META-ANALYSIS

Incidence and risk of severe adverse events associated with trastuzumab emtansine (T-DM1) in the treatment of breast cancer: an up-to-date systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Objectives: We performed an up-to-date meta-analysis to quantify the overall incidence and risk of severe adverse events (AEs) associated with T-DM1 in patients with breast cancer.

Methods: Pubmed, Embase, and oncology conference proceedings were searched for relevant studies. Data were extracted to calculate the summary incidence rate and relative risk (RR) of grade ≥3 AEs.

Results: A total of 5,045 patients from 7 RCTs were included in the meta-analysis. The use of T-DM1 was associated with an increased risk of severe thrombocytopenia (RR 10.66, 95% CI 3.23–35.18, P < 0.001), anemia (RR 1.68, 95% CI 1.15–2.44, P = 0.007), elevated ALT (RR 2.67, 95% CI 1.60–4.47, P < 0.001), and AST (RR 3.76, 95% CI 1.45–9.78, P = 0.007). In addition, the use of T-DM1 can increase the risk of severe hypertension (RR 1.59, 95% CI 1.03–2.45, P = 0.037) and peripheral sensory neuropathy (RR 8.13, 95% CI 1.89–35.03, P = 0.005).

Conclusions: Treatment with T-DM1 increases the risk of severe hematologic toxicities, hepatotoxicity, hypertension, and peripheral sensory neuropathy in patients with breast cancer, while the overall incidence of these AEs is low.

1. Introduction

Approximately 20% of breast cancers (BCs) overexpress the human epidermal growth factor receptor 2 (HER2) [1]. HER2-positive breast cancer has been associated with more aggressive biological processes and poor prognosis [2]. Because of that, HER2-targeted therapies have made significant progress in improving the clinical outcomes of patients with HER2-positive breast cancer. Trastuzumab emtansine (T-DM1, Kadcyla®) is an antibody–drug conjugate (ADC) composed of the antiHER2 antibody trastuzumab conjugated via a stable linker to the highly potent cytotoxin DM1. T-DM1 exerts its anticancer activity by delivering cytotoxic DM1 specifically to HER2-positive cancer cells, and has shown improvement in progression-free survival and overall survival when compared with standard treatments [3–5]. The Food and Drug Administration (FDA) has approved T-DM1 for the treatment of patients with HER2-positive metastatic breast cancer who previously received treatment with trastuzumab and a taxane (paclitaxel or docetaxel), and for the adjuvant treatment of residual invasive HER2-positive breast cancer after neoadjuvant treatment with a taxane and trastuzumab [6,7]. Although several trials have demonstrated that T-DM1 can bring promising clinical benefits for patients with HER2-positive breast cancer, treatment-related severe (grade 3 and grade 4) adverse events (AEs) may lead to the discontinuation of T-DM1 administration. For instance, the previous safety analysis found that thrombocytopenia and hepatotoxicity were the most commonly occurring AEs with T-DM1 [8]. A previous meta-analysis has reported that T-DM1 was associated with more frequent adverse events than other anti-HER2 therapies, but the combined incidence and relative risk of severe AEs were not reported [9]. As serious adverse events associated with T-DM1 treatment are troublesome or even life-threatening, it is essential to gain a better understanding of the incidence and overall risk of developing such events. As a result, we performed this up-to-date meta-analysis of all published randomized controlled trials (RCTs) to evaluate the incidence and overall risk of severe AEs associated with the use of T-DM1-based therapy in patients with breast cancer.

2. Methods

2.1. Data sources

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. However, this study has not been
registered in the International Prospective Register of Systematic Reviews (PROSPERO). We searched the PubMed and Embase from January 2010 to October 2021 using combinations of the following keywords ‘trastuzumab emtansine’ ‘ado-trastuzumab emtansine’ ‘T-DM1’ and ‘breast cancer.’ We also searched abstracts from the following annual meetings: the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO). Additionally, the clinical trial-registration website (http://www.clinicaltrials.gov) was searched to obtain information on registered clinical trials. In cases of duplicate publications, the article providing the most detailed data was included in the meta-analysis. This study did not require an ethical board approval because it was an analysis of published and publicly available data and did not directly involve human subjects.

