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Original Article

The Impact of Trastuzumab Administration Patterns on the Long-Term Clinical Outcomes of Patients with Non-Metastatic Breast Cancer in a Resource-Limited Setting

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Abstract

Background: Administration of trastuzumab (TRA) in resource-limited settings (RLS) is associated with significant deviations from per-label recommendations such as fixed-dose instead of weight-based, interruptions, and a reduced number of cycles. The impact of these deviations on the clinical outcomes of HER2-positive non-metastatic breast cancer is unclear.

Methods: We retrospectively reviewed the records of patients with operable HER2-positive breast cancer treated at our center from 2013 to 2018 for TRA dose deviations. The standard protocol for TRA administration includes a one-year course of TRA with one intravenous dose every three weeks for 17 cycles. We assessed the number of cycles, underdosing based on body weight calculation, and low relative dose intensity (RDI). Cox regression analysis was used to identify predictors of survival and was adjusted for baseline clinical variables.

Results: This analysis included 208 patients with a median age of 45 years. A total of 175 (84%) patients showed at least one per label deviation. Fifty-four patients (26%) were underdosed with a mean maintenance dose defect of 54 ±107 mg, 64 (31%) received a reduced number of courses (≤ 9 cycles), and 103 patients (49.5%) received TRA at low RDI. Reduced number of cycles was the only factor associated with a worse hazard of recurrence-free survival and overall survival (HR: 2.25, 95% CI: 1.35–3.75, adjusted p =0.002) and (HR: 2.48, 95% CI: 1.36-4.52, adjusted p =0.003), respectively.

Conclusion: In our cohort, not all the deviations had adverse impacts on clinical outcomes. Only a reduced number of cycles was associated with a worse recurrence-free and overall survival hazard. Improving access to anti-HER2 therapies in RLS is crucial. Ensuring the full course of TRA in RLS is needed.

Keywords: Breast cancer, Cost-effectiveness, HER2 positive, Resource-limited setting, Trastuzumab dose
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Introduction

HER2-positive breast cancers represent almost 20% of breast cancer cases with more aggressive disease and lower survival rates compared to luminal breast tumors [1]. Treatment of HER2-positive breast cancer has been revolutionized by the wide arena of anti-HER2 therapies. Biologic anti-HER2 drugs such as monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates have raised survival to unprecedented levels across different disease stages [2].

Trastuzumab (TRA)-based therapy is the backbone of HER2-positive breast cancer management in neoadjuvant and metastatic settings, either alone or as a dual blockade using pertuzumab. However, in resource-limited settings (RLS), there are several challenges with the costs of administration of TRA, leading to disparities in TRA administration, which consequently affect disease outcomes. Therefore, HER2-positive patients are subject to TRA dose deviations based on older age, comorbidities, race, and stage [3], secondary to the TRA shortage in RLS. For example, in African countries where the cancer burden is predicted to increase by 85% in 2030 [4], TRA was available in only around 50% of breast cancer care facilities. Only 5% of the patients were able to receive it, according to a pilot survey in sub-Saharan countries [5]. In another analysis of TRA affordability in 11 African countries, adjuvant one year of TRA proved to be cost-ineffective in the analyzed countries due to higher costs [6].

Although the development of biosimilars could potentially improve the cost-effectiveness of TRA administration [7], this remains a subject of debate due to the increasing number of patients and the long course of treatment that puts high pressure on healthcare expenditures. Another appealing option for RLS is endorsing the shorter course of adjuvant TRA administration, i.e., 9 weeks vs. 1 year (8). Indeed, Joensuu et al. [8] reported that a 9-week course was non-inferior to the 1-year course and was associated with a better cardiac safety profile [8]. The dosage is also can vary in RLS, our group previously showed that adopting a fixed dose is a questionable approach, and more studies are needed to evaluate that point [9].

Previously, our group showed that the fixed-dose approach leads to significant per-label deviations in patients treated in RLS [9]. However, the impact of TRA deviations on the long-term clinical outcomes of HER2-positive localized breast cancer is still unclear. Therefore, we aimed to perform a retrospective cohort study by reviewing the records of patients with operable HER2-positive breast cancer who received at least one fixed-dose intravenous TRA during the adjuvant or neoadjuvant and who were treated at our institution from 2013 to 2018. We evaluated the TRA dose deviations from the per-label recommendations based on the number of cycles, underdosing based on body weight calculation, and low relative dose intensity (RDI). We aimed to investigate the association between background characteristics and the insufficient administration of trastuzumab in an Egyptian single-institution cohort. In addition, we tried to assess the impact of TRA dosing defects/deviations on the clinical outcome of breast cancer.

