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Trastuzumab re-treatment following adjuvant trastuzumab and the importance of distant disease-free interval: the HERA trial experience

Otto Metzger-Filho¹, Evandro de Azambuja², Marion Procter³, Magalie Krieguer⁴, Ian Smith⁵, Jose Baselga⁶, David Cameron⁷, Michael Untch⁸, Christian Jackisch⁹, Richard Bell¹⁰, Luca Gianni¹¹, Aron Goldhirsch^{12,13}, Martine Piccart¹⁴, Richard D. Gelber¹⁵, and HREA Study Team

Otto Metzger-Filho: otto_metzger@dfci.harvard.edu; Evandro de Azambuja: evandro.azambuja@bordet.be; Marion Procter: marion.procter@frontier-science.co.uk; Magalie Krieguer: magalie.krieguer@bordet.be; Ian Smith: ian.smith@rmh.nhs.uk; Jose Baselga: baselga@mskcc.org; David Cameron: d.cameron@ed.ac.uk; Michael Untch: michael.untch@helios-kliniken.de; Christian Jackisch: christian.jackisch@klinikum-offenbach.de; Richard Bell: richard@barwonhealth.org.au; Luca Gianni: l.gianni@hsr.it; Aron Goldhirsch: aron.goldhirsch@ibcs.org; Martine Piccart: martine.piccart@bordet.be; Richard D. Gelber: gelber@jimmy.harvard.edu

¹Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue Yawkey, Boston 1238, USA ²Department of Medical Oncology and Breast European Adjuvant Study Team (BrEAST) Data Centre, Institut Jules Bordet and Université Libre de Bruxelles, Brussels, Belgium ³Frontier Science (Scotland) Ltd, Kincaig, Kingussie, UK ⁴Breast European Adjuvant Study Team (BrEAST) Data Centre, Institut Jules Bordet and Université Libre de Bruxelles, Brussels, Belgium ⁵Breast Unit, Royal Marsden Hospital, and Institute of Cancer Research, London, UK ⁶Memorial Sloan-Kettering Cancer Center, New York, NY, USA ⁷Edinburgh Cancer Research Centre, Western general Hospital, University of Edinburgh, Crewe Road South, Edinburgh, UK ⁸Department of Gynecology and Obstetrics and Multidisciplinary Breast Cancer Center, Helios Klinikum, Berlin-Buch, Germany ⁹Department of Gynecology and Obstetrics, Klinikum Off enbach, Off Enbach, Germany ¹⁰Department of Medical Oncology, The Andrew Love Cancer Centre, Deakin University, Geelong, Australia ¹¹Department of Medical Oncology, San Raffaele Institute, Milan, Italy ¹²European Institute of Oncology, Milan, Italy ¹³Swiss Center for Breast Health, Sant'Anna Clinic, Lugano-Sorengo, Switzerland ¹⁴Department of Medicine, Institut Jules Bordet and Université Libre de Bruxelles, Brussels, Belgium ¹⁵Department of Biostatistics and Computational Biology, International Breast Cancer Study Group (IBCSG) Statistical Center, Dana-Farber Cancer Institute, Harvard School of Public Health, Harvard Medical School, Boston, USA

Abstract

This retrospective analysis conducted using data from patients enrolled onto the Herceptin Adjuvant has two objectives: The first is to evaluate the impact of the time interval between the end of adjuvant trastuzumab and distant recurrence (TDRI) upon overall survival (OS). The second is to describe the duration of trastuzumab-based regimens in the metastatic setting for patients previously treated with adjuvant trastuzumab. The first objective included 187 patients treated with adjuvant trastuzumab and diagnosed with distant recurrence at 4-year median follow-up. The second objective included data from questionnaires sent to investigators retreating patients with trastuzumab upon distant recurrence: 144 of 156 questionnaires were returned (93 %), and 90

