzumab vs. no adjuvant trastuzumab[c]	**2.02**	**1.56–2.62**	**<.001**	**1.65**	**1.06–2.58**	**.03**

Bolded values indicate statistically significant results, i.e., $p < .05$.
[a]Age at initial breast cancer diagnosis.
[b]Time from initial breast cancer diagnosis until the first diagnosis of distant metastases.
[c]TP-group vs. TN-group.
Abbreviations: —, no data; CI, confidence interval; CNS, central nervous system; DFI, disease-free interval; HR, hazard ratio; TN, trastuzumab pretreated, i.e. relapsed after adjuvant trastuzumab-treatment; TN, trastuzumab-naïve.

$n = 10$); exclusion of these patients from the analyses showed similar results (supplemental online Fig. 2), as well as the removal of the patients with brain metastases as first metastatic site (11 in the TP-group and 2 in the TN-group) to avoid negative selection bias of patients with brain metastases (OS 18 vs. 30 months, log-rank $p < .001$, TNT 7 vs. 13 months, $p < .001$). In the multivariable Cox regression, OS and TNT in the TP-group were still shorter compared with the TN group (HR 1.84 for OS, 95% CI 1.15–2.96, $p = .01$ and HR 1.65 for TNT, 95% CI 1.06–2.58, $p = .03$, respectively; Tables 2 and 3). After assessing the proportional hazards assumption, a significant interaction was found between the development of brain metastases and the duration of follow-up. Therefore, brain metastases were modeled as a time-dependent covariate in the multivariate Cox regression. No other significant violations of the proportional hazards assumption were detected.

Median OS of ER-positive (ER+) versus ER-negative (ER−) patients in the TP-group was 18 versus 15 months and in the TN-group 31 versus 27 months ($p = .91$ and $p = .20$, respectively). Median TNT of ER+ versus ER− patients in the TP-group was 7 versus 6 months and in the TN-group 14 versus 11 months, respectively ($p = .79$ and $p = .42$, respectively). However, when calculating OS from the first presentation of metastatic disease, median OS of ER− patients was significantly shorter than that of ER+ patients (30 vs. 38 months, $p = .01$), suggesting that the prognostic advantage of ER positivity disappeared once first-line chemotherapy was indicated for disease control.

Since mid-2005, trastuzumab has been available for adjuvant treatment. Therefore, most patients in the TP-group were diagnosed with breast cancer after 2006, whereas the TN-group was largely exposed to older treatment regimens. Repeating the survival analyses with only the patients diagnosed after 2006 (TP-group: $n = 61$, TN-group: $n = 146$), in order to assess bias by difference in treatment regimens, still showed impaired OS and TNT in the TP-group (16 vs. 29 months and 6 vs. 14 months, respectively (both log-rank $p < .001$; supplemental online Fig. 3).

Effect of Taxanes

Previous adjuvant chemotherapy was administered in 159 patients (41.1%) in the TN-group and in all patients in the TP-group. In these patients, previous adjuvant chemotherapy consisting of taxanes was administered in 87.8% of the patients ($n = 72$) in the TP-group compared with 3.9% ($n = 15$) in the TN-group. Due to the strong association between previous adjuvant taxanes and TP/TN-group, we found relatively high variation inflation factors for these two variables (3.1 and 3.2, respectively). To assess the effects of this multicollinearity and to minimize the effect of possible taxane-resistance between both groups, we repeated the univariable survival analyses with only the patients relapsing after taxane therapy. We found that OS in the TP-group was still significantly shorter compared with the TN-group (17 vs. 29 months, log rank $p = .048$). The difference in TNT between both groups did not reach statistical significance (6 vs. 11 months, log rank $p = .07$; Fig. 3). In the univariable Cox regression, previous taxane exposure, which suggests resistance to taxanes, had a large association with OS and TNT (HR 1.75, 95% CI 1.34–2.28, $p < .001$ and HR 1.93, 95% CI 1.50–2.48, $p < .001$, respectively), but this was no longer statistically significant after adjustment for previous trastuzumab exposure in the multivariable Cox regression.