Methods

Patient data retrieval

Data were retrieved from records of histologically proven non-metastatic breast cancer (stages I–III) patients treated at the Clinical Oncology Department, Cairo University Hospitals, who received TRA in the period between 2013 and 2018. Patients must have a positive HER2 score of 3+ by IHC or 2+ with a HER2 amplification by in situ hybridization (ISH) technique. Eligible patients' data were recorded and analyzed. Relevant clinicopathological variables derived from the main data to be included in the analysis were age, body weight, TNM stage, and hormone receptor (HR) status.

The loading and maintenance dose, number of courses, duration, dose intensity, adverse effects, and toxicity were all extracted and compared to the drug label recommendation of a loading dose of TRA 8 mg/kg and a maintenance dose of 6 mg/kg for one year. The study was conducted with the approval of the institutional ethical committee, ensuring no breach of the confidentiality of the patient's data retrieved for the analysis. Dose intensity is defined as the drug dose in mg delivered per week (mg/week). We assumed that low relative dose intensity (LRDI) was ≤ 65% of the intended dose intensity.

Deviations from per-label recommendations are defined as:

- Underdosage (for loading and/or maintenance) secondary to fixed-dose usage.
- Reduced total number of courses to less than 9 courses.
- Change in dose density by interruptions between cycles to more than 3 weeks.

Synthetic historical control

It is unclear if the deviations in TRA administration in RLS would mitigate its clinical benefit. To identify the clinical benefit of TRA in our cohort, we compared the clinical outcomes of this cohort to a matched cohort of HER2-positive patients who did not receive TRA. We retrieved data on 164 patients from the

publicly available METABRIC project who are HER2-positive localized breast cancer treated in the UK and Canada with a median follow-up of 42.85 months. We used this individual patient dataset as a synthetic historical control arm. All the METABRIC patients were treated in neoadjuvant or adjuvant settings before approval of anti-HER2 therapies in such settings.

Study outcomes

The primary outcome of our study was the impact of TRA irregularity and dosing interruptions on recurrence-free survival (RFS) compared to regular dosing. Secondary outcomes included: the patterns of dosing schedule interruptions/irregularities in our cohort; the determinants of causes of such administration patterns; the impact of irregularities on OS compared to the SOC group (no relevant dosing deviations); and the RFS, overall survival (OS) comparison between our cohort and the no-TRA cohort (historical control).

Statistical analyses

The R program w was used to conduct descriptive and inferential survival analysis and visualize the data in graphs and figures. Descriptive analysis for the entire cohort, alongside cohorts receiving a reduced number of courses and standard courses Multivariable linear and logistic regression analyses, were done for significant variables in univariable analysis and clinically relevant parameters: age, nodal status, HR status (positive versus negative), and tumor stage (T3/T4 versus T1/T2).

Survival analysis was calculated through Cox regression analysis with corresponding Kaplan-Meier curves in STATA 15. The Wilcoxon test was used as a non-parametric test to assess the significant difference in cumulative dose intensity between undermaintained cases or not and residents in ≥ or <27 km from the medical center. A further Spearman test was used to assess the correlation between cumulative dose and residence in kilometers.

Results

Baseline clinical characteristics

Our cohort included 208 patients; 163 patients (78%) were premenopausal, and 45 (22%) were postmenopausal. The median age was 45 (22–70), the mean weight (kg) was 82.34 (±17.8), and the mean body mass index (BMI) was 33.35±8.8. Patients with the T1-T2 stage were 140 (67.3%), followed by 68 (32.69%) with T3-T4. Patients with the N0 stage represented 95 patients (45.67%) in our cohort. The Minister of Health sponsored treatment for 203 patients (97.5%). 170 (81.7%) patients were from Greater Cairo. Most of the patients (78% were premenopausal), most of the patients were hormone receptor-positive (58%), and IHC was the most used test to assess her2neu status (88%). Table 1 summarizes the baseline characteristics of our cohort.

TRA administration patterns

A total of 139 (66.8%) patients showed at least one per label deviation. A total of 69 patients (33.2%) received standard of care (SoC). SoC is defined as no significant maintenance dose defect (> 100 mg), no significant reduction in the number of TRA courses (> 9 courses), and no significant low RDI (<65%). Overall, 167 patients (80.28%) were underloaded, 54 patients (25.96%) were significantly undermaintained, and 103 patients (49.5%) received LRDI. A reduced number of courses (≤ 9 courses) was observed in 64 patients (30.77%).