2.2. Study selection and data extraction

Phase I and single-arm phase II trials were excluded as lacking control groups. Clinical trials that met the following criteria were included in this analysis: (1) prospective phase II or III-randomized clinical trials (RCTs) of patients with breast cancer; (2) random assignment of participants to treatment with T-DM1 or control, and (3) available data for extraction. Data abstraction was conducted by one investigator and checked by another investigator, and any discrepancy between the reviewers was resolved by consensus. We extracted the following information: first author’s name, year of publication, trial phase, treatment arms and control arms, number of patients in treatment arms, median PFS, and median OS. Severe AEs (grade ≥ 3) were assessed according to versions 3 or 4 of the Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0 or 4.0; http://ctep.cancer.gov).

2.3. Statistical analysis

For the calculation of incidence, the number of severe AEs and the total number of patients receiving T-DM1 based therapy were extracted from the selected clinical trials. To calculate the relative risk (RR) of severe AEs, patients assigned to the T-DM1 containing therapy group were compared with those assigned to control treatment in the same trial. We used the classic half-integer correction to calculate the RR and variance for trials with zero events in either the T-DM1-based therapy or control arm [10]. Heterogeneity among treatment groups was assessed by chi-square-based Q statistic, and inconsistency was quantified with the $I^2$ statistic. Heterogeneity was considered statistically significant when $P < 0.1$. If heterogeneity existed, data was analyzed using a random-effect model. In the absence of heterogeneity, the pooled estimate was calculated based on the fixed-effect model. A statistical test with a P-value less than 0.05 was considered significant. All of the calculations were carried out by version 2 of the Comprehensive Meta Analysis (Biostat, Englewood, NJ, USA) program.

3. Results

3.1. Search results

As the literature retrieving process shown in Figure 1, our search yielded 782 potentially relevant studies. After reviewing each publication, 775 studies were excluded according to the inclusion and exclusion criteria. Finally, we selected 7 RCTs, including five phase III and 2 phase II trials after removing duplicated reports and reports with insufficient data [5,11–16]. In total, 5,045 patients were included for analysis. The characteristics of patients and studies are listed in Table 1.

3.2. Study characteristics

In the seven randomized control trials, two trials investigated T-DM1 treatment as first-line therapy [11,12], two trials investigated T-DM1 treatment in patients previously treated with trastuzumab-based therapy [5,13], one trial evaluated T-DM1 treatment in the adjuvant setting [14] and two trials evaluated T-DM1 treatment in the neoadjuvant setting [15,16]. Seven RCTs were included for the analysis of the incidence or RRs of hepatotoxicity; six RCTs were used to evaluate the incidence or RRs of hematological AEs; five RCTs were used to evaluate the incidence or RRs of hypertension and fatigue; four RCTs were used to calculate the incidence or RRs of peripheral sensory neuropathy. As docetaxel plus carboplatin are accompanied by significant toxicities, the KRISTINE study was not used for the calculation of the combined RRs of severe AEs [15].

3.3. Meta-analysis of severe AEs

3.3.1. Hematologic toxicities

The calculated incidence of severe thrombocytopenia was 6.6% (95% CI: 4.4–10.0%) using the random-effect model (heterogeneity test: $I^2 = 86.45\%$, $P < 0.001$) and the calculated incidence of severe anemia 3.8% (95% CI: 2.6–5.5%) with the random-effect model (heterogeneity test: $I^2 = 71.16\%$, $P = 0.002$) (Figure S1). The combined RR of developing hematologic toxicities was 10.66 (95% CI: 3.23–35.18, $P < 0.001$) (heterogeneity test: $I^2 = 71.72\%$, $P = 0.003$) for thrombocytopenia and 1.68 (95% CI: 1.15–2.44, $P = 0.007$) (heterogeneity test: $I^2 = 0\%$, $P = 0.472$) for anemia (Figure 2) (Table 2).

3.3.2. Hepatotoxicity

The calculated incidence of severe hepatotoxicity was 2.6% (95% CI: 1.4–4.6%) (heterogeneity test: $I^2 = 81.43\%$, $P < 0.001$) for elevated ALT and 3.4% (95% CI: 1.9–6.1%) (heterogeneity test: $I^2 = 83.43\%$, $P < 0.001$) for elevated AST (Figure S2). The pooled RR of developing hepatotoxicity was 2.67 (95% CI: 1.60–4.47, $P < 0.001$) (heterogeneity test: $I^2 = 12.13\%$, $P = 0.337$) for ALT and was 3.76 (95% CI: 1.45–9.78, $P = 0.007$) (heterogeneity test: $I^2 = 56.83\%$, $P = 0.041$) for AST (Figure 3) (Table 2).

