

## Cardiotoxicity Related to Long-Term Trastuzumab Therapy in Metastatic Breast Cancer: The Potential Role of Treatment Duration and Cardiac Risk Factors

To the Editor:

Since its approval, trastuzumab (Herceptin, F. Hoffmann-La Roche Ltd., Basel Switzerland) has dramatically improved outcomes of patients with Human Epidermal growth factor Receptor 2 (HER2+) metastatic breast cancer (MBC) and has ushered in a new era in clinical practice, providing innovative insights on long-term treatment (1–3). Indeed, several studies have shown that long-term HER2 suppression should be maintained in HER2+ MBC both beyond disease response(4,5) and progression (6,7). Therefore, a growing number of patients have been receiving long-term trastuzumab administration, as maintenance monotherapy or in combination with multiple lines of chemotherapy.

However, over the last 10 years, trastuzumab cardiotoxicity, ranging from asymptomatic left ventricular dysfunction to congestive heart failure (1,8,9), has emerged as a critical concern. Differently than anthracycline, trastuzumab cardiotoxicity is neither dose-related nor cumulative and appears generally reversible (6). Its pathogenesis seems partly due to antibody-directed cellular cytotoxicity, to HER2 downregulation in cardiomyocytes and, as recently demonstrated, to destabilization of mitochondrial membrane with Adenosin Triphosphate depletion and subsequent cardiomyocyte contractile dysfunction (4).

The large trastuzumab adjuvant trials, including the recent analysis of 2-year arm of HERA trial, showed a low incidence of Cardiac Events (CEs) during adjuvant trastuzumab and demonstrated that the cumulative incidence of CEs tends to plateau after treatment completion, thus suggesting that cardiotoxicity occurs early and mainly while on treatment (5,9). However,

these data refer to patients strictly selected on the basis of cardiac risk factors and exposed to trastuzumab for a well-defined time. Conversely, in metastatic setting the cardiac safety of prolonged trastuzumab administration have yet to be clarified, despite an increasing number of patients having received trastuzumab for several years. Data on incidence, onset, and outcome of cardiotoxicity in MBC patients receiving long-term trastuzumab therapy are lacking. Notably, very few studies have weighed benefits and cardiac harms of prolonged trastuzumab therapies in a “real world” MBC population, in which comorbidities, previous treatments and general aging could represent heavy cardiac risk factors (7,10–12).

To determine whether duration of trastuzumab and the presence of cardiac risk factors can affect the cardiac safety of trastuzumab in metastatic setting, we conducted a retrospective analysis of 62 HER2+ MBC patients treated with trastuzumab and at least one concomitant chemotherapy regimen at our Institution from December 2003 to June 2012. The median age was 52 years (range 29–76 years); the median cumulative time receiving trastuzumab resulted 29.5 months (range 3–99 months). Forty patients (64.5%) received trastuzumab without interruption from the diagnosis of MBC, for a median time of 29 months (range 3–99 months); in the remaining patients 1 or 2 interruptions were recorded with a median interruption time of 7 months (range 2–30 months). According to previous published data (9,10), we evaluated, in univariate and multivariate Cox regression analysis, the following variables as potential cardiac risk factors: age at start of trastuzumab, body mass index (BMI, <25 versus  $\geq 25$  kg/m<sup>2</sup>), antihypertensive therapy, history of cardiac disease, diabetes, smoking, radiotherapy on the left chest wall, prior exposure to anthracyclines, baseline Left Ventricular Ejection Fraction (LVEF), continued/interrupted trastuzumab exposure and duration of concomitant exposure to chemotherapy and trastuzumab. In univariate analysis

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significant risk factors for trastuzumab-related cardiotoxicity resulted: history of cardiac disease (hazard ratio [HR] 6.81, 95% CI: 1.38–33.54) and smoking (HR 5.23, 95% CI: 1.40–19.49). In multivariate analysis smoking remained positively correlated with the risk of cardiotoxicity, but this trend was not statistically significant (HR 3.89, 95% CI: 0.88–17.17,  $p = 0.073$ ), probably due to the limited sample size. To our knowledge, such correlation was reported only in the adjuvant setting and it seems related to a negative effect of cigarette smoking on myocardial longitudinal strain (13,14).