We also found that 95 patients (45.6%) had 2 per label deviation, and 13 13 patients (6.25%) had 3 per label deviation. We found that following a fixed dose of 440 mg resulted in a mean loading dose defect of 219 ±141.8 mg and a mean maintenance dose defect of 54 ±106.8 mg. The cumulative dose intensity was 5197.5 ±2256.39 mg, while the intended was 8563 ±851.55 mg/week.

We found no significant statistical difference between cumulative dose and residence ≥ 27 Km (Mann-Whitney U p =0.9025) and undermaintained status (p =0.9066). Overall, there was no significant correlation between cumulative dose and residence (p =0.7524, r =0.02). Table 2 summarizes the characteristics of TRA administration in our cohort.

Table 1: Baseline characteristics of patients

Characteristics		All patients	Reduced No. of courses	Standard No. of courses
		(*n*=208)	(*n*=64)	(*n*=144)
			Median (IQR)	
Age (years)		45 (22-70)	50 (40-57)	43 (37-52)
			Mean (SD)	
Weight (kg)		82 (18)	81 (19)	83 (17)
Body mass index		33 (9)	35 (12)	33 (7)
			n (%)	
	Normal (18-25)	21 (10)	4 (6)	17 (12)
	Overweight (25-30)	54 (26)	18 (28)	36 (25)
	Obese (>30)	132 (64)	41 (64)	91 (63)
Treatment aim	Adjuvant	145 (70)	39 (61)	106 (74)
	Neoadjuvant	63 (30)	25 (39)	38 (26)
T stage	T1	37 (18)	12 (19)	25 (17)
	T2	103 (50)	27 (42)	76 (53)
	T3	37 (18)	11 (17)	26 (18)
	T4	31 (15)	14 (22)	17 (12)
N stage	N0	95 (46)	30 (48)	65 (45)
	N1	52 (25)	15 (24)	37 (26)
	N2	38 (18)	13 (21)	25 (17)
	N3	22 (11)	5 (8)	17 (12)
Recurrence site	Locoregional	19 (25)	6 (9)	13 (9)
	Distant	53 (74)	22 (34)	31 (22)
Source of finance	Ministry of Health	195 (94)	62 (97)	133 (92)
	Others	13 (6)	2 (3)	11 (8)
Menopausal status	Premenopausal	163 (78)	46 (72)	117 (81)
	Postmenopausal	45 (22)	18 (28)	27 (19)
Hormonal receptor status	Positive	121(58)	30 (47)	91 (63)
	Negative	87 (42)	34 (53)	53 (37)
HER2 testing	Immunohistochemistry	184 (88)	62 (97)	122 (85)
	Silver in situ hybridization	12 (6)	0	12 (8)
	Fluorescence in situ hybridization	12 (6)	2 (3)	10 (7)
Residence region	Greater Cairo	170 (82)	46 (72)	106 (74)
	Others	38 (18)	18 (28)	38 (26)

IQR: Interquartile range, **SD:** Standard deviation

Table 2: Trastuzumab administration pattern

	Description	All patients (*n*=208)	Reduced No. of courses (*n*=64)	Standard No. of courses (*n*=144)
No. of trastuzumab courses	Median (IQR)	13 (1-21)		
Mean weight-based loading dose (mg)	Mean (SD)	659 (142)	652 (153)	662 (138)
Mean defect dose (mg)	Mean (SD)	219 (142)	212 (153)	222 (137)
Rate of underloaded	*n* (%)	167 (80)	50 (78)	117 (81)
Mean weight-based maintenance dose (mg)	Mean (SD)	494 (107)	489 (115)	496 (104)
Mean maintenance defect dose (mg)	Mean (SD)	54 (107)	49 (115)	56 (104)
Rate of undermaintained	*n* (%)	54 (26)	16 (25)	38 (26)
Patients received ≤ 9 courses	*n* (%)	64 (31)	64 (31)	144 (69)
Actual dose intensity (mg/week)	Mean (SD)	110 (36)	112 (52)	109 (26)
Intended dose intensity (mg/week)	Mean (SD)	165(36)	163 (38)	165 (35)
Cumulative dose intensity (mg)	Mean (SD)	5198 (2256)	2317 (1319)	6478 (1113)
Intended dose cumulative (mg)	Mean (SD)	8563(852)	8474 (1985)	8602 (1795)
Relative dose intensity	Median (IQR)	65 (33)	64 (49-81)	66 (51-85)

IQR: Interquartile range, **SD:** Standard deviation

Impact of TRA administration patterns on recurrence-free survival

After a median follow-up period of 48 months, 75 patients (36.06%) developed recurrence with a median RFS of 41.63 months. To define the impact of per-label deviations on the RFS, we run univariable and multivariable Cox regression analyses. Neither maintenance dose defect, low RDI (<65%) nor reduced number of courses (≤ 9 cycles) were significantly associated with worse RFS (HR =1.01; 95% CI: 0.61–1.68; *P*= 0.97), (HR =0.99; 95% CI: 0.62–1.59; *p* =0.97) and (HR =1.44; CI 95%: 0.88-2.34; *p* =0.15), respectively (Table 3).

