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Adverse Events of Trastuzumab Emtansine (T-DM1) in the Treatment of HER2-Positive Breast Cancer Patients

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Summary

The human epidermal growth factor receptor 2 (HER2) is commonly associated with poor prognosis and is overexpressed in approximately 15–20% of all breast cancers. The introduction of HER2-targeted therapies led to significant improvement in the prognosis of patients with HER2-positive breast cancer, for both early and advanced disease. These targeted therapies include the antibodies trastzumab and pertuzumab, the tyrosine kinase inhibitor lapatinib, and the antibody-drug conjugate trastuzumab emtansine (T-DM1). T-DM1 combines the antitumor activity of trastuzumab with that of DM1, a highly potent derivative of the anti-microtubule agent maytansine, resulting in increased anti-tumor activity. Notably, this agent has been demonstrated to be safe and is associated with low toxicity rates. However, maytansinoid, the cytotoxic component of T-DM1, does have the potential to induce various adverse events, particularly radiation necrosis, when used in combination with stereotactic radiosurgery. In this review, we aimed to summarize the current literature regarding T-DM1 safety and toxicity, with special emphasis on the existing landmark studies.

Introduction

Breast cancer (BC) is known to be a biologically heterogeneous disease with a variety of subtypes showing major variance in terms of biological basis, treatment options, and treatment outcomes. Overexpression of the human epidermal growth factor receptor 2 (HER2) and/or *HER2/neu* gene amplification is found in 15–20% of all breast cancers; in the case of metastatic disease, the HER2-positive rate is even higher [1]. Before the advent of HER2-targeted drugs, this subtype was considered as harboring the worst prognosis of all breast cancers [2]. Currently, several targeted agents are available, e.g. the HER-directed antibodies trastuzumab and pertuzumab [3], the HER2 and EGFR tyrosine-kinase inhibitors lapatinib [4] and neratinib [5], and the antibody-drug conjugate (ADC) trastuzumab-emtansine (T-DM1) [6]. These targeted therapies resulted in major improvement in treatment outcomes of both early and advanced-stage HER2-positive BC.

In 2013, the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the clinical use of T-DM1, which was the first ADC that was specifically developed for the treatment of HER2-positive BC. T-DM1, also known as ado-trastuzumab emtansine or Kadcyla®, combines the monoclonal antibody trastuzumab with the cytotoxic mertansine (DM1), a maytansinoid class anti-microtubule agent, linked by a stable thioether. After T-DM1 binds to the HER2 receptor, the complex of HER2 and T-DM1 enters target cells through receptor-mediated endocytosis. This results in antibody degradation within the lysosome, intracellular release of DM1, and subsequent cell cycle arrest and apoptosis induction. Concurrently, trastuzumab sustains its anti-HER2 properties, including the inhibition of HER2 intracellular signaling pathways and the induction of cell-mediated cytotoxicity [6, 7]. A specific feature of T-DM1 includes the selective delivery of the cytotoxic component to the tumor, which mini-

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mizes systemic toxicity and generally improves tolerance of T-DM1 [2, 3]. Due to the favorable safety profile of T-DM1, studies reporting excessive toxicity are relatively sparse. However, considering the increasing use of T-DM1, there is need for a comprehensive assessment of its toxicity. In this review, we summarize the currently available literature on the most important adverse events (AEs) of T-DM1 as a compendium for clinical practice.

Landmark Studies Providing Toxicity Data on T-DM1

T-DM1 is currently approved for the treatment of patients with HER2-positive metastatic BC (MBC), who previously received taxane plus trastuzumab. The approval of T-DM1 was based on the results from the EMILIA trial, a large phase III trial, which compared the outcomes of patients who received lapatinib plus capecitabine to those receiving T-DM1 [8]. Among the 991 randomized patients, the median progression-free survival was 6.4 months in the lapatinib plus capecitabine arm versus 9.6 months in the T-DM1 group (hazard ratio (HR) 0.65; 95% confidence interval (CI) 0.55–0.77; $p < 0.001$). In terms of safety and toxicity of T-DM1, the EMILIA study reported lower rates of grade ≥ 3 AEs in patients receiving T-DM1 compared to those on lapatinib and capecitabine (41% vs. 57%, respectively). The most common AEs in the T-DM1 arm were: nausea, fatigue, thrombocytopenia, headache, constipation, diarrhea, elevated liver enzymes, anorexia, and epistaxis [8].