In our cohort, a high percentage of patients presented at least one comorbidity (54.8%), received previous anthracycline-based therapies (67.7%) and were older than 60 at the start of trastuzumab administration (35.5%). Despite the long-term trastuzumab exposition and the high rate of potential risk factors, we observed a low incidence of CEs (17.7%). Specifically, three patients (4.8%) experienced an asymptomatic LVEF drop of at least 20% points compared with the baseline, with a LVEF not below normal limits; five patients (8.1%) had a grade 2 cardiac toxicity (LVEF range, 40–50%) and three (4.8%) experienced a grade 3 cardiac toxicity (symptomatic CHF, LVEF range, 20–40%). All of them, except one, quickly recovered after temporary trastuzumab discontinuation with or without appropriate cardiologic therapy. These data were similar to those shown in previous series of trastuzumab administration beyond progression (7,11,12), but lower than that previously reported in MD Anderson Cancer Center cohort, in which a 28% rate of CEs was detected (10). The fairly low incidence of CEs might be due to both our limited

sample size and the inclusion of patients receiving trastuzumab for less than 1 year. To better understand the potential interaction between cumulative trastuzumab exposure and cardiotoxicity, we compared the distribution of CEs over different times of trastuzumab administration. Since in our cohort the majority of CEs occurred within the first 36 months (63.6%), similarly to the data reported in the MD Anderson analysis (10), we hypothesized a plateau phenomenon after 3 years of treatment (Fig. 1). Therefore, we compared the distribution of CEs between those patients receiving trastuzumab for up to 36 months and those continuing for more than 36 months, 7/43 (16.3%) and 4/19 (21%), respectively. The difference in CEs rate between those two groups was not statistically significant ( $p = 0.724$ ), likely due to the limited sample size. However, the distribution of CEs in our analysis suggests that the likelihood of trastuzumab cardiotoxicity does not increase over time nor does it seem related to cumulative trastuzumab exposure. These data are in accordance with those reported in the GBG 26 trial, which evaluated the combination capecitabine with trastuzumab versus capecitabine alone in HER2+ MBC beyond progression. It showed a not statistically significant increase in CEs over a median cumulative time of trastuzumab exposure up to 72 weeks (3). Conversely, Morabito and colleagues, reviewing 37 published clinical trials of trastuzumab in HER2+ MBC, concluded that time receiving trastuzumab was associated with an increased risk of developing any grade of cardiotoxicity (15). However in the majority of the evaluated studies, patients received trastuzumab for up to 40 weeks and thus it is likely that the

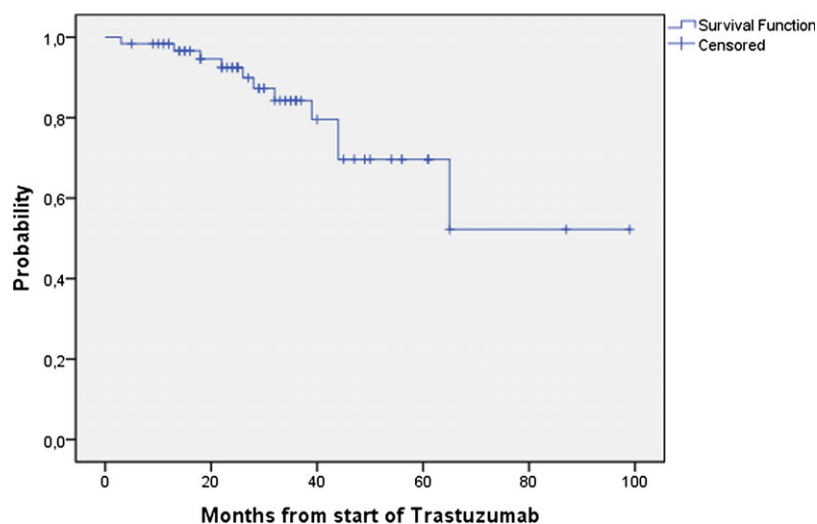


Figure 1. Time to cardiac event.

plateau phenomenon was not reached yet (16). Moreover, in our analysis, the relatively early onset of trastuzumab cardiotoxicity also suggests some consideration on the appropriate cardiac follow-up in MBC patients receiving prolonged trastuzumab administration. In this setting, reliable recommendations for both time and optimal modality of cardiac monitoring and thresholds for trastuzumab discontinuation are lacking (17). In this regard, our findings suggest that cardiac monitoring could be safely delayed in patients with low cardiovascular risk who are continuing uneventfully trastuzumab therapies for more than 36 months.

In conclusion, in daily clinical practice physicians are increasingly called to balance benefits and harms of prolonged trastuzumab-based therapies, especially for patients with several significant cardiovascular risk factors, including elderly people and patients previously exposed to anthracycline. Moreover, the majority of upcoming compounds directed against HER2+ breast cancer are being administered in combination with trastuzumab. Therefore, further studies with larger sample are warranted to provide a thorough knowledge of cardiotoxicity related to long-term trastuzumab administration.

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#### CONFLICTS OF INTEREST

None to declare.

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