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BRIEF REPORT

Effect of early adverse events resulting in ado-trastuzumab emtansine dose adjustments on survival outcomes of HER2+ advanced breast cancer patients

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Abstract

Purpose Ado-trastuzumab emtansine (T-DM1) treatment in HER2+ advanced breast cancer patients is generally well tolerated, but when adverse events occur dose adjustments may be required. This study evaluated the impact of early adverse events requiring T-DM1 dose interruptions or reductions on overall survival (OS) and progression-free survival (PFS) in HER2+ advanced metastatic breast cancer patients in the clinical trials EMILIA and TH3RESA.

Patients and methods The study included 893 participants initiated on T-DM1 treatment. A landmark approach set at 4 months was used to evaluate the association between early adverse events requiring T-DM1 dose interruptions or reductions and OS/PFS. Cox proportional hazard analysis modeled the association between events requiring T-DM1 dose interruptions or reductions and OS/PFS. Associations were reported as hazard ratios with 95% confidence intervals.

Results Adverse events requiring T-DM1 dose interruptions or reductions within the first 4 months of treatment were not significantly associated with OS (hazard ratio (HR) [95% CI]: dose interrupted = 1.15 [0.85–1.55]; dose reduced = 0.75 [0.49–1.14]; $P = 0.214$) nor PFS (hazard ratio (HR) [95% CI]: dose interrupted = 1.13 [0.87–1.48]; dose reduced = 0.90 [0.62–1.31]; $P = 0.534$).

Conclusion The occurrence of early adverse events requiring T-DM1 dose interruptions or reductions do not appear to be associated with altered long-term OS or PFS within a pooled analysis of data from EMILIA and TH3RESA.

Keywords Ado-trastuzumab emtansine · Adverse events · Dose adjustment · Survival · Advanced breast cancer

Introduction

Amplification of the human epidermal growth factor receptor 2 (HER2) protein encoded by the ERBB2 gene occurs in 15–20% of breast cancers [1]. Overexpression of the HER2 protein results in downstream activation of a complex set of mechanisms including the MAPK, PI3K/Akt, and STAT pathways. These pathways promote cell proliferation and oppose apoptosis resulting in uncontrolled cell growth and tumorigenesis [2]. In patients with advanced HER2+ breast cancer, treatment with ado-trastuzumab emtansine (T-DM1)—an antibody–drug conjugate incorporating HER2 antibody trastuzumab and cytotoxic agent DM1—has been shown to provide survival benefits as compared to prior recommended second line and later treatment options [3–7].

Common adverse events from T-DM1 treatment include diarrhea, fatigue, nausea, vomiting, thrombocytopenia, and elevated serum transaminase levels which may range in severity from mild to severe [3, 5–8]. T-DM1 is generally well tolerated, but when adverse events occur, dose adjustments (e.g. dose interruptions, reductions, or withdrawal) may be required, and the effect of these dose adjustments on survival outcomes is currently unknown [8]. The aim of this study was to evaluate the impact of early adverse events requiring T-DM1 dose interruptions or reductions on survival outcomes of HER2+ advanced breast cancer patients.

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Patients and methods

Study design and patients

The study was a pooled analysis of individual-participant data from locally advanced or metastatic breast cancer patients treated with T-DM1 from the randomized clinical trials EMILIA (NCT00829166) [3, 5] and TH3RESA (NCT01419197) [6, 7]. Data were accessed via clinicalstudydatarequest.com. Secondary analysis was approved by the Southern Adelaide Clinical Human Research Ethics Committee.

EMILIA included HER2-positive, unresectable, locally advanced or metastatic breast cancer patients with documented disease progression to previous trastuzumab and a taxane [3, 5]. Patients were excluded if they had received prior T-DM1, lapatinib, or capecitabine [3, 5]. Participants were randomly assigned in a 1:1 ratio to lapatinib plus capecitabine, or to 3.6 mg/kg of intravenous (IV) T-DM1 every 21 days [3, 5].