Discussion

This study shows that patients receiving first-line HER2-targeted-containing chemotherapy for HER2-positive MBC who were previously exposed to adjuvant trastuzumab had a shorter median OS and TNT compared with patients who were never exposed to trastuzumab at the time of diagnosing distant metastases. The unfavorable effect of prior trastuzumab exposure was independent of clinical and tumor characteristics and seems, at least partly, independent of pretreatment with taxanes.

Four retrospective studies have previously reported on this issue and showed conflicting results [4–7]. In two of these studies, some degree of shorter OS was reported in

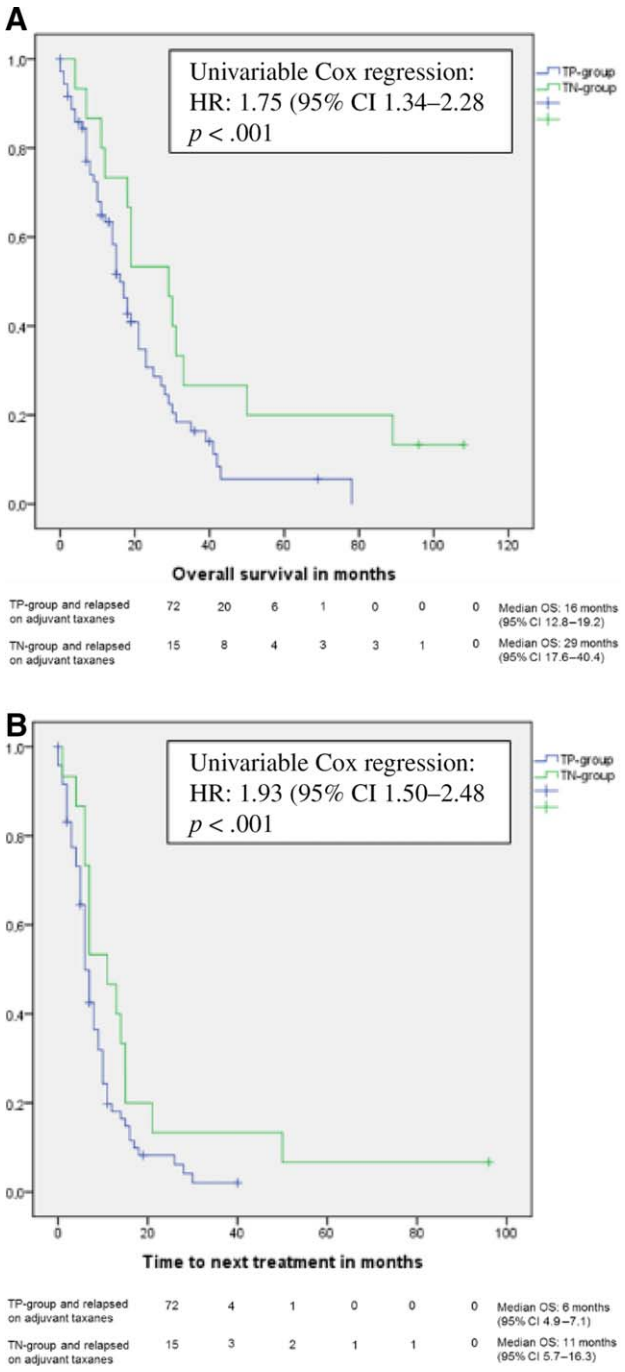

Figure 3. Overall survival **(A)** and time to next treatment **(B)** among patients with previous adjuvant treatment with taxanes.