patients were selected based on available clinical information and consent for subsequent studies. There was no statistically significant relationship between TDRI following 1 year of adjuvant trastuzumab and OS from distant recurrence: hazard ratio 0.991, $p = 0.46$. The median OS from distant recurrence was numerically longer among patients with a TDRI of ≥ 12 months ($n = 103$) than <12 months ($n = 84$) but not statistically significant (23.7 vs. 17.8 months, $p = 0.47$). The median duration of first-line trastuzumab-based regimens for patients previously treated with adjuvant trastuzumab and diagnosed with distant disease recurrence was 8.8 months ($n = 88$). This retrospective, exploratory study suggests that TDRI did not impact on OS measured from distant recurrence. We argue that prospective collection of treatment information beyond disease progression should be included in future clinical studies.

Keywords

Breast cancer; Disease-free survival; HER2+

Introduction

Over the past two decades, there have been significant improvements in the treatment and outcome of women diagnosed with HER2-positive (HER2+) breast cancer [1, 2]. In the early-stage setting, seminal studies have demonstrated significant benefit in outcome with the addition of trastuzumab to chemotherapy-based regimens for patients diagnosed with HER2+ breast cancer [3–5]. The HERA trial represents one of those studies and compares 1 or 2 years of trastuzumab treatment with observation after standard chemotherapy in women with HER2+ breast cancer [3, 6, 7]. Dramatic improvements have also been observed in the metastatic setting. Continuation of HER2 blockade with trastuzumab beyond disease progression proved to be an effective strategy [8–12]. More recently, studies including newer anti-HER2 drugs (e.g., pertuzumab, trastuzumab emtansine) showed substantial gains in OS in patients with HER2+ metastatic breast cancer [1, 2, 13].

While marked gains have been observed in early-stage and metastatic setting, there has been a paucity of data describing the patterns of treatment beyond disease recurrence for patients treated with adjuvant trastuzumab for HER2+ early-stage breast cancer. Therefore, questions such as the impact of disease-free interval (DFI) on the benefit of anti-HER2 regimens in the metastatic setting and the actual benefit of trastuzumab-based regimens upon disease recurrence for patients previously treated with adjuvant trastuzumab remain unclear.

In this exploratory study, we used data from HERA trial and investigated the impact of the interval between the end of adjuvant trastuzumab and distant recurrence (TDRI) upon OS, and the duration of trastuzumab-based regimens in the metastatic setting.

Patients and methods

HERA recruited 5102 patients with HER2+ (centrally confirmed overexpression or amplification), early-stage breast cancer who had completed locoregional therapy (surgery with or without radiotherapy) and received at least four cycles of approved adjuvant chemotherapy. Patients were randomly assigned to observation, 1 year of trastuzumab or 2

years of trastuzumab [3]. Patients randomized to 2 years trastuzumab are not part of this study.

We considered the database with clinical cut-off date 9th June 2008 at 4-year median follow-up data from HERA [7]. Patients treated with adjuvant trastuzumab and diagnosed with distant recurrence after the scheduled treatment period were identified. To obtain further information on the duration of trastuzumab-based regimens in the advanced setting, a questionnaire was sent to investigators retreating patients with trastuzumab upon distant recurrence. Written informed consent was required for patients to enter the HERA trial. Ethics approval was obtained from the centers for the protocol amendment that allowed collection of additional data in the questionnaire for deceased patients.

This study aims at answering two questions: first, the impact of TDRI on OS: here 187 patients randomized to 1 year of trastuzumab and diagnosed with distant recurrence at 4-year median median follow-up were included. Patients with early distant recurrence (e.g., progressing while on adjuvant trastuzumab) are not part of this study. The second is the duration of trastuzumab-based regimens in the advanced setting: here 90 patients retreated with trastuzumab in the metastatic setting were included in our analysis.

Study endpoints

The primary endpoint of HERA was DFS, defined as time from randomization to the first occurrence of any of the following events: recurrence of breast cancer at any site; development of ipsilateral or contralateral breast cancer, including ductal carcinoma in situ; second non-breast malignant disease other than basal-cell or squamous-cell carcinoma in situ of the cervix; or death from any cause without documentation of a cancer-related event. OS was a secondary endpoint and defined as time from randomization to death from any cause, with patients still alive at last follow-up being censored. Additional study details have been described elsewhere [3].