Other phase III studies providing relevant toxicity data were the TH3RESA and MARIANNE trials. In the TH3RESA trial, patients with progressive HER2-positive, advanced BC who had received 2 or more HER2-directed regimens in the advanced setting, including trastuzumab and lapatinib, and previous taxane therapy in any setting, were randomly assigned to T-DM1 (404 patients) or treatment by physician's choice (198 patients). As in EMILIA, a lower incidence rate of grade ≥ 3 AEs was observed in the T-DM1 arm of TH3RESA, as compared to patients randomized to physician's choice of treatment (32% vs. 43%, respectively) [9]. Finally, in the MARIANNE trial, 1,095 patients with HER2-positive advanced BC who had received no prior therapy for advanced disease were randomly assigned, in a 1:1:1 ratio, to 1 of the following 3 groups: T-DM1 plus placebo, T-DM1 plus pertuzumab, and a control arm of trastuzumab plus a taxane [10]. According to this study, the incidence rate of grade ≥ 3 AEs was higher in the control group (54.1%), compared to the T-DM1 (45.4%) and the T-DM1 plus pertuzumab group (46.2%) [10].

Presently, the ongoing KAMILLA trial is investigating the safety and efficacy of T-DM1 in patients with HER2-positive locally advanced BC or MBC, who were previously treated with HER2-targeted therapy and chemotherapy [11]. At the 2016 San Antonio Breast Cancer Symposium (SABCS), the authors of the KAMILLA trial presented an interim analysis, comparing the outcomes of T-DM1 in 399 patients with brain metastases to 1,618 patients without. According to their data, the rates of AEs were similar between both subgroups, except nervous system AEs, which occurred more frequently in patients with brain metastases (28% vs. 1%). In general, treatment was well tolerated with nausea, headache, and fatigue reported as the most common side effects. AEs of grade ≥ 3 occurred in 184 patients with brain metastases and 628 patients without (46% vs. 39%), with the rate of serious AEs in the 2 groups being 28% and 20%, respectively [11].

Meanwhile, results from early BC trials support a satisfactory safety profile of T-DM1. The KRISTINE phase III open-label study compared neoadjuvant T-DM1 plus pertuzumab to docetaxel/carboplatin/trastuzumab/pertuzumab, in patients with HER2-positive early BC. Again, the incidence of grade ≥ 3 AEs was lower in the T-DM1 plus pertuzumab group than the non-T-DM1 group (13% vs. 64%) [12].

Finally, several phase II studies also provided safety and toxicity data for T-DM1 treatment. The WSG-ADAPT trial reported the elevation of liver enzymes as the only grade ≥ 3 AE in 4% of 375 patients with HER2-positive, hormone receptor-positive early BC who were either randomized to neoadjuvant T-DM1 (119 patients), T-DM1 plus endocrine therapy (127 patients), or trastuzumab plus endocrine therapy (129 patients) [13]. These findings coincide with those of other similar phase II trials [14–17]. Table 1 provides a summary of these studies.

The recently published GATSBY trial [18] evaluated the efficacy and tolerability of T-DM1 in patients with pretreated HER2-positive, advanced gastric cancer compared to treatment with either docetaxel or paclitaxel. Pharmacokinetic analyses from previous studies had shown that, at the same starting dose, trastuzumab serum concentrations were lower in patients with gastric cancer as compared to those with BC [18–20]. According to the GATSBY trial, the safety profile of T-DM1 was comparable between gastric cancer and BC patients, without any new safety concerns being identified. Compared to the taxane group, the T-DM1 group showed lower rates of grade ≥ 3 AEs (60% in patients treated with T-DM1 vs. 70% for patients treated with taxanes). The most common grade ≥ 3 AEs in gastric cancer patients who received T-DM1 were anemia (26%) and thrombocytopenia (11%). Generally, T-DM1 was well tolerated in the GATSBY study patients [18].

