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Risk of hepatotoxicity with trastuzumab emtansine in breast cancer patients: a systematic review and meta-analysis

Amani M. Cobert, Catherine Helms, Chris Larck and Donald C. Moore

Abstract

Background: Trastuzumab emtansine (T-DM1) is an anti-HER2 antibody-drug conjugate indicated for the treatment of HER2-positive breast cancer. One of the most severe adverse events reported with T-DM1 is hepatotoxicity. The objective of our meta-analysis is to investigate the risk of hepatic adverse events in patients with breast cancer receiving T-DM1 compared with controls.

Methods: We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) comparing T-DM1 with a control treatment in patients with HER2-positive breast cancer. Phase II/III RCTs with available event number or event rate of hepatic toxicity with an assessable sample size were included. Relative risk (RR) and corresponding 95% confidence intervals (CI) for all grade and high-grade (grade 3/4) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations were calculated.

Results: Seven RCTs were deemed eligible and were included in the meta-analysis. The RR for all-grade AST and ALT elevations were 3.24 (95% CI 2.16–4.86; $p < 0.00001$) and 2.90 (95% CI 1.98–4.23; $p < 0.00001$), respectively. The RR for high-grade AST and ALT elevations were 2.73 (95% CI 1.07–6.93; $p = 0.03$) and 2.17 (95% CI 1.34–3.50; $p = 0.002$), respectively.

Conclusions: Our meta-analysis demonstrates that T-DM1-based therapy is associated with an increased risk of AST and ALT elevations.

Keywords: adverse drug event,breast cancer trastuzumab emtansine

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Introduction

Amplification or overexpression of the human epidermal growth factor receptor 2 (HER2) is found in approximately 20% of breast cancer cases.[1] HER2-positive breast cancer has been associated with a more aggressive biological disease course compared with HER2-negative cases of breast cancer.[2] Targeting the HER2 pathway in patients with HER2-positive breast cancer has made significant progress in improving the clinical outcomes of this patient population. The anti-HER2 antibody trastuzumab, in combination with either chemotherapy or pertuzumab plus chemotherapy, has demonstrated improvements in overall survival in the first-line treatment setting for patients with metastatic HER2-positive breast cancer.[3–5] In addition, the addition of anti-HER2 antibodies in the adjuvant and neoadjuvant setting has also led to improvements in outcomes for patients with early stage breast cancer.[6,7]

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate composed of a cytotoxic microtubule polymerization inhibitor, DM1, conjugated to trastuzumab. T-DM1 exerts its anticancer activity by selectively delivering the cytotoxic agent to HER2-positive tumor cells. T-DM1 has demonstrated clinical activity in the setting of metastatic, HER2-positive breast cancer, both as a single-agent and in combination with pertuzumab.[8–11] Recently, a multicenter,

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randomized, phase III trial evaluated T-DM1 in patients with residual disease following neoadjuvant chemotherapy plus HER2-targeted therapy.[12]

While a promising treatment with a novel mechanism of action, T-DM1 can be associated with serious, grade 3 or higher, adverse events. Grade 3 or higher adverse events have been reported in up to 45% of patients receiving T-DM1 therapy.[9] Serious adverse events in patients receiving T-DM1 in both the palliative and curative settings can be troublesome, and it is important to gain a better understanding of the overall risk of developing such events. One of the most serious adverse events that has been reported with T-DM1 is hepatotoxicity.[13]

We conducted a systematic review of the literature to identify published clinical trials evaluating T-DM1 for the treatment of HER2-positive breast cancer. We then performed a meta-analysis to determine the overall risk of developing liver function test abnormalities in patients receiving T-DM1-based therapy compared with control.

Methods

Data sources

Electronic searches of PubMed and Embase (searches with no time limits) were undertaken using the keywords 'trastuzumab emtansine' OR 'T-DM1'. Abstracts from the following annual meetings were also reviewed to identify unpublished studies: American Society of Clinical Oncology, San Antonio Breast Cancer Symposium, and European Society of Medical Oncology. This literature search was implemented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The need for ethics approval by the institutional review board was not required because the present study did not directly involve human subjects and was an analysis of published and publicly available data.