Abbreviations: CI, confidence interval; HR, hazard ratio; TP, Trastuzumab pretreated, i.e. relapsed after adjuvant trastuzumab-treatment; TN, Trastuzumab-naïve.

patients previously treated with adjuvant trastuzumab (univariable HRs 1.47 and 1.16) [4, 6], although these associations were not retained after adjustment for other clinical risk factors. However, these could be false-negative observations, as the 95% CIs of the HR of previous adjuvant trastuzumab treatment in these studies showed overlap with our 95% CI (0.87–1.75 and 0.80–1.74, respectively, vs. 1.00–2.91 in our study). This implicates that no survival difference was detected, despite patients with relatively high HRs of death. In the third study with 96 patients in the TP-group, 2-year OS was the only study endpoint and was not affected (HR 0.79, 95% CI 0.50–1.26) by previous adjuvant trastuzumab treatment [7]. A fourth study reported that patients with trastuzumab retreatment also less often obtained long-term clinical benefit from reintroduction of HER2-targeted-based chemotherapy [5]. Although in line with our study results, this study had a short time of follow-up after the registration of trastuzumab in adjuvant setting, which might have led to a negative selection of patients with relatively rapid development of distant metastases in the TP-group. Thus, small numbers of patients, short duration of follow-up, small number of events, and possible selection bias could have influenced these previous study results.

The survival of the patients in our study seemed to be somewhat shorter when compared with prospective studies recently done in patients with HER2-positive MBC, including the CLEOPATRA and RHEA trials [10, 11]. The median OS of our entire cohort was 28 months, compared with 37.6 months in the control-arm of the CLEOPATRA trial [11]. The median OS of our TP-group was 17 months, compared with 25 months in the RHEA trial (which included only trastuzumab-pretreated patients). The median TNT in our study (TP-group: 7 months, entire cohort: 11 months) was comparable with the PFS of both the RHEA trial (8 months) and the control-arm of the CLEOPATRA trial (12.4 months) [12].

Possible explanations for the shorter median OS in our study could be the differences in inclusion and exclusion criteria, favoring the patients in both the CLEOPATRA and RHEA trials. In these studies, patients needed to have an ECOG performance status of 0 or 1, a relapse-free interval after adjuvant treatment of $\geq$6 months, and a life expectancy of $\geq$3 months. These (prognostic positive) restrictions were not applied to our study cohort, which might have influenced OS.

We aimed to strengthen the interpretation of the analyses by investigating whether possible selection could have biased the current findings. Excluded patients could have caused a selection bias of preferentially poor prognosis patients in the TP-group or a selection bias of preferentially good prognosis patients in the TN-group; however, this was not observed when comparing the included and excluded patients (supplemental online Table 2). Furthermore, patients in the TP-group more frequently had brain metastases as first presentation of metastatic disease than patients in the TN-group, possibly predisposing the TP-group to unfavorable outcomes. However, exclusion of these patients from the analyses still showed worse OS and TNT in the TP-group. Also, possible selection by difference in treatment period was unlikely. A larger percentage of the TP-group compared with the TN-group was treated in recent time periods, so patients in the TP-group had a shorter disease-free interval (time between the initial breast cancer diagnosis and the development of distant metastases), but also could have benefited from newer recently developed anti-HER2 agents than the TN-group. Analyzing only the patients included after January 1, 2006, in order to compare patients with comparable disease-free interval and treated according to the same guidelines, did not alter the results. Finally, the TP-group more often received adjuvant taxanes (87.8% vs. 3.9%), possibly causing impaired sensitivity to taxanes in the advanced setting, which might have contributed to the worse outcome in the TP-group. However, selecting only the patients who were treated with

adjuvant taxanes still showed shorter OS and TNT in the TP-group. Altogether, after showing comparable results in different subgroup analyses, we believe that the lower efficacy of first-line palliative trastuzumab in the TP-group is possibly due to less sensitivity to trastuzumab or resistance among a subset of MBC patients pretreated with trastuzumab.

This study was not designed to unravel exact mechanisms of resistance among treated patients but nevertheless showed signs of possible clinically relevant unresponsiveness to trastuzumab (primary or acquired during previous adjuvant therapy), which could have implications for treatment decision-making after short progression-free intervals in the palliative setting.