On the other hand, multivariable Cox regression analysis showed that a reduced number of courses (≤ 9 cycles) was associated with a significantly worse RFS (HR = 2.25; 95% CI: 1.35-3.76; *p* =0.001).

While low RDI, maintenance dose defect > 100 mg did not significantly affect RFS adversely (HR = 0.97; 95% CI: 0.6–1.55; *p* =0.89) and (HR = 1.34; 95% CI: 0.79–2.26; *p* =0.27), respectively (Table 3).

Impact of TRA administration patterns on the overall survival

Using univariable Cox regression analysis, patients with undermaintained dosage and low RDI did not show a significant impact on OS (HR = 1.27; 95% CI: 0.71–2.29; *p* =0.42) and (HR = 0.84; 95% CI: 0.48–1.47; *p* =0.55), respectively.

While the reduced number of courses (≤ 9) significantly affected OS adversely (HR = 2.55; 95% CI: 1.45–4.50; *p* =0.001) (Table 4).

Meanwhile, using multivariable Cox analysis, a reduced number of courses (≤ 9) was associated with significantly worse OS (HR = 2.48; 95% CI: 1.36 – 4.52; *p* =0.003). Undermaintained dosage and low relative dose intensity (RDI) were insignificant predictors for OS (HR = 1.42; 95% CI: 0.77–2.62; *p* =0.27) and (HR = 0.82; 95% CI: 0.47–1.44; *p* =0.5) (Table 4).

Clinical outcomes compared with standard of care subgroup

We found that 69 patients received standard of care (SoC) treatment with no deviation in any of the three selected parameters. We conducted a Cox regression analysis to investigate the clinical outcomes in the SoC subgroup in comparison to patients who had one of the three deviations.

Table 3: Univariable and multivariable Cox regression analysis of recurrence-free survival

	HR	Coefficient	95% CI		*p* value
Univariable Cox-regression analysis of recurrence-free survival					
Loading defect (>100 mg)	1.13	0.12	0.61	2.07	0.70
Maintenance defect (>100)	1.01	0.01	0.61	1.68	0.97
Weigh (≥70 Kg)	1.10	0.10	0.64	1.91	0.73
Age	1.00	-0.0049	0.97	1.02	0.68
Number of courses (≤9)	1.44	0.36	0.88	2.34	0.15
Number of courses	0.97	-0.03457	0.93	1.01	0.09
T stage (T3-T4)	1.48	0.40	0.92	2.39	0.10
Nodal involvement (positive)	1.11	0.10	0.69	1.78	0.67
Hormone receptor status (positive)	0.82	-0.20	0.51	1.31	0.40
Relative dose intensity (low)	0.99	-0.01	0.62	1.59	0.97
Relative dose intensity	1.00	0.00	0.99	1.00	0.82
Multivariable Cox-regression analysis of recurrence-free survival (with the No. of courses as a continuous variable)					
No. of courses	0.94	-0.07	0.90	0.98	**<0.001**
Nodal involvement (positive)	1.10	0.10	0.68	1.77	0.69
Age	0.99	-0.01	0.96	1.01	0.34
Hormone receptor status (positive)	0.71	-0.34	0.44	1.15	0.16
T stage (T3-T4)	1.29	0.26	0.79	2.13	0.31
Multivariable Cox-regression analysis of recurrence-free survival (with the No. of courses as a categorical variable)					
No. of courses (≤ 9)	2.25	0.81	1.35	3.76	**0.001**
Nodal involvement (positive)	1.06	0.06	0.66	1.71	0.81
Age	0.99	-0.01	0.96	1.01	0.34
Hormone receptor status (positive)	0.71	-0.34	0.44	1.15	0.16
T stage (T3-T4)	1.35	0.30	0.83	2.22	0.23
Multivariable Cox-regression analysis of recurrence-free survival (with the relative dose intensity as a categorical variable)					
Relative dose intensity (low)	0.97	-0.03	0.60	1.55	0.89
Nodal involvement (positive)	1.09	0.09	0.68	1.76	0.72
Age	1.00	0.00	0.97	1.02	0.77
Hormone receptor status (positive)	0.64	-0.44	0.40	1.03	0.07
T stage (T3-T4)	1.54	0.43	0.95	2.51	0.08
Multivariable Cox-regression analysis of recurrence-free survival (with the relative dose intensity as a continuous variable)					
Relative dose intensity	1.00	0.00	0.99	1.01	0.84
Nodal involvement (positive)	1.10	0.09	0.68	1.77	0.70
Age	1.00	0.00	0.97	1.02	0.77
Hormone receptor status (positive)	0.64	-0.44	0.40	1.03	0.07
T stage (T3-T4)	1.55	0.44	0.95	2.52	0.08
Multivariable Cox-regression analysis of recurrence-free survival (with maintenance defect as a categorical variable)					
Maintenance defect (> 100)	1.34	0.29	0.79	2.26	0.27
Nodal involvement (positive)	1.06	0.06	0.66	1.71	0.81
Age	0.99	-0.01	0.97	1.02	0.61
Hormone receptor status (positive)	0.64	-0.44	0.40	1.03	0.07
T stage (T3-T4)	1.61	0.48	0.99	2.64	0.06