Incidence of T-DM1-Induced Adverse Events

The most frequently occurring all-grade AEs in patients receiving T-DM1 include fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation, and epistaxis [21]. A recent meta-analysis reported incidence rates of 46% for fatigue, 43% for nausea, 32% for thrombocytopenia, 29% for headache, and 26% for constipation [22]. Although most of these AEs are generally low grade and manageable, severe thrombocytopenia, which is the most frequent grade ≥ 3 AE, might necessitate dose reduction or discontinuation of treatment [21, 22]. The following section provides an overview of the incidence of the most frequently occurring AEs, as reported by the previously mentioned landmark studies (table 2).

Table 1. Landmark studies providing data on T-DM1-induced adverse events

Study	Phase	Year	Patients, n	Study groups (n)	Primary endpoints	Main finding	Ref.
EMILIA	III	2012	991	T-DM1 (495) vs. lapatinib plus capecitabine (496)	PFS	median PFS T-DM1: 9.6 months vs. median PFS lapatinib plus capecitabine 6.4 months	[4]
					OS	median OS at the second interim analysis crossed the stopping boundary for efficacy (30.9 vs. 25.1 months)	
					safety	grade ≥ 3 AEs higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%).	
TH3RESA	III	2014	602	T-DM1 (404) vs. physician's choice (198)	PFS	median PFS: T-DM1 6.2 months vs. physician's choice 3.3 months	[5]
					OS	OS showed a trend favoring T-DM1, but stopping boundary was not crossed	
					safety profile	lower incidence of grade ≥ 3 AEs with T-DM1 than with physician's choice (8.0% vs. 32%)	
WSG-ADAPT	II	2015	375	T-DM1 (119) vs. T-DM1 plus ET (127) vs. trastuzumab plus ET (129)	pCR rates of each T-DM1 arm (± ET)	pCR 41% T-DM1 and 41.5% T-DM1 plus ET vs. 15.1% trastuzumab plus ET	[9]
					safety	grade ≥ 3 AE with significant difference between arms (pooled T-DM1 vs. trastuzumab plus ET)	
					toxicity	very low overall toxicity	
KAMILLA	III	2016	2,017	T-DM1 for CNS metastases at baseline (399) vs. no CNS metastases at baseline (1618)	PFS	median PFS 5.5 months in patients with CNS metastases at baseline vs. 7.9 months in patients with no CNS metastases at baseline	[7]
					safety profile	grade ≥ 3 AEs higher in patients with CNS metastases at baseline than in patients without CNS metastases at baseline (46% vs. 39%)	
KRISTINE	III	2016	432	T-DM1 plus pertuzumab (223) vs. docetaxel plus carboplatin plus trastuzumab and pertuzumab (219)	pCR rate	pCR rate T-DM1 44.4% vs. docetaxel plus carboplatin plus trastuzumab and pertuzumab 55.7%	[8]
					safety profile	grade ≥ 3 AEs T-DM1 13.0% vs. docetaxel plus carboplatin plus trastuzumab and pertuzumab 64.4%	
MARIANNE	III	2017	1,095	T-DM1 with pertuzumab (363) or T-DM1 with placebo (367) vs. trastuzumab plus taxane (365)	PFS	median PFS T-DM1 with pertuzumab 15.2 months vs. median PFS T-DM1 14.11 months vs. median trastuzumab plus taxane 13.7 months Addition of pertuzumab to T-DM1 did not improve PFS	[6]
					safety profile	grade ≥ 3 AEs higher in the trastuzumab plus taxane (54.1%) vs. T-DM1 arm (45.4%) and T-DM1 plus pertuzumab arm (46.2%)	

T-DM1 = trastuzumab emtansine, AE = adverse event, CI = confidence interval, CNS = central nervous system, ET = endocrine therapy, HR = hazard ratio, PFS = progression-free survival, OS = overall survival, pCR = pathological complete response.