It must be noted that the current standard of care of first-line HER2-targeted therapy is dual HER2 blockade with trastuzumab and pertuzumab, instead of single trastuzumab, after the results of the CLEOPATRA trial [12]. In this trial, trastuzumab pretreated patients seemed to have shorter PFS than trastuzumab-naïve patients in both the pertuzumab-arm (16.9 vs. 21.6 months) and the control-arm (10.4 vs. 12.6 months). Although trastuzumab pretreated patients seemed to derive similar benefit from the addition of pertuzumab, as compared with trastuzumab-naïve patients, the benefit of dual HER2 blockade above trastuzumab monotherapy was not statistically significant in trastuzumab pretreated patients, as shown by the 95% CI (HR 0.65, 95% CI 0.35–1.07). However, the number of patients with previous adjuvant trastuzumab was only 11% of the entire cohort, which could explain the loss of statistical significance. A future study is needed to determine the impact of trastuzumab resistance on first-line dual HER2 blockade in trastuzumab pretreated patients.

Several limitations of this study have to be mentioned. First, fewer patients than the needed number of patients determined by the power calculation were included. The main cause for this was the well-known low incidence (about 10%) of developing distant metastases among patients in the TP-group, thus among those who were treated with adjuvant trastuzumab [13]. However, more events (deaths) occurred, so the power in our study was not substantially limited. Second, patients with lapatinib were included in this study, so the analysis was not restricted to only patients with trastuzumab retreatment. However, we chose to include all patients with any type of palliative first-line HER2-targeted therapy, in order to include a study population as close to the "real world" as possible. Furthermore, we provided a subgroup analysis without the patients treated with lapatinib, which showed similar results. Third, the loss of HER2 overexpression in distant metastases, which might result in trastuzumab unresponsiveness, could not be estimated due to the lack of metastatic biopsies. This has, however, been reported to be only 3%–6% of the cases [14–16]. Fourth, first-line HER2-targeted therapy nowadays consists of the combination trastuzumab and pertuzumab [11], so cohorts treated with first-line single HER2 blockade with trastuzumab will dissappear in the near future. However, the results of this study might still be useful, as single blockade of the HER2 receptor is still the standard of care in second-line regimens and beyond. Finally, information about subsequent treatment lines and decisions was lacking, which also could affect survival. Nevertheless, this is not the case for TNT, which was clearly different between TN-and TP-group and was not affected by subsequent treatment lines.

Conclusion

First-line trastuzumab containing chemotherapy is less effective in patients treated with adjuvant trastuzumab compared with those not treated with adjuvant trastuzumab for primary breast cancer. Although resistance against taxane treatment could not be fully excluded, our study provides evidence that at least a subset of the patients derive less clinical benefit from HER2-targeted therapy, possibly due to trastuzumab resistance. Whether this resistance might also influence the response on dual HER2 blockade in first-line treatment is currently unknown and needs further investigation.

Acknowledgments

This study was funded by the ORAS foundation (Oncological Research Albert Schweitzer hospital) and the Leerhuis of the Albert Schweitzer hospital, Dordrecht, The Netherlands. We thank Corry Leunis and Edith van Druten for the coordination of the data management in two of the participating centers. The foundations had no involvement in the conduct of the study.

Author Contributions

Conception/Design: Hánah N. Rier, Mark-David Levin, Stefan Sleijfer, Agnes Jager
Provision of study material or patients: Hánah N. Rier, Mark-David Levin, Monique M. E. M. Bos, Jan C. Drooger, Paul de Jong, Johanneke E. A. Portielje, Elisabeth M. P. Elsten, Albert-Jan ten Tije, Stefan Sleijfer, Agnes Jager
Collection and/or assembly of data: Hánah N. Rier, Elisabeth M. P. Elsten
Data analysis and interpretation: Hánah N. Rier, Mark-David Levin, Joost van Rosmalen, Stefan Sleijfer, Agnes Jager
Manuscript writing: Hánah N. Rier, Mark-David Levin, Joost van Rosmalen, Monique M. E. M. Bos, Jan C. Drooger, Paul de Jong, Johanneke E. A. Portielje, Elisabeth M. P. Elsten, Albert-Jan ten Tije, Stefan Sleijfer, Agnes Jager
Final approval of manuscript: Hánah N. Rier, Joost van Rosmalen, Monique M. E. M. Bos, Jan C. Drooger, Paul de Jong, Johanneke E. A. Portielje, Elisabeth M. P. Elsten, Albert-Jan ten Tije, Stefan Sleijfer, Agnes Jager

Disclosures

The authors indicated no financial relationships.