Study selection

Articles that met the following criteria were included: phase II or III randomized clinical trials (RCTs) recruiting patients with breast cancer, patients randomly assigned to receive T-DM1 or control, and an available event number or event rate of hepatic toxicity with an assessable sample size. Exclusion criteria included phase I trials and incomplete reporting of safety data in either the meeting abstract, full text publication, or supplemental data.

Two reviewers (A.C. and D.M.) independently screened the search results for potential inclusion and exclusion in two phases. In the first phase, title and abstract of all identified articles were screened for potential inclusion. In the second phase, full text copies of all articles considered for inclusion were reviewed to ensure the article met the inclusion criteria. The final decision to include an article was determined by an agreement between the two reviewers. Disputes for inclusion or exclusion of an article were resolved *via* a third review (C.L.).

The following information was extracted from each study included in the analysis: primary author's name, year of publication, study phase, treatment arms, number of patients evaluable for analysis in each study arm, number of patients that developed all-grade and high-grade (grade 3/4) AST and ALT elevations.

Statistical analysis

Relative risk (RR) and corresponding 95% confidence intervals (CI) for each hepatic adverse event were the principle measures. The number of events of each all-grade and high-grade AST and ALT elevation were compared between study participants randomized to T-DM1 or control treatment in each eligible study. A random-effect model with the Mantel–Haenszel method was used to calculate the pooled estimates of RR and 95% CIs for each endpoint. Forest plots were constructed to present the estimates. Outcome heterogeneity between the studies in this analysis was evaluated through the I^2 statistic and Cochrane's Q test. An I^2 statistic $>75\%$ indicates considerable heterogeneity. A p-value <0.10 in the Cochrane's Q-test also indicates potential heterogeneity. Data analyses were done using Review Manager, version 5.3 (Nordic Cochrane Center; Copenhagen, Denmark).

Results

A total of 1145 records were identified through a PubMed and Embase search. After removing 207 duplicate records, 938 unique titles and abstracts were reviewed for relevancy (Figure 1). After the

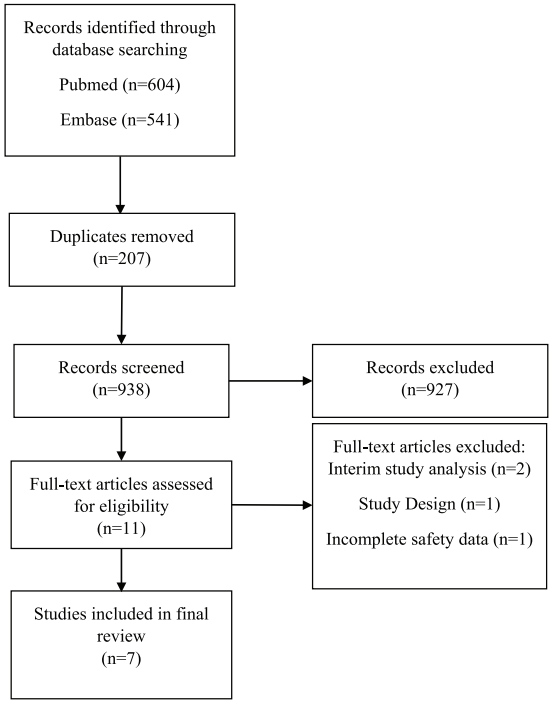

Figure 1. Flowchart of the systematic review process.

initial screening phase, 11 articles were found relevant and the full-text articles were then evaluated for inclusion. Seven articles met our inclusion criteria and were included in the meta-analysis. Four studies evaluated T-DM1 in the setting of metastatic, HER2-positive breast cancer; three studies evaluated T-DM1 in patients with early-stage, HER2-positive breast cancer (Table 1). Four of the seven identified studies evaluated the efficacy and safety of T-DM1 as a single-agent.

