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Autoimmunity and Benefit from Trastuzumab Treatment in Breast Cancer: Results from the HERA Trial

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Abstract. *Background/Aim: This study sought to determine whether an autoimmune background could identify patients with HER2-positive early breast cancer (EBC) who derive differential benefit from primary adjuvant trastuzumab-based therapy. Patients and Methods: HERA is an international randomized trial of 5,102 women with HER2-positive EBC, who were enrolled to either receive adjuvant trastuzumab or not. In this exploratory analysis, the interaction between autoimmune history and the magnitude of trastuzumab benefit was evaluated. Results: A total of 5,099 patients were included in the current analysis. Among them, 325 patients (6.4%) had autoimmune disease history, 295 of whom had active disease. Patients were randomly assigned to trastuzumab or no-trastuzumab groups. Similar reductions in the risk of events in patients with and without autoimmune history were observed (interaction p=0.95 for disease-free survival, and p=0.62 for overall survival). Conclusion: No evidence of a differential benefit from trastuzumab in patients with a medical history of autoimmune disease was found.*

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The ErbB2/HER2 (human epidermal growth factor receptor 2) oncogene encoding for a member of the epidermal growth factor family, was found to be amplified in about 20% of breast cancer patients and is associated with a shorter time to relapse and a lower survival rate (1, 2). Trastuzumab, a monoclonal antibody against HER2 received approval for the treatment of patients with HER2-positive metastatic breast cancer on the basis of a pivotal trial (3). At the turn of the 21st century, a number of randomized prospective clinical trials

were launched to evaluate the role of trastuzumab given in addition to chemotherapy in the adjuvant setting. These studies generated highly consistent results, showing that the addition of trastuzumab to chemotherapy decreased recurrence by approximately 50% and mortality by 30% (4-7).

One of these trials was the HERA (BIG 1-01) trial, which randomized 5,102 patients who were enrolled after completion of their postoperative chemotherapy. The final analysis of an 11 years follow-up showed that the addition of 1 year of adjuvant trastuzumab resulted in a constant 24% relative reduction in the risk of a disease-free survival event (DFS), and a 26% relative reduction in the risk of death (5).

In the last few decades the role of the immune system in the outcome of cancer treatment has moved rapidly from preclinical evidence to clinical practice. The innate immune system involves activation of dendritic cells, natural killer cells, granulocytes as well as other cells and the complement system, and is associated with a rapid non-specific quick immune response without the need of memory or previous exposure (8). On the other hand, the adaptive immune response develops slowly and is mediated by a response to a specific antigen by B cells and T cells. Adaptive and innate immune mechanisms are essential players in the therapeutic effects of monoclonal antibody-based anti-HER2 therapy (9-11). Higher levels of tumor infiltrating lymphocytes (TILs) in the primary tumor at diagnosis are associated with increased benefit from trastuzumab (12).

Autoimmune diseases may cause significant and chronic morbidity, and women have a 2.7-times greater risk than men to develop an autoimmune disease (13). In this HERA exploratory analysis, we sought to examine whether autoimmunity background is associated with a different outcome in patients treated with primary trastuzumab-based therapy.

Patients and Methods

Study patients. HERA is an open-label, phase III, international multicenter randomized trial. A detailed description of the trial, its regimens, and key eligibility criteria are provided in the original report (4). Briefly, between Dec 7, 2001, and June 20, 2005, 5,102 patients were recruited and randomly assigned (1:1:1) to one of the three treatments arms: observation (without trastuzumab), adjuvant treatment of trastuzumab for 1 year or for 2 years.

The comparison of the trastuzumab arms *versus* observation was based on the intention-to-treat (ITT) principle, after exclusion of three patients (one from each group) because of no record of written informed consent (Figure 1). To be eligible, participants had to have central laboratory (Kassel, Germany) confirmation of locally assessed HER2-positive disease and left ventricular ejection fraction (LVEF) of at least 55% after completion of chemotherapy and radiotherapy if applicable. History of autoimmune diseases was prospectively collected in the clinical database and was retrieved for the sake of this analysis. Of note, this analysis was not preplanned as a part of the data analysis plan of the trial. The HERA trial was approved by the ethics committees of all participating sites and this exploratory analysis was approved by the HERA executive committee.