TDRI was defined as the time interval between the end of adjuvant trastuzumab and first documented distant recurrence (Fig. 1). OS from distant recurrence was defined as the time interval from distant disease recurrence to death from any cause. The duration of trastuzumab treatment in the advanced setting (data obtained from questionnaires) was defined as the number of days between the treatment start date and end date +1. For patients with no treatment end date reported, the duration was censored at the date of the questionnaire.

Statistical considerations

The impact of TDRI on OS in months from distant recurrence was evaluated in an unstratified and a stratified Cox proportional hazards model. The stratification factors considered were local hormone receptor status, nodal status, and tumor size (cm).

Kaplan–Meier plots of OS after distant recurrence are presented. Statistical analyses used SAS software (version 9.2 and 9.3).

Results

As noted, the first objective involved 187 patients. Table 1 shows baseline clinicopathologic characteristics of these 187 patients according to TDRI (<12 or ≥12 months). The proportion of patients with hormone receptor-positive status was higher in the cohort with TDRI ≥12 months compared to that in the cohort with TDRI <12 months. The distribution of nodal status was balanced among the cohorts with TDRI <12 months and TDRI ≥12 months.

Overall survival from distant recurrence according to time to distant recurrence interval

The median OS from distant recurrence was numerically longer among patients with a TDRI of ≥12 months ($n = 103$) than <12 months ($n = 84$) but not statistically significant (23.7 vs. 17.8 months, $p = 0.47$), as detailed in Fig. 2.

There was no statistically significant relationship between TDRI (in months) and OS from distant recurrence (in months) (HR 0.99, $p = 0.46$). Similar results (HR 0.98, $p = 0.27$) were observed when adjusting for prognostic factors in a stratified Cox proportional hazards model such as nodal status, hormone receptor status, and tumor size.

Duration of trastuzumab-based regimens as first-line treatment in the advanced setting

As noted, the duration of trastuzumab-based regimens in the advanced setting was assessed using information obtained from questionnaires. 144 out of the 156 questionnaires were returned (92.3 %), and 90 patients were selected based on available clinical information and consent for further studies. Of note, 14 of these 90 patients were randomized to observation and received adjuvant trastuzumab after selective crossover.

As detailed in Fig. 3, the median duration of trastuzumab-based regimens for metastatic disease was 8.8 months ($n = 90$), 9.4 months in the ER+ cohort ($n = 36$) and 8.8 months in the ER– cohort ($n = 52$); ($n = 2$, unknown).

Discussion

The results from this retrospective exploratory study suggest that time to distant recurrence upon completion of adjuvant trastuzumab did not impact on OS of patients experiencing distant recurrence.

Historically, the duration of disease-free interval from the end of adjuvant chemotherapy to disease recurrence has been used as an indicator of resistance to the previous line of therapy. Bonadonna et al. [14] reported in 1985 that the benefits with Cyclophosphamide, Methotrexate, and Fluorouracil (CMF) re-treatment were clearly related to the duration of DFI and encouraged physicians to consider administering the same drug combination when relapse occurs after 12 months of DFI, whereas for shorter remission duration, non-cross resistant regimens should be used. Similarly, the concept of DFI and benefit of chemotherapy had been addressed by Buzdar et al. [15] in 1981 who demonstrated that objective responses to FAC (Fluorouracil, Doxorubicin [Adriamycin], and Cyclophosphamide) occurred only among patients who had relapses after discontinuation of

chemotherapy, but there was no correlation between time to recurrence after discontinuation of adjuvant chemotherapy and subsequent response with doxorubicin-containing regimens.