HR: Hazard ratio, **CI:** Confidence interval

Table 4: Univariable and multivariable Cox-regression analysis of overall survival

	HR	Coefficient	95% CI		*p* value
Univariable Cox-regression analysis of overall survival					
Loading defect (>100 mg)	1.10	0.10	0.54	2.28	0.79
Maintenance defect (>100)	1.27	0.24	0.71	2.29	0.42
Weight (≥70 Kg)	0.99	-0.01	0.52	1.87	0.97
Age	0.99	-0.01	0.96	1.02	0.58
Number of cycles	0.92	-0.08	0.88	0.97	**0.0009**
Number of courses (≤9)	2.55	0.94	1.45	4.50	**0.001**
T stage (T3-T4)	1.53	0.43	0.87	2.70	0.14
Nodal involvement (positive)	1.34	0.29	0.76	2.36	0.31
Hormone receptor status (positive)	0.53	-0.63	0.30	0.93	**0.03**
Relative dose intensity	1.00	0.00	0.99	1.01	0.49
Relative dose intensity (low)	0.84	-0.17	0.48	1.47	0.55
Multivariable Cox-regression analysis of overall survival (with the No. of courses as a continuous variable)					
No. of courses	0.92	-0.08	0.87	0.97	**<0.001**
Nodal involvement (positive)	1.34	0.29	0.75	2.37	0.32
Age	0.98	-0.02	0.95	1.01	0.18
Hormone receptor status (positive)	0.59	-0.53	0.33	1.04	0.07
T stage (T3-T4)	1.18	0.16	0.65	2.13	0.59
Multivariable Cox-regression analysis of overall survival (with the No. of courses as a categorical variable)					
No. of courses (≤ 9)	2.48	0.91	1.36	4.52	**0.003**
Nodal involvement (positive)	1.29	0.25	0.73	2.29	0.4
Age	0.98	-0.02	0.95	1.01	0.19
Hormone receptor status (positive)	0.58	-0.55	0.33	1.02	0.06
T stage (T3-T4)	1.25	0.23	0.70	2.26	0.45
Multivariable Cox-regression analysis of overall survival (with the relative dose intensity as a categorical variable)					
Relative dose intensity (low)	0.82	-0.19	0.47	1.44	0.50
Nodal involvement (positive)	1.31	0.27	0.74	2.32	0.35
Age	0.99	-0.01	0.96	1.02	0.55
Hormone receptor status (positive)	0.52	-0.66	0.29	0.91	**0.02**
T stage (T3-T4)	1.50	0.41	0.85	2.66	0.16
Multivariable Cox-regression analysis of overall survival (with the relative dose intensity as a continuous variable)					
Relative dose intensity (low)	1.01	0.00	1.00	1.01	0.30
Nodal involvement (positive)	1.36	0.31	0.77	2.42	0.29
Age	0.99	-0.01	0.96	1.02	0.56
Hormone receptor status (positive)	0.51	-0.67	0.29	0.90	**0.02**
T stage (T3-T4)	1.53	0.42	0.86	2.71	0.15
Multivariable Cox-regression analysis of overall survival (with maintenance defect as a categorical variable)					
Maintenance defect (> 100)	1.42	0.35	0.77	2.62	0.27
Nodal involvement (positive)	1.27	0.24	0.71	2.25	0.42
Age	0.99	-0.01	0.96	1.02	0.39
Hormone receptor status (positive)	0.52	-0.65	0.30	0.92	**0.02**
T stage (T3-T4)	1.57	0.45	0.88	2.81	0.13