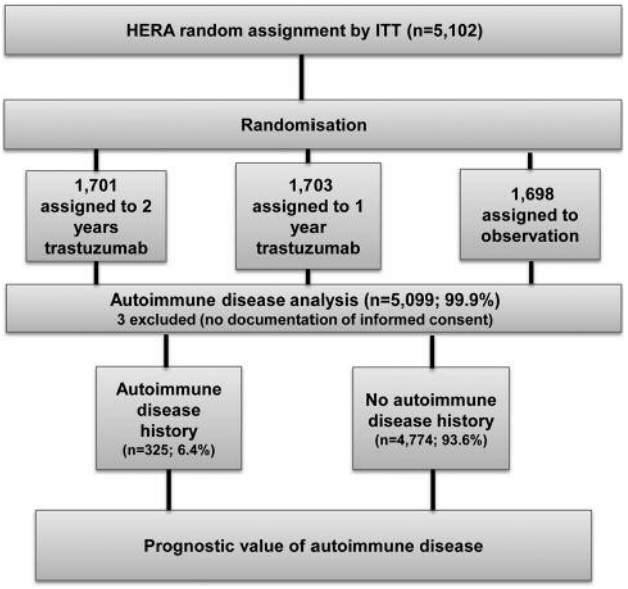

Figure 1. *CONSORT diagram. Study flowchart shows the process of patient selection.*

Statistical analysis. In the current analysis, we investigated the potential impact of autoimmune diseases on patient's outcome. We hypothesized that autoimmune history of the patients may elicit robust antitumor immune response, boosting the antitumor activity of trastuzumab, thus prolonging survival. Therefore, the a priori hypothesis was that patients with autoimmune disease background would have superior long-term outcomes when treated with trastuzumab. We evaluated the association between autoimmune background and classic clinicopathological factors using Chi-squared tests. Autoimmune diseases as well as other comorbidities in the HERA database were coded using the WHO-DDE (World Health Organization Drug Dictionary Enhanced). This analysis was restricted to autoimmune predefined diseases for which there was direct or indirect evidence for autoimmune pathogenesis (13). Two survival endpoints were investigated: disease-free survival (DFS) and overall survival (OS), which were defined in the HERA study (4). In these exploratory analyses, the two trastuzumab treatment arms were combined. A Cox proportional hazards regression model was used to assess the interaction between autoimmune history and treatment (1+2 years trastuzumab and observation). Cox modelling was also used with the overall population and for the two autoimmune status sub-populations to estimate unadjusted hazard ratios (HR) and 95%CIs, comparing 1+2 years trastuzumab and observation.

Results

Association between autoimmune disease history and clinicopathological characteristics. The HERA clinical database was screened for preferred terms of predefined autoimmune comorbidities (13), for which there was clear direct or indirect evidence for autoimmune pathogenesis. All

Table I. *Summary of autoimmune disease at baseline*.

Thyroid background	Autoimmune disease preferred term	Diagnosis		Total (N=325)
		Active (N=295)	Not active (N=30)	
Hyperthyroidism	Hyperthyroidism	41	11	52
	Total	41	11	52
Hypothyroidism	Hypothyroidic Goitre	5	1	6
	Hypothyroidism	213	5	218
	Primary Hypothyroidism	1	0	1
	Total	219	6	225
Thyroiditis	Autoimmune Thyroiditis	7	1	8
	Thyroiditis	2	3	5
	Thyroiditis Chronic	1	0	1
	Total	10	4	14
No Thyroid Background	Cutaneous Lupus Erythematosus	2	0	2
	Lupus Nephritis	1	0	1
	Multiple Sclerosis	2	1	3
	Myasthenia Gravis	1	1	2
	Rheumatoid Arthritis	12	6	18
	Systemic Lupus Erythematosus	2	1	3
	Type 1 Diabetes Mellitus	4	0	4
	Vitiligo	1	0	1
	Total	25	9	34

patients who were enrolled in the HERA trial were included in the current analysis (N=5,099), of whom 4,774 (93.6%) patients had no history of autoimmune disease at baseline, while 325 patients (6.4%) had autoimmune disease history (Figure 1).