Contemporary metastatic breast cancer studies usually do not allow the enrollment of patients with a short DFI. In the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) phase III study, patients could have received adjuvant or neoadjuvant chemotherapy with or without trastuzumab, but with an interval of at least 12 months between completion of adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer [2]. In the EMILIA phase III study (An Open-label Study of Trastuzumab Emtansine (T-DM1) versus Capecitabine + Lapatinib in Patients With HER2-positive Locally Advanced or Metastatic Breast Cancer) [1], eligibility criteria included disease progression after a first-line treatment in the advanced setting and patients diagnosed with metastatic disease within 6 months after treatment for early-stage disease.

Our results suggests TDRI following 1 year of adjuvant trastuzumab did not impact on OS measured from the time of distant recurrence among patients diagnosed with early-stage HER2+ breast cancer. Distant recurrence was selected as a preferred endpoint to DFS to eliminate the confounder effect of potentially curative DFS events (e.g., contralateral breast cancer, ductal carcinoma in situ). The median OS from distant recurrence was numerically longer among patients with a TDRI of 12 than <12 months, but not statistically significant. While our study does not support the concept of inferior OS outcome from distant recurrence for patients experiencing a shorter TDRI, it is unclear whether similar results would be observed in different studies.

Of importance, the lack of detailed information on systemic therapies administered for patients experiencing disease recurrence is a limitation to the interpretation of the current results. We attempted to collect further information on the duration of trastuzumab-based regimens in the first-line advanced setting through questionnaires, and data were obtained from a reduced number of patients ($n = 90$). In a previous phase II study including 43 patients treated with adjuvant trastuzumab and diagnosed with disease recurrence after a relapse-free interval interval of 6 months, the median progression-free survival (PFS) to trastuzumab-based regimens was 8.0 months (95 % CI, 6–11 months) [16]. Despite different patient populations and limited numbers, our results showed similar median duration of trastuzumab in the advanced setting for patients previously treated with adjuvant trastuzumab.

Data from recent studies showed longer duration for trastuzumab-based regimens in the first-line advanced setting when compared to our results. In CLEOPATRA, the median PFS in the control arm of study with a trastuzumab-based regimen was 12.4 months [17]. Of importance, only 10 % of enrolled patients received prior trastuzumab-based regimens (i.e., adjuvant or neoadjuvant), and the median PFS in this subset was 10.4 months. The addition of per-tuzumab to a trastuzumab-based regimen in CLEOPATRA added similar benefit in the subsets treated and not treated with trastuzumab for both PFS and OS [18].

Retrospective series have demonstrated prolonged benefit from trastuzumab-based regimens among patients without prior exposure to trastuzumab in the adjuvant setting [19, 20]. In the

largest retrospective series [19], trastuzumab naïve patients ($n = 438$) derived higher clinical benefit to trastuzumab-based regimens in the advanced setting when compared to patients ($n = 75$) previously treated with adjuvant trastuzumab. In a subsequent study aimed at investigating the clinicopathological features associated with prolonged benefit from first-line trastuzumab-based regimen, patients with prolonged treatment duration (highest tertile, > 14 months) were more likely to have not received adjuvant trastuzumab [20]. Of importance, a controlled cohort study showed similar estimates of OS from trastuzumab-based regimens in the metastatic setting among patients with and without prior exposure to trastuzumab in the adjuvant setting [21].

To conclude, we did not provide definitive answers on the impact of TDRI upon OS and the duration of trastuzumab-based regimens in the metastatic setting for patients previously treated with adjuvant trastuzumab.

In spite of limitations, the current work provides two important messages: 1) Prospective collection of treatment information beyond disease progression should be routinely included in adjuvant clinical studies. 2) Historical concepts such as DFI greater than 6 months or greater than 12 months may need to be challenged in the design of future studies in the metastatic setting.