TH3RESA included HER2-positive, unresectable, locally advanced, recurrent or metastatic breast cancer patients with documented disease progression to previous trastuzumab and lapatinib in the advanced setting and had received a taxane in any setting [6, 7]. Participants were randomly assigned in a 1:2 ratio to a treatment of physician's choice, or to 3.6 mg/kg of IV T-DM1 every 21 days [6, 7].

Dose reductions were permitted within EMILIA and TH3RESA in response to adverse events; first from 3.6 to 3.0 mg/kg of IV T-DM1 every 21 days and then from 3.0 to 2.4 mg/kg [5, 6]. If further dose reductions were required, patients were withdrawn from treatment (EMILIA) or study assessment (TH3RESA) [5, 6]. Dose interruptions of up to 42 days were permitted, and patients requiring dose delay further than 42 days were withdrawn from study treatment [5, 6].

Predictor and outcome data

Evaluated outcomes were overall survival (OS) and progression-free survival (PFS). OS was defined as the interval between randomization to death from any cause. EMILIA defined PFS as the interval from randomization to progression or death from any cause, according to an independent assessment of the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [3, 5, 9]. TH3RESA defined PFS as the interval from randomization to progression or death from any cause, according to investigators assessment of RECIST version 1.1 [6, 7, 10].

Adverse events requiring dose adjustments were categorized as 'dose reduced,' 'dose interrupted,' or 'dose withdrawn.'

Statistical analysis

A conditional landmark analysis [11] was used to evaluate the association between early adverse events requiring T-DM1 dose interruptions or reductions and OS/PFS. The landmark was set at 4 months (126 days, end of 6th cycle). Dose adjustments were only evaluated in the first 4 months, and only individuals who were alive and progression-free at 4 months were included in the analysis.

Cox proportional hazard analysis modeled the association between adverse events requiring T-DM1 dose interruptions or reductions within the first 4 months of T-DM1 treatment and survival outcomes (comparing patients requiring versus not requiring dose interruption/reduction in the first 4 months of T-DM1 treatment). Associations were reported as hazard ratios (HR) with 95% confidence intervals (95% CI). All analyses were stratified by study. Due to in the infrequency of adverse events requiring T-DM1 withdrawal within the first 4 months of treatment ($n=21$), its association with OS/PFS was not assessed [3, 5–7].

Kaplan–Meier analysis was used to plot OS and PFS for patients treated with T-DM1 based upon dose adjustments. All analyses were undertaken using the R statistical environment (version 3.4.3).

Results

The pooled dataset included 893 participants treated with T-DM1. Participant characteristics are summarized in Supplementary Table 1.

Figure 1 presents the incidences of dose adjustments occurring within the first 17 cycles (first year) of T-DM1 treatment in the pooled dataset. Within 4 months of T-DM1 treatment, 70% of the total number of dose adjustments had occurred.

Within 4 months, 266 participants either had disease progression, death or were lost to follow-up and subsequently excluded from the landmark analysis dataset. Of the participants within the landmark analysis dataset, 467 had no dose changes, 86 had dose interruption, 53 had dose reduction, and 21 withdrew from T-DM1 therapy due to adverse events.

At 4 months, there were no significant associations between early adverse events requiring T-DM1 dose interruptions ($n=86$) or reductions ($n=53$) with OS ($P=0.214$) nor PFS ($P=0.534$) (Table 1; Fig. 2). There was no observed heterogeneity in results between studies (Supplementary Table 2). Of the 86 participants that required a maximum dose adjustment of 'interruption' within the first 4 months of T-DM1 therapy, 40 participants required 1 dose interruption, 12 required 2 interruptions and 34 required 3 + dose interruptions. Of the 53 participants that required a maximum