HR: Hazard ratio, **CI:** Confidence interval

Table 5: Univariable Cox-regression analysis comparing clinical outcomes of the standard of care subgroup to subgroups with different deviations

	HR	Coefficient	95% CI		*p* value
Overall survival					
SoC vs any deviation	0.57	-0.56	0.30	1.09	0.09
SoC vs non-intense	1.75	0.56	0.56	5.43	0.33
SOC vs undermaintained	0.49	-0.72	0.11	2.18	0.35
SOC vs reduced number of courses (≤9 cycles)	0.30	-1.19	0.13	0.69	**0.004**
Recurrence-free survival					
SoC vs any deviation	0.58	-0.54	0.33	1.03	0.06
SoC vs non-intense	0.74	-0.30	0.33	1.65	0.47
SOC vs undermaintained	0.39	-0.65	0.12	2.32	0.39
SOC vs reduced number of courses (≤9 cycles)	0.46	-0.77	0.23	0.93	**0.03**

HR: Hazard ratio, **CI:** Confidence interval, **SoC:** Standard of care

Our analysis found that neither low RDI nor undermaintained groups showed a significantly worse OS (HR = 1.75; 95% CI: 0.56–5.43; p =0.33), (HR =0.49; 95% CI: 0.11–2.18; p =0.35) or RFS (HR = 0.74; 95% CI 0.33–1.65; p =0.47), (HR =0.39; 95% CI: 0.12–2.32; p =0.39) in comparison to SoC subgroup. Meanwhile, patients who received a reduced number of courses (≤ 9) showed significantly worse OS (HR =0.30; 95% CI: 0.13–0.69; p =0.004) and RFS (HR =0.46; 95% CI: 0.23–0.93; p =0.03) compared with SoC subgroup (Table 5).

Comparing our TRA-treated cohort with historical control

We identified significant differences between the two cohorts. The TRA-treated cohort was younger (mean age 46 vs. 57, t-test p <0.0001), had more patients with T3-4 stage (33% vs. 19%, p =0.001), and more HR-positive patients (58.2% vs. 46%, p =0.008). No significant difference in the rate of node-positive patients (53% vs. 58%, p =0.23). we performed a propensity score matching. According to the baseline clinical variables, a total of 196 TRA-treated patients were matched to 104 TRA-naïve patients in a well-balanced comparison. The densities of the propensity scores for the TRA-treated and TRA-naive patients appeared to have the same support, with densities ranging from 0.2-0.8. The average treatment effect on the risk of recurrence was -0.39 and the risk of death was -0.52, suggesting that TRA-treated patients had a 39% reduction in risk of disease recurrence and a 52% reduction in risk of death compared to TRA-naïve. The relative benefit rate observed in our cohort compared to the matched synthetic control arm was like the relative benefit observed in the registrational HERA study [10, 11]. These data suggest that patients with TRA deviations from per label still draw a significant clinical benefit than no TRA.

Discussion

This analysis highlights that more than two-thirds of our HER2-positive cohort in RLS receive suboptimal doses of TRA with at least one deviation from the standard doses. The sub-optimum loading dose is the most frequently observed deviation secondary to the fixed loading dose of 440mg (one vial), with the mean weight of our patients being 88 kg. In addition, we assessed TRA RDI, the ratio of the total doses of TRA delivered over the total treatment course compared to the standard dose protocol, emphasizing the impact of dose delays on treatment outcomes. Our results revealed that 50% of our patients receive low RDI regimens, and one-third receive a short course of therapy (≤9 courses).

Some studies have investigated the magnitude of TRA access for HER2-positive patients. In a large multinational retrospective study based on national registries and the procurement rate of trastuzumab, there was a major discrepancy between the United States and Western Europe (which have achieved the needs-based procurement level of TRA) and the Eastern European countries, which have procured insufficient TRA compared to their needs [12].

Several methods have been investigated to overcome the TRA shortage in the RLS. Intravenous TRA per-label dosing is weight-based, which might be

problematic in overweight and obese populations (like our population). Studies of IV TRA have shown that a fixed-weekly dose ≥250 mg can achieve the target C_{trough} of >20 mg/mL, unlike the phase 2 trials (H0551g and H0552g) that used a weight-based regimen and reported that variability in TRA pharmacokinetics between the patients was related to the body weight [13].

Wu et al. compared regular weight-based 3-weekly TRA to a monthly fixed dose schedule regarding survival and cardiotoxicity. Like our results, there was no progression-free survival or OS difference between both groups, with p-values of 0.23 and 0.19, respectively. Even after neutralizing the confounders (age, hormone status, LVI, and tumor grade), there was no statistically significant difference reported in both survival outcomes [14].