The meta-analysis included a total of 5045 patients; 2893 received T-DM1 and 2152 received a control. In the T-DM1 arms of the identified studies, the incidence of all-grade transaminitis ranges from 11.3% to 43.5% for AST and 9.2–26.1% for ALT (Table 2). The incidence of high-grade (grade 3/4) AST and ALT elevations ranged from 0% to 8.7% and 0.4–10.1%, respectively.

The RR for all-grade AST and ALT elevations were 3.24 (95% CI 2.16–4.86; $p < 0.00001$, $I^2 = 76\%$) and 2.90 (95% CI 1.98–4.23;

Table 1. Baseline characteristics of the seven included studies in the analysis.

Study	Trial phase	Sample size of safety analysis	T-DM1 arm	T-DM1 dose	Control arm	Treatment setting
Hurvitz[14]	II	135	T-DM1	3.6 mg/kg every 3 weeks[a]	Trastuzumab + docetaxel	Advanced stage
EMILIA	III	978	T-DM1	3.6 mg/kg every 3 weeks[a]	Capecitabine + lapatinib	Advanced stage
MARIANNE	III	1095	T-DM1 +/– pertuzumab	3.6 mg/kg every 3 weeks[a]	Trastuzumab + taxane	Advanced stage
KRISTINE	III	442	T-DM1 + pertuzumab	3.6 mg/kg every 3 weeks for 6 cycles	TCHP	Early stage, neoadjuvant
Harbeck[15]	II	363	T-DM1 +/– endocrine therapy	3.6 mg/kg every 3 weeks for 4 doses	Trastuzumab + endocrine therapy	Early stage, neoadjuvant
TH3RESA	III	587	T-DM1	3.6 mg/kg every 3 weeks[a]	Physician's choice per local practice	Advanced stage
KATHERINE	III	1460	T-DM1	3.6 mg/kg every 3 weeks for 14 cycles	Trastuzumab	Early stage, adjuvant

[a]Until disease progression or intolerable toxicity.
TCHP, docetaxel, carboplatin, trastuzumab, pertuzumab.

Table 2. The incidence of liver function test abnormalities among the seven eligible studies.

	Hurvitz[14]		EMILIA		MARIANNE		KRISTINE		Harbeck[15]		TH3RESA		KATHERINE	
	Case (n = 69)	Control (n = 66)	Case (n = 490)	Control (n = 488)	Case (n = 727)	Control (n = 353)	Case (n = 223)	Control (n = 219)	Case (n = 241)	Control (n = 122)	Case (n = 403)	Control (n = 184)	Case (n = 740)	Control (n = 720)
AST elevation, all-grade	30 (43.5%)	4 (6.1%)	123 (25.1%)	53 (10.9%)	82 (11.3%)	9 (2.5%)	33 (14.8%)	17 (7.8%)	44 (18.3%)	5 (4.1%)	50 (12.4%)	13 (7.1%)	210 (28.4%)	40 (5.6%)
AST elevation, high-grade	6 (8.7%)	0	22 (4.5%)	7 (1.4%)	35 (4.8%)	1 (0.3%)	1 (0.4%)	1 (0.5%)	0	0	10 (2.5%)	5 (2.7%)	4 (0.5%)	2 (0.3%)
ALT elevation, all-grade	18 (26.1%)	4 (6.1%)	93 (19.0%)	48 (9.8%)	76 (10.5%)	10 (2.8%)	48 (21.5%)	22 (10.0%)	48 (19.9%)	6 (4.9%)	37 (9.2%)	10 (5.4%)	171 (23.1%)	41 (5.7%)
ALT elevation, high-grade	7 (10.1%)	0	15 (3.1%)	9 (1.8%)	35 (4.8%)	3 (0.8%)	3 (1.3%)	4 (1.8%)	1 (0.4%)	0	6 (1.5%)	4 (2.2%)	3 (0.4%)	2 (0.3%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

$p < 0.00001$, $I^2 = 71\%$), respectively. The RR for high-grade AST and ALT elevations were 2.73 (95% CI 1.07–6.93; $p = 0.03$, $I^2 = 51\%$) and 2.17 (95% CI 1.34–3.50; $p = 0.002$, $I^2 = 41\%$), respectively. Figures 2–5 illustrate the forest plots for all-grade and high-grade AST and ALT elevations for T-DM1 compared with control treatments.