3.3.3. Hypertension

The summary incidence of severe hypertension was 1.9% (95% CI: 0.9–3.8%) using a random-effects model (heterogeneity test: $I^2 = 80.38\%$, $P < 0.001$) (Figure S3). The pooled RR of
severe hypertension was 1.59 (95% CI 1.03–2.45; P = 0.037) by a fixed-effect model (I² = 0%, p = 0.958) (Figure 4) (Table 2).

3.3.4. Peripheral sensory neuropathy
The summary incidence of severe peripheral sensory neuropathy was 1.6% (95% CI: 0.98–2.9%) by using a random-effect model (heterogeneity test: I² = 52.69%; P = 0.096) (Figure S4). T-DM1-containing therapy was associated with increased risk of severe peripheral sensory neuropathy with an RR of 8.13 (95% CI: 1.89–35.03, P = 0.005) using a fixed-effect model (heterogeneity test: I² = 0%, P = 0.581) (Figure 5) (Table 2).

3.3.5. Fatigue
Using a fixed-effect model (heterogeneity test: I² = 45.97%; p = 0.116), the summary incidence of severe fatigue was 2.0% (95% CI: 1.5–2.8%) (Figure S5). The pooled RR of severe fatigue was 0.93 (95% CI: 0.54–1.59; P = 0.793) without significant

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**Table 1.** Baseline characteristics of 7 trials included in the meta-analysis.

| Study                  | Trial design | Treatment arm          | Control arm               | No. of patients in treatment arm | Median OS (months) | Median PFS (months) | Jadad score | CTCAE version |
|------------------------|-------------|------------------------|---------------------------|---------------------------------|--------------------|--------------------|-------------|---------------|
| Hurvitz et al 2013[11] | Phase II    | T-DM1 3.6 mg/kg q3w    | Trastuzumab + docetaxel   | 69                              | NA                 | 14.2               | 3           | 3             |
| Perez et al 2017[12]   | Phase III   | T-DM1 3.6 mg/kg q3w    | Trastuzumab + Taxane      | 361                             | NA                 | 14.1               | 3           | 4             |
|                        | Phase III   | T-DM1 3.6 mg/kg q3w+   | Trastuzumab + Pertuzumab   | 366                             | NA                 | 15.2               | 4           | 4             |
| Krop et al 2017[13]    | Phase III   | T-DM1 3.6 mg/kg q3w    | Physician’s choice         | 403                             | 22.7               | 6.2                | 3           | 4             |
| Diéras et al 2017[5]   | Phase III   | T-DM1 3.6 mg/kg q3w    | Capecitabine plus lapatinib| 490                             | 29.9               | 9.6                | 3           | 4             |
| von Minckwitz et al 2019[14]| Phase III | T-DM1 3.6 mg/kg q3w    | Trastuzumab                | 740                             | NA                 | NA                 | 3           | 4             |
| Hurvitz et al 2019[15] | Phase III   | T-DM1 3.6 mg/kg q3w+   | TCH+P                      | 223                             | NA                 | NA                 | 3           | 4             |
| Harbeck et al 2017[16] | Phase II    | T-DM1 3.6 mg/kg q3w+   | Trastuzumab + ET           | 241                             | NA                 | NA                 | 3           | 4             |

TCH+P: docetaxel, carboplatin, and trastuzumab plus pertuzumab; ET: endocrine therapy; OS: overall survival; PFS: progression free survival; CTCAE, common toxicity criteria adverse events; NA, not available.
Figure 2. Relative risk of T-DM1 associated severe hematologic toxicities versus control from randomized controlled trial. a the combined relative risk of thrombocytopenia; b the combined relative risk of anemia.

Table 2. Incidence and relative risk of severe adverse events comparing T-DM1 containing therapy vs control.

| Adverse events                  | T-DM1-containing therapy | Incidence (95% CI) | RR (95% CI) | P value |
|---------------------------------|--------------------------|--------------------|-------------|---------|
| Thrombocytopenia[5,11–15]       | 195/2652                 | 6.6 (4.4–10.0)     | 10.66 (3.23–35.18) | <0.001 |
| Anemia[5,11–15]                 | 95/2652                  | 3.8 (2.6–5.5)      | 1.68 (1.15–2.44)  | 0.007  |
| ALT[5,11–16]                    | 71/2893                  | 2.6 (1.4–4.6)      | 2.67 (1.60–4.47)  | <0.001 |
| AST[5,11–14]                    | 77/2429                  | 3.4 (1.9–6.1)      | 3.76 (1.45–9.78)  | 0.007  |
| Hypertension[5,12–15]           | 55/2583                  | 1.9 (0.9–3.8)      | 1.59 (1.03–2.45)  | 0.037  |
| Peripheral sensory neuropathy[5,13–15] | 28/1856               | 1.6 (0.9–2.9)      | 8.13 (1.89–35.03) | 0.005  |
| Fatigue[5,11,13–15]             | 35/1925                  | 2.0 (1.5–2.8)      | 0.93 (0.54–1.59)  | 0.793  |

heterogeneity among included studies ($I^2 = 31.46\%$; $P = 0.224$) (Figure 6) (Table 2).