Hematopoietic System

Thrombocytopenia is a common AE in patients receiving T-DM1. According to the WSG-ADAPT, TH3RESA, and EMILIA trials, all-grade thrombocytopenia occurs in up to 28% of patients [8, 9, 13]. According to the EMILIA trial, severe thrombocytopenia, (i.e. grade ≥ 3 (platelets (PLT) 25,000–50,000/mm^3) was reported in up to 12% of the treated patients [8]. Notably, almost all patients receiving T-DM1 experience a transient decline in their platelet count, with the nadir most frequently occurring 8 days after treatment completion, with subsequent recovery at day 15 [8,

Table 2. Incidences in percent of T-DM1-induced adverse events according to landmark studies

Adverse event	MARIANNE				KRISTINE		WSG-ADAPT		TH3RESA		EMILIA	
	T-DM1		T-DM1 plus pertuzumab									
	any grade	grade ≥ 3	any grade	grade ≥ 3	any grade	grade ≥ 3	any grade	grade ≥ 3	any grade	grade ≥ 3	any grade	grade ≥ 3
Thrombocytopenia	n/a	6.4	n/a	7.9	n/a	1.8	10.4	n/a	15.0	4.7	28.0	12.9
Fatigue	n/a	n/a	n/a	n/a	n/a	n/a	22.8	n/a	27.0	2.0	35.1	2.4
Nausea	47.1	n/a	52.2	n/a	n/a	n/a	20.7	n/a	n/a	n/a	39.2	0.8
Vomiting	21.6	n/a	30.1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	19.0	0.8
Headache	32.1	n/a	32.2	n/a	n/a	n/a	16.2	n/a	n/a	n/a	n/a	n/a
Diarrhea	25.2	n/a	48.1	n/a	n/a	0.9	n/a	n/a	10.0	n/a	23.3	1.6
Epistaxis	31.0	n/a	34.7	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
AST increased	n/a	6.6	n/a	3.0	n/a	n/a	17.0	n/a	8.0	2.0	22.4	4.3
ALT increased	n/a	4.4	n/a	5.2	n/a	n/a	18.7	n/a	n/a	n/a	16.9	2.9
Arthralgia	22.2	n/a	18.9	n/a	n/a	n/a	8.3	n/a	n/a	n/a	n/a	n/a
Myalgia	17.7	n/a	16.9	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pyrexia	27.7	n/a	32.2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mucositis	n/a	n/a	n/a	n/a	n/a	0.9	7.5	n/a	n/a	n/a	6.7	0.2

AST = aspartate aminotransferase, ALT = alanine aminotransferase, n/a = not available.

14, 15, 23]. Furthermore, experimental studies evaluating the mechanism of thrombocytopenia in patients receiving T-DM1 suggested an uptake of the drug by megakaryocytes through a non-target-mediated mechanism (e.g. pinocytosis), whereas the intracellular generation of the active catabolite results in the disruption of microtubules and inhibition of pro-platelet production [24, 25].

In most patients, the first occurrence of thrombocytopenia grade ≥ 3 was observed during the first 2 treatment cycles [8]. Despite a higher percentage of dose modification or treatment delays among the affected patients, most were able to continue T-DM1 [8, 15]. Dose modification guidelines suggest treatment interruption in case of grade 3 thrombocytopenia until the platelet count recovers to grade ≤ 1 (i.e. PLT ≥ 75,000/mm^3) [26]. In case of a grade 4 thrombocytopenia (i.e. PLT < 25,000/mm^3), T-DM1 treatment should be re-initiated at a lower dose level after recovery.