The risk of bias for each included study was assessed using the Cochrane risk of bias tool. The results of the risk of bias assessment are summarized in Figure 6. Heterogeneity was found in the analyses of all-grade AST and ALT elevations and high-grade AST elevations. Heterogeneity in these results could come from differences in the duration of T-DM1 therapy and overall drug exposure. Three of the seven studies administered fixed durations of T-DM1 therapy; the remaining four trials administered T-DM1 until disease progression or intolerable toxicity. In addition, heterogeneity in our results could be accounted for by differences in baseline patient characteristics between studies. All the eligible studies included in our meta-analysis were randomized trials. However, six of the included trials were open-label in nature and both the investigator and study subject were aware of the study drug being administered, which can lead to the potential of bias.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the risk of hepatotoxicity associated with T-DM1 therapy in both the early and advanced stage settings of breast cancer. Our meta-analysis suggests that T-DM1-based therapy, whether given as monotherapy or in combination with pertuzumab, increases the risk of all-grade and high-grade AST and ALT elevations.

T-DM1 is an antibody-drug conjugate that consists of the anti-HER2 monoclonal antibody trastuzumab, the microtubule inhibitor DM1, and 4-[N-maleimidolmethyl] cyclohexane-1-carboxylate, the thioether linker that covalently connects the two anticancer agents together.[16] DM1 is a derivative of maytansine, a cytotoxic agent first evaluated in early phase clinical trials in the 1970s.[17–19] These early phase trials demonstrated that aminotransferase elevation was a frequently reported adverse event with maytansine. Preclinical

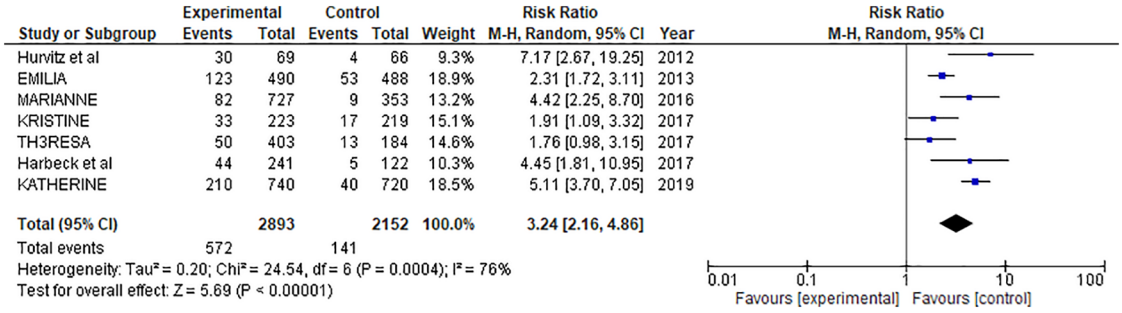

Figure 2. All-grade AST elevations.
AST, aspartate aminotransferase; CI, confidence interval.

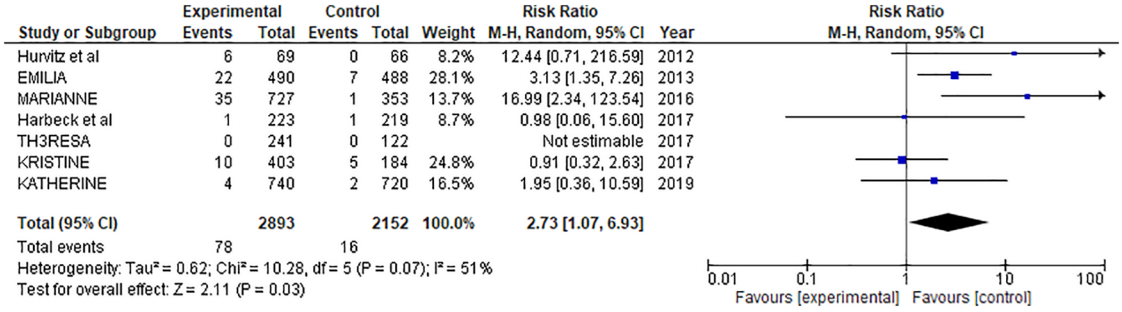

Figure 3. High-grade AST elevations.
AST, aspartate aminotransferase; CI, confidence interval.