3.4. Meta-analysis of treatment discontinuation associated with AEs

The pooled incidence of treatment discontinuation associated with AEs in T-DM1-containing group was 15.6% (95% CI:12.8–18.8%) by using a random-effect model (heterogeneity test: $I^2 = 74.87\%$; $P = 0.001$) (Figure S6). T-DM1-containing group had a significantly lower risk of treatment discontinuation than treatment group including single-agent chemotherapy (RR 0.62, 95% CI 0.44–0.88, $P = 0.007$; heterogeneity test: $I^2 = 76.65\%$; $P = 0.002$), but showed a significantly higher risk of treatment discontinuation than trastuzumab or trastuzumab plus pertuzumab therapy (RR 7.13, 95% CI 4.65–10.94, $P < 0.001$; heterogeneity test: $I^2 = 34.55\%$; $P = 0.216$) (Figure S7).

4. Discussion

Trastuzumab emtansine (T-DM1) is an ADC combining trastuzumab and the cytotoxic microtubule inhibitor DM1. Although T-DM1 treatment has brought promising clinical benefits for patients with HER2-positive breast cancer, several severe AEs may result from T-DM1 treatment. Our meta-analysis, including 5,045 patients from 7 RCTs, demonstrated that the use of T-DM1 was associated with an increased risk of severe hematologic toxicities, hepatotoxicity, hypertension, and peripheral sensory neuropathy. Early detection and effective management of these severe AEs are crucial for safer use of this drug. In addition, we found that the risk of treatment discontinuation associated with AEs in T-DM1-containing group was lower than treatment group including single-agent chemotherapy, but higher than trastuzumab or trastuzumab plus pertuzumab therapy.
Figure 3. Relative risk of T-DM1 associated severe hepatotoxicity versus control from randomized controlled trial. a the combined relative risk of ALT; b the combined relative risk of AST.

Figure 4. Relative risk of T-DM1 associated severe hypertension versus control from randomized controlled trial.

Figure 5. Relative risk of T-DM1 associated severe peripheral sensory neuropathy versus control from randomized controlled trial.
Thrombocytopenia is the most common AE associated with T-DM1 treatment and the calculated incidence of severe thrombocytopenia was 6.6%. The mechanisms underlying the development of thrombocytopenia induced by T-DM1 targeting drugs are not fully clarified. One possible mechanism of T-DM1-mediated thrombocytopenia might be an off-target action that megakaryocytes uptake T-DM1 through pinocytosis. Then, the intracellular generation of the active catabolite results in the disruption of microtubules and inhibit megakaryocyte differentiation and disrupt proplatelet formation [17,18]. Severe thrombocytopenia might lead to dosage reduction or even termination of T-DM1, thus preventing patients from obtaining benefits for this treatment. Dose modification guidelines recommend that in the event of decreased platelet count to Grade ≥ 3 (<50,000/mm³), T-DM1 treatment should be discontinued until the platelet count is restored to Grade 1 (≥75,000/mm³). However, in cases of grade 4 thrombocytopenia (<25,000/mm³), T-DM1 therapy should be resumed only at a lower dose following recovery [19]. Closely monitoring is recommended for patients on anti-coagulant treatment during treatment with T-DM1.

Hepatotoxicity is also the most common serious AEs associated with T-DM1 treatment. A recent meta-analysis found that T-DM1-based therapy is associated with an increased risk of severe AST and ALT elevations, but the pooled incidence was not reported [20]. Similarly, our analysis showed that the pooled incidence of severe ALT and AST elevations was 2.6% and 3.4%, respectively. The use of T-DM1 was associated with an increased risk of severe hepatotoxicity. As the DM1, a cytoxic component, is metabolized mainly by CYP3A4, liver function should be monitored at baseline and during T-DM1 therapy. In addition, concomitant use of CYP3A4 inhibitors should be avoided due to the potential for an increase in serum concentrations of T-DM1, leading to increased risk of hepatotoxicity [21].