Epistaxis is a frequent AE that occurs because of thrombocytopenia. It has been reported in up to 36% of patients on T-DM1 [14–16]. According to the MARIANNE trial, the incidence rate of all-grade epistaxis was 31% in the T-DM1 alone arm, compared to almost 35% in the T-DM1 plus pertuzumab study arm [10]. Patients in the KAMILLA study developed epistaxis in 16% and 21% of the cases with and without brain metastases, respectively [11].

Neutropenia is another hematological AE reported in patients receiving T-DM1. Regarding the TH3RESA, MARIANNE, and EMILIA trials, the incidence of all-grade neutropenia ranged from 5% to 11% in patients receiving T-DM1 alone [8–10, 16]. Severe neutropenia (grade ≥ 3, including febrile neutropenia) was reported in up to 6% of the study patients, which shows the rarity of this toxicity in T-DM1 compared to traditional cytotoxic agents [8–10, 16]. The suggested underlying mechanism of neutropenia is similar to that of taxanes. The incidence rate of anemia was reported to be as low as 2.7% according to the EMILIA and TH3RESA trials [8, 9].

Cardiovascular System

Cardiotoxicity was an unusual finding among patients treated with T-DM1 after anthracycline-based chemotherapy [27]. Nevertheless, patients with T-DM1 are at an increased risk of developing left ventricular dysfunction. The current EMA recommendation includes the routine scan of the individual cardiac function either by an echocardiogram or a multi-gated acquisition (MUGA) scan prior to the therapy initiation. Moreover, re-evaluation for this cardiac dysfunction is recommended at regular intervals throughout treatment. If a left ventricular dysfunction already exists, administration of the next dose may be delayed, and/or treatment discontinued if necessary. Verma et al. [8] reported that the rate of change of the left ventricular ejection fraction (LVEF) was similar between the T-DM1 and lapatinib plus capecitabine arms of the EMILIA trial. In particular, 97% of patients receiving T-DM1 maintained an LVEF of ≥ 45% [8]. This is consistent with the results of other landmark studies reporting that very few patients discontinue treatment due to cardiotoxicity [9, 16, 27]. From a clinical perspective, treatment with T-DM1 should be stopped if the LVEF is either < 40% or 40–45% with a ≥ 10% absolute decrease below the pretreatment value (table 3). Consequently, the LVEF should be monitored within 3 weeks, and T-DM1 should be withheld for as long as the LVEF is not sufficient.

Cases of hemorrhagic events have been reported in clinical trials with T-DM1. In the TH3RESA trial, grade 5 subarachnoid hemorrhage was reported in a few cases, and was associated with grade 4 thrombocytopenia. The affected patients also received concomitant anticoagulant therapy. Of 403 patients who received T-DM1, 9 (2%) had grade 3 or worse hemorrhage of any type. Although rare, the reporting of a grade 5 hemorrhage event in the TH3RESA trial suggests that T-DM1 has the potential to lead to severe hemorrhage with fatal outcome [9]. In the EMILIA

Table 3. Dose adjustment in case of severe T-DM1-induced adverse events

Adverse event	Severity	Adjustment
Elevated liver enzymes (AST and/or ALT)	grade 2: > 2.5 to ≤ 5× ULN	continue treatment in the same dosage
	grade 3: > 5 to ≤ 20× ULN	discontinue treatment until recovery to grade ≤ 2
	grade 4: > 20× ULN	end treatment with T-DM1
Thrombocytopenia	grade 3: 25,000 to <50,000 platelets/mm^3	discontinue treatment until recovery grade ≤ 1 (i.e. ≥ 75,000/mm^3), then continue treatment in the same dosage
	grade 4: < 25,000 platelets/mm^3	
Cardiac dysfunction	LVEF > 45%	continue treatment in the same dosage and check LVEF after 3 weeks (discontinue if < 40%)
	LVEF 40–45% and LVEF decrease of < 10% compared to pretreatment value	continue treatment in the same dosage and check LVEF after 3 weeks
	LVEF 40–45% and LVEF decrease of ≥ 10% compared to pretreatment value	discontinue treatment and check LVEF after 3 weeks (end treatment if LVEF increase is < 10%)
	congestive heart failure	end treatment with T-DM1