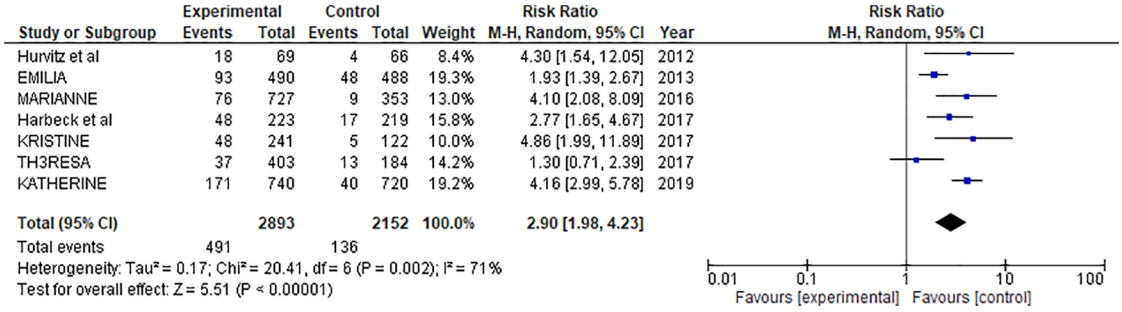

Figure 4. All-grade ALT elevations.
ALT, alanine aminotransferase; CI, confidence interval.

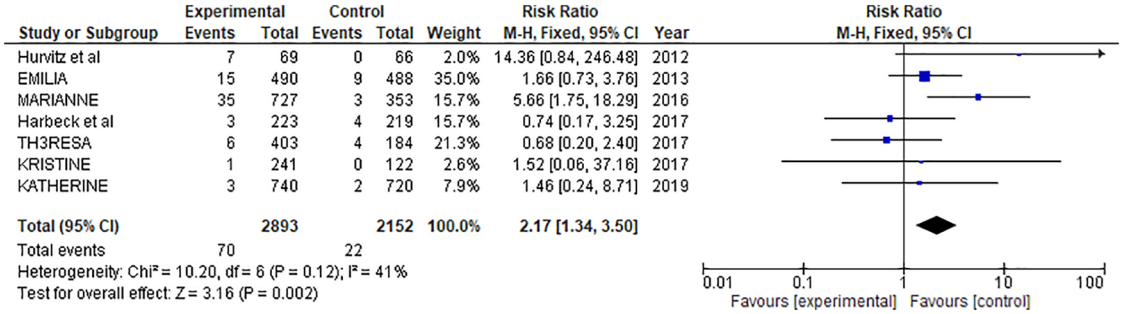

Figure 5. High-grade ALT elevations.
ALT, alanine aminotransferase; CI, confidence interval.