A summary of the autoimmune diseases (preferred terms) that were detected in the HERA database are reported in Table I. Most of the autoimmune diseases were reported as active at baseline (N=295, 90.7%) and the majority of them were associated with hypothyroidism (N=219, 67.4%). Table II lists the patients' characteristics according to autoimmune diseases history. There was some evidence that patients with an autoimmune background were more likely to be older ($p<0.001$) and postmenopausal ($p<0.001$) (Table II).

Prognostic value of the autoimmune background in trastuzumab treated patients. The association between autoimmune background and DFS and OS at a median follow-up of 11 years (IQR=10.09-11.53) was evaluated. During this follow-up period, 1,631 patients experienced a DFS event and 1,037 patients an OS event. One or two years of trastuzumab treatment of patients with no autoimmune history, compared to no trastuzumab, reduced the risk of DFS event (Hazard Ratio (HR)=0.77, 95% Confidence Interval (CI)=0.69-0.85) and death (0.74, 95%CI=0.65-0.84). In patients with autoimmune history treated with trastuzumab, the estimated magnitude of reduction in the risk of DFS or OS events was similar to that seen in the no-immune history group (DFS HR=0.76, 95%CI=0.51-1.12; OS HR=0.65, 95%CI=0.40-1.07) (Table III). Evaluation of the interaction between autoimmune disease and treatment suggests that there is no evidence to reject the null hypothesis that there is no interaction (DFS $p=0.95$, OS $p=0.62$).

Discussion

In the present study, we sought to determine whether an autoimmune disease background could identify patients who derive different benefit from primary trastuzumab-based therapy. While there is a growing body of evidence that shows that the immune system contributes substantially to the therapeutic effects of trastuzumab, we were not able to demonstrate an interaction between autoimmune disease background and the level of benefit from trastuzumab treatment.

In HER2 positive breast cancer, the presence of TILs has been shown to have a prognostic value for improved probability of cure in early stages (14) and predictive for trastuzumab benefit (12). These TILs may represent a basic host anti-tumour immune response, which can be further boosted by immunotherapeutic agents. The presence of an autoimmune response is the defining characteristic of an autoimmune disease. Autoimmune diseases can be initiated by different antigens and despite their diverse etiology they are characterized by the presence of self-reactive T lymphocytes (15) and the loss of inhibitory pathways in the

Table II. *Summary of patient's demographic and breast cancer characteristics according to autoimmune background.*

Characteristic	Autoimmune history (N=325)	No autoimmune history (N=4774)	*p*-Value chi-square
Age at study entry (years) - no.(%)			
<35	11 (3.4)	367 (7.7)	<0.001
35-49	111 (34.2)	2153 (45.1)	
50-59	130 (40.0)	1509 (31.6)	
≥60	73 (22.5)	745 (15.6)	
Previous (neo)adjuvant chemotherapy - no.(%)			
No anthracycline	13 (4.0)	289 (6.1)	0.168
Anthracycline but no taxane	217 (66.8)	3252 (68.1)	
Anthracycline and taxane	95 (29.2)	1233 (25.8)	
Menopausal status – no.(%)			
Premenopausal	38 (11.7)	679 (14.2)	<0.001
Uncertain	102 (31.4)	1961 (41.1)	
Postmenopausal	185 (56.9)	2134 (44.7)	
Pathological tumor size (cm) – no.(%)			
0-2	130 (40.0)	1873 (39.2)	0.907
2-5	138 (42.5)	2087 (43.7)	
>5	16 (4.9)	257 (5.4)	
Not assessed (neoadjuvant chemotherapy)	38 (11.7)	525 (11.0)	
Missing size	3 (0.9)	32 (0.7)	
Pathological nodal status – no.(%)			
Negative	103 (31.7)	1543 (32.3)	0.966
1-3 Positive nodes	95 (29.2)	1369 (28.7)	
≥4 Positive nodes	89 (27.4)	1336 (28.0)	
Not assessed (neoadjuvant chemotherapy)	38 (11.7)	525 (11.0)	
Missing	0 (0.0)	1 (0.0)	
Local hormone-receptor status – no.(%)			
Negative	174 (53.5)	2354 (49.3)	0.152
Positive	151 (46.5)	2420 (50.7)	
Histological grade of tumor – no.(%)			
G1	3 (0.9)	103 (2.2)	0.084
G2	104 (32.0)	1548 (32.4)	
G3	210 (64.6)	2879 (60.3)	
Not assessed	8 (2.5)	243 (5.1)	
Missing	0 (0.0)	1 (0.0)	