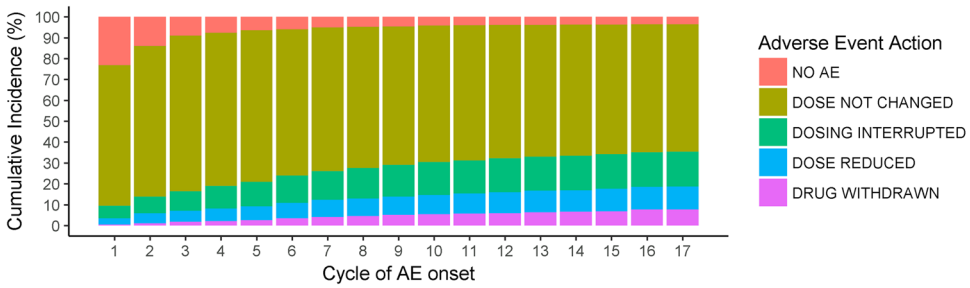

Fig. 1 Cumulative incidence of adverse event actions across first 17 cycles of T-DM1 treatment Note: patients who had disease progression, death or lost to follow-up are included in this figure

Table 1 Summary of association between dose adjustments following adverse events within first 4 months of T-DM1 treatment with OS and PFS

Variable	N	OS		PFS	
		HR [95% CI]	*P* value	HR [95% CI]	*P* value
Dose adjustment			0.214		0.534
No change	467	1.00		1.00	
Interrupted	86	1.15 [0.85–1.55]		1.13 [0.87–1.48]	
Reduced	53	0.75 [0.49–1.14]		0.90 [0.62–1.31]	

N sample size, *CI* confidence interval, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival

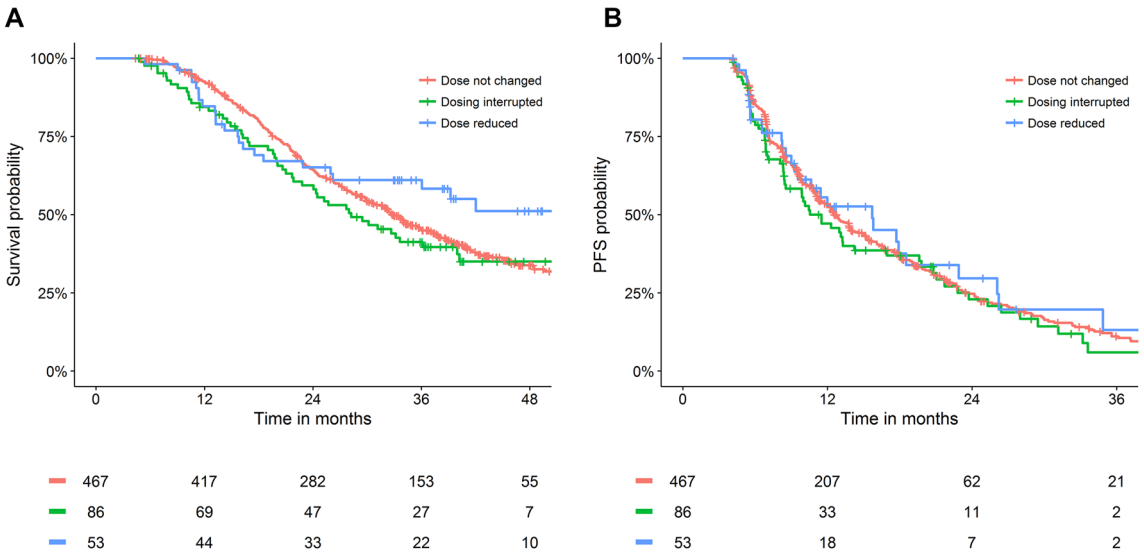

Fig. 2 Kaplan–Meier curve showing OS (**a**) and PFS (**b**) stratified by occurrence of dose adjustments following adverse events within the first 4 months of treatment with T-DM1

dose adjustment of 'reduction' within the first 4 months of T-DM1 therapy, 12 participants required 1 dose interruption, 7 required 2 interruptions, and 7 required 3 + interruptions; further of the 53 'dose reduced' participants, 30 required 1 reduction and 23 required 2 + dose reductions.