AST = aspartate aminotransferase, ALT = alanine aminotransferase, ULN = upper limit of normal, LVEF = left ventricular ejection fraction.

trial, the overall incidence of bleeding events was higher with T-DM1 (29.8% vs. 15.8% with lapatinib plus capecitabine). However, rates of grade 3 and 4 bleeding events were very low (0.8%). The only grade 4 bleeding event was a gastrointestinal hemorrhage in a patient treated with T-DM1, whose platelet counts were within the normal range during the study treatment [8]. In 43 patients with MBC and central nervous system metastases, the frequency of any-grade hemorrhage was 27.9%, with no case of cerebral bleeding reported in the T-DM1 arm [26]. It has been suggested that patients with thrombocytopenia and those on anticoagulant treatment should be monitored closely during T-DM1 treatment [9].

Gastrointestinal System

Gastrointestinal disorders are frequent AEs among patients who are treated with T-DM1. These AEs include nausea/vomiting, stomatitis, abdominal pain, diarrhea, and constipation. In several landmark studies, nausea appeared to be the most frequent AE with an all-grade rate of up to 47% being reported [10]. However, in the pooled T-DM1 arms (T-DM1 alone plus T-DM1 combined with endocrine therapy) of the WSG-ADAPT trial, the incidence of grade ≥ 3 nausea was very low (<1%) [12]. The incidence of vomiting ranged from 14% to 20%, with significantly higher rates observed in cases with brain metastases [8, 11]. Hypokalemia was reported in 9% of 490 patients receiving T-DM1 in the EMILIA trial [8], but higher incidences were reported by other studies [14, 15]. As reported by Burris et al. [14], hypokalemia was not associated with vomiting, diarrhea, or diuretics.

According to the WSG-ADAPT trial, the incidence of stomatitis was 7.5% in the pooled T-DM1 arms [13]. Similar results were reported by the EMILIA trial (6.7%) [8]. Abdominal pain may occur in 6–9% of patients [9, 15]. In the EMILIA and TH3RESA trials, all-grade diarrhea occurred in 23% and 10%, respectively, with grade 3 diarrhea being reported in up to 2% of cases [8, 9]. Results of the MARIANNE trial showed that diarrhea occurred less frequently in patients who received T-DM1 alone (25.2%), when compared to those receiving the combination of T-DM1 with pertuzumab (48.1%) [10]. Regarding constipation, the KAMILLA study reported an all-grade constipation rate of 20% and 19% in patients with and without brain metastases, respectively [11]. In summary, these data suggest a favorable gastrointestinal toxicity profile.

Hepatobiliary System

Besides thrombocytopenia, the second most commonly reported grade 3 AE in patients receiving T-DM1 is the elevation of liver enzymes. Grade 3 or 4 elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum concentrations were reported in 2–10% of patients on T-DM1 [8–10, 16]. However, most of these patients were able to continue treatment [8]. Similar to thrombocytopenia, the elevation of the liver enzymes does not correlate with a greater exposure to T-DM1, but typically improves with dose reduction [28]. Nevertheless, the clearance of T-DM1 depends mainly on the hepatobiliary and gastrointestinal route, necessitating that patients with hepatic disease should be kept under closer surveillance [22, 29].

Kosmin et al. [30] reported an increase in splenic volume in 12 patients with MBC who received T-DM1. The authors of this study also found an association between T-DM1 treatment and splenic enlargement with bone marrow hyperplasia. Hence, caution should be applied to avoid misinterpretation of T-DM1-induced bone marrow hyperplasia as diffuse disease progression in bone. T-DM1-induced splenic enlargement should also be considered in case of a period of prolonged thrombocytopenia [30].