Larger prospective studies are needed to compare weight-based versus fixed IV dosing schedules in obese patients. The optimal duration of adjuvant TRA is another area of controversy. Five randomized studies have compared the shorter duration of TRA versus the standard 12-month schedule. A large individual patient data meta-analysis of the five non-inferiority studies presented in ESMO 2021 Congress has concluded non-inferiority of the 6-month course of TRA with HR for iDFS of 1.14 (95% CI: 0.88-1.47) but not for the 9-week course. [15]

However, the results of the ShortHER trial showed that lower and intermediate-risk N0–3 may receive 9 weeks of trastuzumab instead of the standard dose [16].

These results seem compelling to adopt the nine-course course for adjuvant TRA in the RLS. However, these findings should be interpreted with caution in patients with high-risk criteria. For example, in the PHARE study, the HR for DFS in tumors less than 2 cm was 1.02 (95% CI: 0.72-1.44) compared to 1.41 (95% CI: 1.09-1.81) in patients with tumors larger than 2. This highlights the value of baseline tumor risk stratification on the non-inferiority of short versus long duration of adjuvant TRA. This might be the reason for the poorer outcome with shorter TRA duration in our cohort given the relatively higher stage compared to the PHARE study [17].

Several other studies found poorer disease outcomes in obese patients. Krasniqi and colleagues proved that BMI ≥ 30 significantly worsens the OS and PFS among patients with early and advanced breast cancer cases when treated with TRA plus chemotherapy [18]. One of the suggested reasons for such poor outcomes is the lower drug (including TRA) serum concentrations in obese patients [19]. Nevertheless, the difference in serum concentrations was not proven to cause a poorer outcome in the clinical setting. Quartino et al. showed that body weight affects the pharmacokinetics of TRA by a 28% difference in minimum concentration >20 μg/mL (20). In addition, the pCR rate was not significantly different between different weight levels, denoting that the fixed 600mg SC dose can be effectively used irrespective of the patient's weight compared to weight-based IV TRA [20].

Moreover, the CANTO trial investigated the correlation between body weight and cardiac toxicity in early breast cancer with HER2 positivity, and it highlighted that 50% of the study population was overweight or obese. The obese group was more liable to cardiac toxicity than the normal-weight group (odds ratio 3.02; 95% CI: 1.10–8.25; p = 0.03) [21], which can explain the poorer outcome in obese patients [22].

The key limitations of our study are its retrospective nature and relatively small sample size. However, we were able to identify a significant effect size on clinical outcomes using long-term follow-up data. A larger prospective registry is needed to validate our findings.

In conclusion, our cohort of high-risk early HER2-positive breast cancer had a relatively poorer outcome than expected from prospective randomized data. Several factors may be implicated with access to life-saving medication, like TRA, among the most important. Most of our cohort suffered deviations from standard dosing schedules, with the most detrimental deviation being the shorter duration of adjuvant TRA. Improving access to anti-HER2 therapies in RLS is crucial and requires global action. RLS practice must ensure receiving an adequate number of adjuvant TRA courses.

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Authors' contribution

Conception & Design: Kassem L, Hassan M; Acquisition, analysis, or interpretation of data: Abd-Elhafeez AAM, Almeldin D, Abbas KS, Abdelazeem B, Saba M, Ahmed E, Shohdy K; Drafting the manuscript: Abd-Elhafeez AAM, Almeldin D, Abbas KS, Abdelazeem B, Saba M, Ahmed E, Shohdy K; Revising the manuscript: Kassem L, Hassan M; Approval of the final version of the manuscript: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Data is available from the corresponding author upon request.

Ethical considerations

The study was conducted after the approval of the Research Ethics Committee of the Faculty of Medicine, Cairo University (code # MS-495-2020).

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Study registration

Not applicable.