Discussion

One of the key concerns for patients and clinicians with the occurrence of adverse events requiring treatment dose adjustments, is that the dose adjustments will ultimately lead to worse survival outcomes. The results of this study highlight that adverse events requiring T-DM1 dose reductions and interruptions do not lead to unfavorable OS or PFS outcomes in patients surviving to 4 months as compared to patients who do not experience adverse events requiring T-DM1 dose adjustments.

An important challenge to clinical practice is minimizing the variability in response and toxicity to cancer medicines. Adverse events and subsequent dose adjustments of medicines are most likely to be associated with therapeutic outcomes when the adverse events reflect 'on-target' pharmacodynamics, or both efficacy and toxicity have

a strong relationship to drug concentration [12]. Previously, Wang et al. [13] identified that increased exposure to T-DM1 therapy in metastatic breast cancer patients was not associated with increased incidence of severe adverse events. Combined with the results identified herein, it may be hypothesized that patients experiencing toxicity and requiring dose adjustments are more pharmacodynamically sensitive to T-DM1 therapy, as opposed to it being a pharmacokinetically driven process.

The strength of this study is the large sample size and consistency of demonstrated associations across studies, providing confidence in the generalizability of assessed associations. Further, the landmark analysis time of 4 months was assessed as this is a time period which may be early enough to provide useful information in the clinic as to long-term outcomes, while capturing a significant proportion of dose adjustments that occur for T-DM1 treatment. The employed landmark approach also minimizes for potential immortal bias problems [11]. While the study has large, high-quality data, the absolute number of participants in the dose reduction/interruption cohorts are less than the large 'no change' cohort. Observing the OS Kaplan–Meier plot (Fig. 2), it may be hypothesized that with a larger sample size the observed trend toward differing OS between the 'no change', 'dose interrupted' and 'dose reduced' cohorts may become apparent—this may be an area for future investigation.

T-DM1 is generally well tolerated and as such, the proportion of patients requiring drug withdrawal ($n = 21$) was minimal even within the large pooled dataset. Thus, the association between early adverse events that required drug withdrawal and OS/PFS was not assessed, although it would be reasonable to hypothesize that drug withdrawal will be associated with poorer survival outcomes given EMILIA and TH3RESA indicate T-DM1 therapy to be superior to alternate treatment options [3, 5–7]. Subsequently the results of this study demonstrate a preference to manage patients through adverse events as dose interruptions or reductions are not associated with worsened survival outcomes.

This study did not include 266 patients who were excluded from the landmark analysis due to either disease progression, death or loss to follow-up before the 4-month landmark. This indicates that patients requiring T-DM1 dose interruptions/reductions who survive to 4 months without progression are unlikely to be subsequently affected in regard to OS/PFS. In clinical practice, this allows for evidence-based counselling to this particular population of patients that their dose adjustment is not associated with poorer survival outcomes. An important area for further investigation would be the development of a baseline prediction model that implements data at an earlier landmark to predict the future risk of adverse survival outcomes before disease progression or death.

In conclusion, the occurrence of early adverse events requiring T-DM1 dose interruptions or reductions do not appear to be associated with altered long-term OS or PFS within a pooled analysis of data from EMILIA and TH3RESA.

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Author contribution All authors were involved in literature search, design, analysis, interpretation and manuscript preparation for this project.

Data availability Individual-participant data utilized were accessed via clinicalstudydatarequest.com, according to Roche's policy and process for clinical study data sharing [14].

Compliance with ethical standards

Conflict of interest Michael J. Sorich and Andrew Rowland report investigator-initiated project grants from Pfizer, outside the scope of the submitted work. Ashley M. Hopkins, Ethan Tang, Ross A. McKinnon have no conflicts of interest to disclose.

Ethical approval Secondary analysis of anonymized participant-level trial data was approved by Southern Adelaide Clinical Human Research Ethics Committee.

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