Central Nervous System

Headache is a common AE in patients exposed to T-DM1 either with or without brain metastases. All-grade headache occurred in 32% of patients on T-DM1 as reported in the MARIANNE trial [10]. Other studies reported both lower (16%) and higher (41%) incidence rates [13, 15, 16]. In the KAMILLA study, the all-grade headache incidence was reported to be 28% in patients treated with T-DM1 who had brain metastases, and 21% in patients without brain metastases at baseline [11].

According to the literature, microtubule-inhibiting chemotherapy (e.g. DM1) is often accompanied by neurotoxicity. DM1 causes notable degeneration of the axons, which may be irreversible [28]. In the MARIANNE trial, any-grade peripheral neuropathy was reported in 13% of patients in the T-DM1 alone arm and almost 18% of the patients in the T-DM1 plus pertuzumab arm [10]. However, peripheral neuropathy of grade ≥ 3 was rare in the KRISTINE trial, and occurred in 1% of patients who received T-DM1 plus pertuzumab [12]. Considering that 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 (i.e. grade ≤ 2).

Skin and Subcutaneous Tissue

Rash is common among patients who receive epidermal growth factor receptor (EGFR) and HER2-targeting agents. However, in comparison to single EGFR inhibitors (i.e. erlotinib, panitumumab, and cetuximab), HER2-specific inhibitors, (i.e. trastuzumab or T-DM1), and dual inhibitors of EGFR and HER2, (i.e. lapatinib or pertuzumab), show lower incidence of rash [31, 32]. According to the data provided by the MARIANNE trial, all-grade rash occurred in 17% of the patients in the T-DM1 alone arm and 23% of the patients in the T-DM1 plus pertuzumab arm [10]. A much lower incidence rate (1–4%) was reported for cellulitis [9, 15]. Sibaud et al. [33] published a case series on cutaneous and mucosal telangiectasia associated with T-DM1 treatment. Lesions often form as papules with an erythematous halo, as well as surrounding small radiating vessels, which appear representative of vascular ectasia. The pathological mechanism of telangiectasia from T-DM1 is unknown, but it may be associated with the disruption of microtubules in endothelial cells [33]. A single case report of a patient with MBC who developed mucocutaneous telangiectasia and pulmonary arterial hypertension (PAH) after T-DM1 treatment was recently published [34]. Both AEs resolved after discontinuation of T-DM1. According to the authors of this report, the emtansine component of T-DM1 might explain the occurrence of mucocutaneous telangiectasia, and a vasculopathy of the distal small vessels finally led to the PAH [34].

Other Adverse Events

One of the most common AEs in patients with T-DM1 is fatigue, which is mainly attributed to the DM1 component [22]. All-grade fatigue was reported in up to 65% of the patients receiving T-DM1 treatment, with grade 3 fatigue in up to 5% [8, 9, 14–16]. In the presence of brain metastases, the incidence rates of this AE are higher.

Peripheral edema was reported in 9% of patients in the T-DM1 arm of the MARIANNE trial. Chills developed during treatment in another 15% of the patients with T-DM1 alone and 27% of patients with T-DM1 plus pertuzumab [10]. Patients receiving T-DM1 frequently develop pyrexia, with any grade pyrexia ranging from 23% to 41% [14–16]. The incidence of pyrexia seems to be even higher in cases where T-DM1 is combined with pertuzumab [10].

Regarding musculoskeletal disorders, results of the MARIANNE trial showed that 18–22% of patients in the T-DM1 alone arm versus 16–19% of patients in the T-DM1 plus pertuzumab arm suffered from any grade myalgia and arthralgia [10].