References

1. Waks AG, Winer EP. Breast cancer treatment: A review. JAMA. 2019; 321(3): 288-300.
2. Tarantino P, Trapani D, Curigliano G. Mastering the use of novel anti-HER2 treatment options. JCO Oncol Pract. 2021; 17(10): 605-606.
3. Reeder-Hayes K, Peacock Hinton S, Meng K, Carey LA, Dusetzina SB. Disparities in use of human epidermal growth hormone receptor 2-targeted therapy for early-stage breast cancer. J Clin Oncol. 2016; 34(17): 2003-2009.
4. Morhason-Bello IO, Odedina F, Rebbeck TR, Harford J, Dangou J-M, Denny L, et al. Challenges and opportunities in cancer control in Africa: A perspective from the African Organisation for Research and Training in Cancer. Lancet Oncol. 2013; 14(4): e142-e151.
5. Vanderpuye VDNK, Olopade OI, Huo D. Pilot survey of breast cancer management in Sub-Saharan Africa. J Glob Oncol. 2016;3(3):194-200.
6. Gershon N, Berchenko Y, Hall PS, Goldstein DA. Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer. Cost Eff Resour Alloc. 2019; 17: 5.
7. Blackwell K, Gligorov J, Jacobs I, Twelves C. The global need for a trastuzumab biosimilar for patients with HER2-positive breast cancer. Clin Breast Cancer. 2018; 18(2): 95-113.
8. Joensuu H, Fraser J, Wildiers H, Huovinen R, Auvinen P, Utriainen M, et al. Effect of adjuvant trastuzumab for a duration of 9 weeks vs 1 year with concomitant chemotherapy for early human epidermal growth factor receptor 2-positive breast cancer: The SOLD randomized clinical trial. JAMA Oncol. 2018; 4(9): 1199-1206.
9. Kassem L, Shohdy KS, Abdel-Azeez AM, Attia H. Is the fixed-dose intravenous trastuzumab policy warranted in limited-resource settings? J Glob Oncol. 2019; 5: 1-3.
10. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: Final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017; 389(10075): 1195-1205.
11. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005; 353(16): 1659-1672.
12. Ades F, Senterre C, Zardavas D, de Azambuja E, Popescu R, Piccart M. Are life-saving anticancer drugs reaching all patients? Patterns and discrepancies of trastuzumab use in the European Union and the USA. PLoS One. 2017; 12(3): e0172351.
13. Kolberg HC, Jackisch C, Hurvitz SA, Winstone J, Barham H, Hanes V, et al. Is weight-based IV dosing of trastuzumab preferable to SC fixed-dose in some patients? A systematic scoping review. Breast. 2021; 57: 95-103.
14. Wu YY, Huang TC, Tsai TN, Chen JH, Dai MS, Chang PY, et al. The clinical efficacy and cardiotoxicity of fixed-dose monthly trastuzumab in HER2-positive breast cancer: A single institutional analysis. PLoS One. 2016; 11(3): e0151112-e.
15. Earl HM, Hiller L, dunn JA, Conte PF, D'Amico R, Guarneri V, et al. LBA11 - Individual patient data meta-analysis of 5 non-inferiority RCTs of reduced duration single agent adjuvant trastuzumab in the treatment of HER2 positive early breast cancer. Ann Oncol. 2021; 32 (Suppl 5): S1283.
16. Conte PF, Bisagni G, Piacentini F, Sarti S, Minichillo S, Anselmi E, et al. Nine-weeks versus one-year trastuzumab for early-stage HER2+ breast cancer: 10-year update of the Short-HER phase III randomized trial. J Clin Oncol. 2023; 41, (17_suppl): LBA637-LBA637.
17. Pivot X, Romieu G, Debled M, Pierga JY, Kerbrat P, Bachelot T, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol. 2013; 14(8): 741-748.
18. Krasniqi E, Pizzuti L, Barchiesi G, Sergi D, Carpano S, Botti C, et al. Impact of BMI on HER2+ metastatic breast cancer patients treated with pertuzumab and/or trastuzumab emtansine. Real-world evidence. J Cell Physiol. 2020; 235(11): 7900-7910.
19. Gonzalez Garcia J, Gutierrez Nicolas F, Nazco Casariego GJ, Batista Lopez JN, Ceballos Lenza I, Ramos Diaz R, et al. Influence of anthropometric characteristics in patients with HER2-positive breast cancer on initial plasma concentrations of trastuzumab. Ann Pharmacother. 2017; 51(11): 976-980.
20. Quartino AL, Hillenbach C, Li J, Li H, Wada RD, Visich J, et al. Population pharmacokinetic and exposure-response analysis for trastuzumab administered using

a subcutaneous "manual syringe" injection or intravenously in women with HER2-positive early breast cancer. Cancer Chemother Pharmacol. 2016; 77(1): 77-88.

21. Kaboré EG, Guenancia C, Vaz-Luis I, Di Meglio A, Pistilli B, Coutant C, et al. Association of body mass index and cardiotoxicity related to anthracyclines and trastuzumab in early breast cancer: French CANTO cohort study. PLoS Med. 2019; 16(12): e1002989.
22. Guenancia C, Lefebvre A, Cardinale D, Yu AF, Ladoire S, Ghiringhelli F, et al. Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: A systematic review and meta-analysis. J Clin Oncol. 2016; 34(26): 3157-3165.