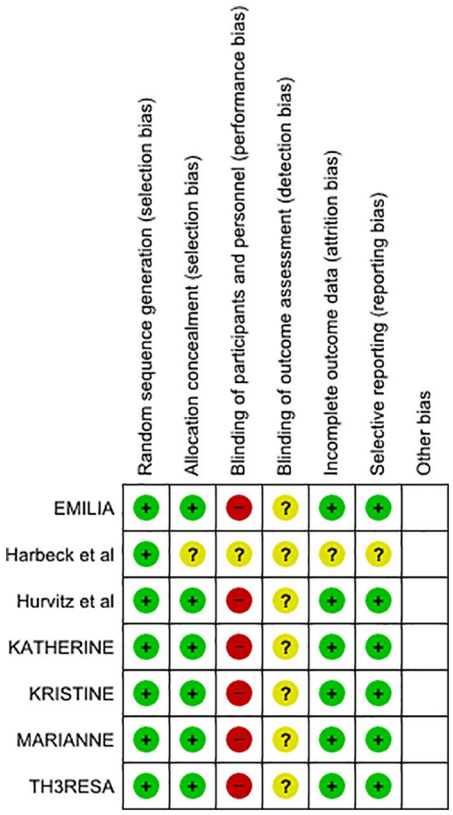

Figure 6. Risk of bias summary.

animal studies in rats and monkeys demonstrated that T-DM1 can cause elevations in aminotransferase levels, and histopathologic changes in the liver including hepatocellular and biliary necrosis.[16] Due to the risk and potential of serious liver injury secondary to T-DM1 therapy, the medication currently has a boxed warning in the product labeling.[13]

The DM1 portion of T-DM1 undergoes hepatic metabolism *via* the CYP3A4/5 pathway.[13] Liver function tests should be monitored at baseline and prior to each dose of T-DM1. The systemic exposure of T-DM1 has been shown to be 38% and 67% lower in patients with Child-Pugh class A and class B hepatic impairment, respectively. Although there are no dose adjustments recommended for patients with pre-existing hepatic impairment, T-DM1 should be used cautiously considering the risk of hepatic injury it possesses. In addition, by undergoing CYP3A4-mediated metabolism, it is important to limit the utilization of strong and moderate CYP3A4 inhibitors in combination with T-DM1 as they can increase serum concentrations of T-DM1, leading to overexposure and an increased risk for adverse drug events, including hepatotoxicity.[13]

The management of T-DM1-induced hepatotoxicity consists of therapy interruption and dose adjustments. Different recommendations exist for the different settings in which T-DM1 can be utilized to treat breast cancer.[13] In the adjuvant setting, the development of grade 2 AST or ALT elevations should be managed by temporarily holding treatment until transaminases have recovered to at least grade 1. Following recovery, grade 2 AST elevations do not require dose reductions, but grade 2 ALT elevations should lead to a dose reduction with further T-DM1 treatment. In the event grade 3 AST or ALT elevations occur, T-DM1 should be held until recovery to grade $\leqslant$1. Treatment can resume at a lower dose upon transaminase recovery.

T-DM1 therapy can continue at the same dose without treatment delay for grade 2 AST or ALT elevations when utilized in the setting of metastatic breast cancer.[13] Treatment should be held temporarily for grade 3 AST or ALT elevations until recovery to grade $\leqslant$2. Once recovery has occurred, T-DM1 can be resumed at a lower dose. It is recommended to permanently discontinue T-DM1 if grade 4 AST or ALT elevations (>20 times upper limit of normal) develop at any time during treatment, regardless of treatment setting.

Our meta-analysis has some limitations. This study was not an individual patient data level analysis, therefore potential individual confounders were not accounted for in our study. Liver function test abnormalities can occur secondary to a variety of other etiologies, including medications and comorbid conditions; these are confounders that could not be accounted for that could have confounded our results. Additionally, there was heterogeneity among the included studies with regards to the incidence of all-grade and high-grade AST and all-grade ALT abnormalities. Heterogeneity could be secondary to differences in T-DM1 duration of therapy, overall drug exposure, and patient populations between the included studies. Also, most of the included studies were open-label trials in which both investigator and study subject were aware of the trial allocation. This could have led to bias in the reporting of safety outcomes. Finally, it is difficult to ascertain the overall clinical impact on patient

outcomes related to the hepatic adverse events reported in the included clinical trials as information regarding duration of liver function test abnormalities and impact on survival was not available.

Conclusion

In conclusion, our systematic review and meta-analysis demonstrates that T-DM1-based therapy is associated with an increased risk of both all-grade and high-grade AST and ALT elevations. Liver function tests should be monitored closely in patients undergoing treatment with T-DM1.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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