Cases of interstitial lung disease (ILD), such as pneumonitis, have been reported in patients receiving T-DM1. All-grade pneumonitis shows an incidence rate of up to 9%, whereas severe pneumonitis (grade ≥ 3) occurs in 1–6% of all patients with T-DM1, as demonstrated in the KRISTINE trial [12, 16]. Signs and symptoms of this AE include dyspnea and cough [9, 14–16]. Therefore, T-DM1 should be discontinued permanently in patients diagnosed with ILD or pneumonitis.

Finally, the development of acute pancreatitis [35], vasculitis [36], or carotenoderma [37] has described in single case reports. Since T-DM1 is a relatively new agent, post-marketing pharmacovigilance can be of significant importance in recognizing and treating AEs [35]. Reporting and the evaluation of potential new AEs should be essential to further improving drug safety and patient care.

T-DM1 and Stereotactic Radiosurgery

Since T-DM1 may be used in patients with MBC or brain metastases, there is interest in the safety and toxicity of combining T-DM1 with either whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS). Preliminary experience of the concurrent use of SRS and T-DM1 has recently been published [38]. Authors compared patients from 2 groups, patients who received T-DM1 during SRS and those with sequential treatment, where T-DM1 treatment was interrupted prior to SRS. The most commonly reported AEs in both groups was radiation necrosis (RN) with an incidence of 50% and 28.6%, for both T-DM1 during treatment and T-DM1 discontinued before SRS, respectively. Therefore, the combination of T-DM1 with SRS induced a clinically relevant increase in the risk of RN, when compared to previously published data [38–40]. Moreover, Carlson et al. [40] found an association with cerebral swelling in patients on T-DM1 who underwent SRS.

Recently, Mitsuya and colleagues [41] published a report of 2 cases with expansive hematoma and delayed cerebral RN after SRS for single brain metastases. Prior to the RN, patients were heavily pretreated with trastuzumab, paclitaxel, lapatinib and capecitabine, followed by the initiation of T-DM1 almost 5.5 years after SRS. After surgical resection of the RN, pathological examination revealed necrosis, hematoma, granulation tissue, and telangiectasia without neoplastic cells. The authors concluded that there might be an enhanced risk for RN when T-DM1 is administered to patients after SRS. The pathophysiological pathway involved might include nodular granulation, neovascularization, microbleeding, telangiectasia with hemorrhage, and thrombocytopenia. From these results, the need for a careful follow-up of patients after concomitant or sequential treatment of T-DM1 and SRS should be emphasized [41].

T-DM1 Dose Adjustment and Discontinuation

The recommended standard dose of T-DM1 is 3.6 mg/kg administered as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity [21, 22]. In the event that toxicity occurs, treatment of the T-DM1-induced AE should be primarily based on the patients' individual symptoms. The symptomatic treatment of fatigue, nausea, musculoskeletal pain, headache, or constipation is of paramount importance to ensure satisfactory quality of life. In addition to these AEs, hemorrhage, thrombocytopenia, liver dysfunction, and cardiac dysfunction may require dose adjustment, which should be performed in increments of 0.6 mg/kg. After a maximum of 2 dose reductions, discontinuation of T-DM1 is recommended, with no increase in dose after dose reduction. Generally, the planned treatment schedule should be resumed as soon as possible without waiting for the next scheduled cycle. The application plan must be adapted consequently, so that a time interval of 3 weeks is maintained between every application. Adjustment guidelines for the most important severe AEs are shown in table 3.

Conclusions

Overall, the currently available data suggest that T-DM1 is a relatively safe and well-tolerated agent in the treatment of metastatic HER2-positive BC. T-DM1 is better tolerated than conventional cytotoxic agents, with common adverse events being, in general, easily manageable. However, in case of severe cardiac dysfunction, increase of liver enzymes, or in cases with severe thrombocytopenia, patients should undergo dose adjustment. In some rare cases, the discontinuation of T-DM1 treatment may become necessary. Patients should undergo thorough surveillance when concomitant radiosurgery of brain metastases is performed, or when they have significant preexisting cardiac, hepatic, or neurological disorders.

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Disclosure Statement

The authors have declare that no conflict of interest exists.

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