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References

1. Verma S, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012; 367(19):1783–1791. [PubMed: 23020162]
2. Baselga J, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012; 366(2):109–119. [PubMed: 22149875]
3. Piccart-Gebhart MJ, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005; 353(16):1659–1672. [PubMed: 16236737]
4. Romond EH, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005; 353(16):1673–1684. [PubMed: 16236738]
5. Slamon D, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011; 365(14):1273–1283. [PubMed: 21991949]
6. Smith I, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007; 369(9555):29–36. [PubMed: 17208639]
7. Gianni L, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol*. 2011; 12(3):236–244. [PubMed: 21354370]
8. Tripathy D, et al. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol*. 2004; 22(6):1063–1070. [PubMed: 15020607]
9. Petrelli F, Barni S. A pooled analysis of 2618 patients treated with trastuzumab beyond progression for advanced breast cancer. *Clin Breast Cancer*. 2013; 13(2):81–87. [PubMed: 23276465]
10. Campiglio M, et al. Increased overall survival independent of RECIST response in metastatic breast cancer patients continuing trastuzumab treatment: evidence from a retrospective study. *Breast Cancer Res Treat*. 2011; 128(1):147–154. [PubMed: 21479926]

11. Extra JM, et al. Efficacy of trastuzumab in routine clinical practice and after progression for metastatic breast cancer patients: the observational Hermine study. *Oncologist*. 2010; 15(8):799–809. [PubMed: 20671105]
12. von Minckwitz G, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03–05 study. *J Clin Oncol*. 2009; 27(12):1999–2006. [PubMed: 19289619]
13. Krop IE, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014; 15(7):689–699. [PubMed: 24793816]
14. Valagussa P, Tancini G, Bonadonna G. Salvage treatment of patients suffering relapse after adjuvant CMF chemotherapy. *Cancer*. 1986; 58(7):1411–1417. [PubMed: 3755647]
15. Buzdar AU, et al. Management of breast cancer patients failing adjuvant chemotherapy with adriamycin-containing regimens. *Cancer*. 1981; 47(12):2798–2802. [PubMed: 7260870]
16. Lang I, 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(2):81–89. [PubMed: 24051172]
17. Baselga J, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2011; 366(2):109–119. [PubMed: 22149875]
18. Swain SM, 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(6):461–471. [PubMed: 23602601]
19. Murthy RK, et al. Effect of adjuvant/neoadjuvant trastuzumab on clinical outcomes in patients with HER2-positive metastatic breast cancer. *Cancer*. 2014; 120(13):1932–1938. [PubMed: 24677057]
20. Vaz-Luis I, 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(4):254–263. [PubMed: 23829891]
21. Negri E, et al. Effectiveness of trastuzumab in first-line HER2+ metastatic breast cancer after failure in adjuvant setting: a controlled cohort study. *Oncologist*. 2014; 19(12):1209–1215. [PubMed: 25355843]

Fig. 1.
Schematic representation of time to distant recurrence interval

Fig. 2.
Overall survival according to TDRI

Fig. 3.
Duration of trastuzumab-based regimens in the advanced setting

Table 1

Baseline patient and tumor characteristics

	TDRI <12 months (N = 84)	TDRI 12 months (N = 103)
Local hormone receptor status		
Positive	30 (35.7 %)	57 (55.3 %)
Negative	54 (64.3 %)	46 (44.7 %)
Nodal status		
Any nodal status, neoadjuvant chemotherapy	12 (14.3 %)	16 (15.5 %)
Negative	8 (9.5 %)	13 (12.6 %)
1–3 positive nodes	21 (25.0 %)	22 (21.4 %)
4 positive nodes	43 (51.2 %)	52 (50.5 %)
Pathological tumor size		
Not assessed (neoadjuvant chemotherapy)	12 (14.3 %)	16 (15.5 %)
2 cm	19 (22.6 %)	28 (27.2 %)
>2 cm	53 (63.1 %)	57 (55.3 %)
Missing	0 (0.0 %)	2 (1.9 %)
Histologic grade		
Not assessed	0 (0.0 %)	3 (2.9 %)
1	3 (3.6 %)	1 (1.0 %)
2	22 (26.2 %)	35 (34.0 %)
3	59 (70.2 %)	64 (62.1 %)