form of clonal anergy or immunological ignorance (16).

Our hypothesis of enhanced immune response during trastuzumab therapy for early breast cancer in patients with a history of autoimmune diseases is based on studies that demonstrated that part of the trastuzumab therapeutic effect is immune-dependent. It is possible that trastuzumab induces antibody-dependent cellular cytotoxicity (ADCC) by directing effector cells to kill HER2-expressing cancer cells (17). ADCC is directed mainly by the Fc receptor, which is present on natural killer cells that recognize the Fc portion of trastuzumab. This results in an improved response in subjects with a high percentage of TILs in their tumours and an augmented capacity to mediate ADCC (18). Other immune mechanisms involved in trastuzumab activity include: complement-dependent cytotoxicity, phagocytosis of monoclonal antibody-opsonised target cells through receptors for the Fc portion of IgG, induction of production of immunomodulatory cytokines, induction of cross-presentation of tumour antigens and induction of cross-talk among immune cells (9, 19-25). While these mechanisms may enhance trastuzumab activity, trastuzumab treatment is not associated with increased clinical manifestations of autoimmunity (5). This may be related to the specific nature of anti-HER2 treatment and may be also the reason why the presence of autoimmune diseases is not associated with an increased benefit from trastuzumab administration. Indeed, our data suggest that autoimmune comorbidities do not influence trastuzumab effects in the adjuvant setting. This information might be helpful information for clinicians who are reluctant to provide trastuzumab to patients with autoimmune diseases.

The strengths of this study include the analysis of a homogenous population, which was observed prospectively and randomized to trastuzumab adjuvant therapy and has a

Table III. *Hazard ratios for DFS and OS of autoimmune diseases with treatment arm.*

	DFS			OS	
	Patients	Events	HR (95%CI)	Events	HR (95%CI)
Overall population					
1+2 years trastuzumab	3402	1023	0.77 (0.69-0.85)	632	0.73 (0.65-0.83)
Observation	1697	608	-	405	-
Autoimmune disease					
1+2 years trastuzumab	204	61	0.76 (0.51-1.12)	34	0.65 (0.40-1.07)
Observation	121	43	-	29	-
No autoimmune disease					
1+2 years trastuzumab	3198	962	0.77 (0.69-0.85)	598	0.74 (0.65-0.84)
Observation	1576	565		376	

long follow-up period. Moreover, the clinical data and characteristics were well annotated including the presence of autoimmune conditions. Conversely, there are limitations that should be taken into account. As this is not a pre-planned analysis, it is possible that unidentified confounders were non-randomly distributed between groups of interest. Autoantibody (such as anti-thyroglobulin) levels were not collected and information regarding autoimmunity was analyzed on the basis of baseline data only, which excluded post-treatment effects and dynamics. Another weakness of our study is that the selected cases with autoimmune disease history are composed mainly of patients with thyroid diseases especially hypothyroidism of different levels of severity which could have an influence on the end-point. Moreover, the numbers in the autoimmune group are very small; therefore, the test of interaction will be correspondingly low powered.

In conclusion, in this unplanned analysis of a prospective trial we did not confirm the hypothesis that autoimmunity could activate trastuzumab-directed responses triggering an immune response, such that the benefit from trastuzumab would be greater in such patients than those without a history of autoimmune disease.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

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