Regarding peripheral neuropathy, our results showed that T-DM1-containing regimens can increase the risk of severe peripheral sensory neuropathy, and the calculated incidence was 1.6%. In the analysis conducted by Diéras V et al., the rate of all grade peripheral neuropathy was 29.1%, but the rate of severe event (grade 3 or 4) was 2.5%, which is similar to our finding [8]. Microtubule-inhibiting chemotherapy is often accompanied by neurotoxicity. Active DM1 catabolites inhibit microtubule polymerization in the target cells, which may be irreversible [22,23]. As the incidence of peripheral neuropathy increased with the duration of therapy, T-DM1 should be discontinued in patients experiencing grade 3 or 4 peripheral neuropathy until significant clinical improvement [24]. It is noteworthy that T-DM1 might increase the risk of severe hypertension when compared with controls. The calculated incidence of severe hypertension ranged from 0.2 to 4.9% with the highest incidence noted in the Phase III MARIANNE Study [12]. Although the overall incidence of severe hypertension is low, appropriate management is needed for safer use of this drug.

There are several limitations that need to be considered in this meta-analysis. Firstly, this is a meta-analysis at study level, therefore, the confounding factors at the patient level including age, performance status, previous therapeutic exposure cannot be assessed properly and incorporated into the analysis. Secondly, most clinical trials will formally exclude patients with poor hematological and hepatic functions, so the incidence of severe AEs could be higher in daily clinical work. Thirdly, all of included clinical trials were open-label trials, and both investigator and study subject were aware of the trial allocation, which may affect the evaluation and reporting of severe AEs.

5. Discussion

Gene amplification and overexpression of HER2 in breast cancer is associated with an aggressive form of disease and poor prognosis. The introduction of HER2-targeted therapies has greatly improved clinical outcomes in patients with HER2-positive breast cancer. Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate consisting of the humanized antiHER2 antibody trastuzumab covalently linked to the cytoxic agent DM1. Although T-DM1 has proved its effectiveness in advanced metastatic breast cancer as well as in the adjuvant setting, treatment-related severe (grade 3 and grade 4) adverse events (AEs) may lead to dosage reduction or discontinuation of T-DM1 administration.

This meta-analysis found that the use of T-DM1 is associated with increased risk of developing severe hematologic toxicities, hepatotoxicity, hypertension, and peripheral sensory neuropathy, but the incidence of these AEs is low. Thrombocytopenia is the most common hematologic toxicity associated with T-DM1 treatment, and it is a primary cause of drug dosage reduction or discontinuation in some patients.
As patients with thrombocytopenia experience increased bleeding risk, caution should be exercised for safer use of this agent, especially when coadministered with antiplatelet and anticoagulation drugs. Hepatotoxicity is another common AE associated with T-DM1 treatment. The DM1 is a highly potent microtubule inhibitory drug and metabolized mainly by CYP3A4. Therefore, liver function should be monitored at baseline and during T-DM1 therapy. In addition, concomitant use of CYP3A4 inhibitors should be avoided due to the potential for an increase in serum concentration of this agent, leading to increased risk of hepatotoxicity. Furthermore, T-DM1 treatment is also associated with an increased risk of developing peripheral neuropathy, which should be discontinued in patients experiencing grade 3 or 4 peripheral neuropathy until significant clinical improvement. Notably, we found that T-DM1 may increase the risk of severe hypertension. Hypertension is an independent risk factor for the development of cardiovascular and renal disease. Patients with poorly controlled hypertension are at increased risk for serious cardiovascular events and life-threatening consequences. Thus, close monitoring and appropriate management of hypertension are recommended for safer use of this drug.

T-DM1 was generally well tolerated in this analysis, with a significantly lower risk of treatment discontinuation than treatment group including single-agent chemotherapy. In order to prevent premature discontinuation of this agent, it is important for physicians to be aware of the incidence and risk of severe AEs associated with T-DM1 to monitor and treat them appropriately.

6. Conclusion

In conclusion, our study suggests that the use of T-DM1 is associated with increased risk of developing severe hematologic toxicities, hepatotoxicity, hypertension, and peripheral sensory neuropathy, whereas the pooled incidence of these severe AEs is low. As this drug gains greater clinical use in patients with breast cancer, physicians, and patients should be aware of these risks and appropriate management are recommended for safer use of this drug.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contributions

JH Zhang and HY Shi conceived and designed the study. K Liu and YH Li assisted with search and collection of the data. X Zhang, L Su, and JH Li were involved in the analysis and interpretation of the data. K Liu and X Zhang drafted the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of work.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

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Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.

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