References

1. Jackisch C, Piccart MJ, Gelber RD et al. HERA trial: 10 years follow up of trastuzumab after adjuvant chemotherapy in HER2 positive early breast cancer – Final analysis. SABCS 2015;PD5-01a.

2. Slamon DJ, Eiermann W, Robert NJ et al. Ten year follow-up of the BCIRG-006 trial comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC+T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC+TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer patients. SABCS 2015;S5-04a.

3. Eiermann W, International Herceptin Study Group. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: Pivotal trial data. Ann Oncol 2001;12(suppl 1): S57–S62.

4. Murthy RK, Varma A, Mishra P et al. Effect of adjuvant/neoadjuvant trastuzumab on clinical outcomes in patients with HER2-positive metastatic breast cancer. Cancer 2014;120:1932–1938.

5. Vaz-Luis I, Seah D, Olson EM et al. Clinicopathological features among patients with advanced human epidermal growth factor-2-positive breast cancer with prolonged clinical benefit to first-line trastuzumab-based therapy: A retrospective cohort study. Clin Breast Cancer 2013;13:254–263.

6. Lambertini M, Ferreira AR, Poggio F et al. Patterns of care and clinical outcomes of first-line trastuzumab-based therapy in HER2-positive metastatic breast cancer patients relapsing after (neo)adjuvant trastuzumab: An Italian multicenter retrospective cohort study. ***The Oncologist*** 2015;20:880–889.

7. Negri E, Zambelli A, Franchi M et al. Effectiveness of trastuzumab in first-line HER2+ metastatic breast cancer after failure in adjuvant setting: A controlled cohort study. ***The Oncologist*** 2014;19:1209–1215.

8. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957;11:359–377.

9. Gradishar WJ, Anderson BO, Balassanian R et al. Invasive breast cancer version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016;14:324–354.

10. Láng I, Bell R, Feng FY et al. Trastuzumab retreatment after relapse on adjuvant trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer: Final results of the Retreatment after HErceptin Adjuvant trial. Clin Oncol (R Coll Radiol) 2014;26:81–89.

11. Swain SM, Kim SB, Cortés J et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013;14:461–471.

12. Baselga J, Cortés J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–119.

13. Krell J, James CR, Shah D et al. Human epidermal growth factor receptor 2-positive breast cancer relapsing post-adjuvant trastuzumab: Pattern of recurrence, treatment and outcome. Clin Breast Cancer 2011;11:153–160.

14. Hoefnagel LD, van de Vijver MJ, van Slooten HJ et al. Receptor conversion in distant breast cancer metastases. Breast Cancer Res 2010;12:R75.

15. Nakamura R, Yamamoto N, Onai Y et al. Importance of confirming HER2 overexpression of recurrence lesion in breast cancer patients. Breast Cancer 2013;20:336–341.

16. Arihiro K, Oda M, Ogawa K et al. Discordant HER2 status between primary breast carcinoma and recurrent/metastatic tumors using fluorescence in situ hybridization on cytological samples. Jpn J Clin Oncol 2013;43:55–62.

See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:

Jasmeet C. Singh, Anita Mamtani, Andrea Barrio et al. Pathologic Complete Response with Neoadjuvant Doxorubicin and Cyclophosphamide Followed by Paclitaxel with Trastuzumab and Pertuzumab in Patients with HER2-Positive Early Stage Breast Cancer: A Single Center Experience. ***The Oncologist*** 2017;22:139–143.

Implications for Practice:

This is the first study describing the role of doxorubicin and cyclophosphamide followed by paclitaxel and dual anti-HER2 therapy with trastuzumab and pertuzumab (ACTHP) in patients with early stage HER2-positive breast cancer. Total (breast + lymph node) pathological complete remission (pCR) remission (ypT0/is ypN0) and German Breast Group pCR rates (ypT0/ypN0) were high at 72% and 53%, respectively, with the ACTHP regimen. Rate of axillary clearance in patients with known axillary involvement was high at 85%, which may translate into less extensive axillary surgeries in this subset in the future.