Review Article

Gastrointestinal Toxicity of Antibody Drug Conjugates (ADCs) in Metastatic Breast Cancer: A Pooled Analysis

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Abstract

Trastuzumab emtansine (T-DM1), sacituzumab govitecan (SG), and trastuzumab deruxtecan (T-DXd) are three ADCs approved for the treatment of metastatic breast cancer (MBC). Since gastrointestinal toxicities have been commonly observed with these drugs in clinical trials, a pooled analysis evaluating gastrointestinal adverse events (AEs) in patients with MBC treated with ADCs in clinical trials was performed. PubMed, Embase, and the Cochrane Library were searched from inception until May 2023 for phase II and III clinical trials reporting frequency and severity of gastrointestinal AEs during treatment with ADCs. Data were retrieved for nausea, vomiting, diarrhea, constipation, and abdominal pain: overall and grade 3-4 toxicity rates according to NCI-CTCAE were collected and expressed as proportions. A pre-specified subgroup analysis according to the agent was also carried out. Fourteen studies, comprising 5608 patients, were included in the analysis. Gastrointestinal AEs were frequently registered with SG and T-DXd. A significantly higher frequency of nausea (65.6% with SG, 75% with T-DXd), vomiting (43.7% with SG, 45% with T-DXd), and diarrhea (59.7% with SG, 29% with T-DXd) was noticed with these ADCs compared to TDM-1. Furthermore, diarrhea was more frequently associated with SG (grade 3 in 7.5% of patients), while constipation and abdominal pain were less common. Gastrointestinal AEs, notably nausea and diarrhea, were frequently reported by MBC patients treated with SG and T-DXd in clinical trials. Since these ADCs are administered continuously until disease progression or occurrence of unbearable AEs, gastrointestinal toxicity may have a negative impact on patient quality of life. Therefore, appropriate management of gastrointestinal AEs is mandatory to ensure treatment efficacy and adherence.

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Introduction

Breast cancer is the most common cancer among women worldwide and it is currently the principal cause of cancer-related mortality amongst females.[1]

Although early-stage breast cancer has an excellent prognosis, treatments for metastatic breast cancer (MBC) are palliative and the median overall survival is about 3-5 years.[2]

Antibody drug conjugates (ADCs) represent an appealing novel class of anticancer agents, which exploit the specificity of monoclonal antibodies for a targeted release of a potent cytotoxic drug (payload), thus having an increased activity and a potential reduced toxicity compared with traditional chemotherapeutic drugs.[3,4] Trastuzumab emtansine (T-DM1) was the first ADC developed for the treatment of human epidermal growth factor receptor 2 (HER2)-positive MBC,[5,6] Sacituzumab govitencan (SG)

Abbreviations: ADC, antibody drug conjugate; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; CT, chemotherapy; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; MBC, metastatic breast cancer; AEs, adverse events; FDA, Food and Drug Administration; PFS, progression-free survival; OS, overall survival; CBR, clinical benefit rate; 5-HT3, 5-hydroxytryptamine; HRQoL, health-related quality of life; TPC, treatment of physicians' choice; LEC, low emetogenic chemotherapy; HEC, highly emetogenic chemotherapy; MEC, moderate emetogenic chemotherapy; NK1, Neurokinin-1; CPT-11, irinotecan.

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and Trastuzumab deruxtecan (T-DXd) were subsequently introduced.

SG is a novel ADC targeting Trop-2, a glycoprotein which is overexpressed in many epithelial cancers but rarely in normal tissue.[7,8] Sacituzumab is conjugated with SN-38 (7-ethyl-10-hydroxycamptothecin), a topoisomerase I inhibitor and the active metabolite of irinotecan.[9]

T-DXd is composed of a humanized monoclonal antibody, having the same amino acid sequence as trastuzumab, and specifically targeting HER2, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor as payload.[10-12]

Randomized studies, that led to the registration of these drugs for the use in clinical practice, have shown an increase in progression free survival (PFS) and overall survival (OS) associated with the administration of TDM-1,[13], SG[14,15], and T-DXd,[16,17] over the respective control arms.

Based on these results, SG have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a new treatment option for pretreated patients with advanced triple negative MBC, while TDM-1 and T-DXd for HER2-positive MBC. Further, FDA and EMA approved T-DXd for HER2-low MBC patients previously treated or whose disease recurred within 6 months of adjuvant treatment following surgery. More recently, FDA approved SG for patients with hormone receptor positive/HER2 negative MBC who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

Although an improved tolerance was expected with these therapies in comparison to chemotherapy, a wide variety of adverse events (AEs) can affect both the physical and social functioning in many patients.

The most commonly reported adverse AEs of TDM-1 were nausea, fatigue, thrombocytopenia, diarrhea, vomiting and elevated serum concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[13]

The most commonly reported AEs of SG were neutropenia, anemia, diarrhea, nausea, fatigue, and alopecia,[14,15] while those reported with T-DXd were neutropenia, anemia, nausea, vomiting, fatigue and alopecia.[12,16,17]

Hence gastrointestinal toxicities were the most frequently observed AEs of these new ADCs.

Indeed, nausea, vomiting, diarrhea, constipation, and abdominal pain were relevant AEs of SG[14,18,19] and T-DXd,[12,20] which seem to be higher than those reported with other ADCs such as T-DM1[6,13] and comparable to those of chemotherapeutic drugs such as anthracyclines or docetaxel.[21]

Considering that ADCs are usually administered continuously until disease progression or occurrence of unbearable AEs for MBC, the optimal management of side effects is of key importance to improve patients' quality of life and maintain adherence to the treatment, avoiding early discontinuation which may compromise treatment efficacy.

To the best of our knowledge no study has addressed this relevant topic so far.

In the present paper the frequency and severity of gastrointestinal side effects resulting from the administration of these three ADCs were evaluated by a pooled analysis of all published studies to discuss about their management in clinical practice.

Patients and Methods

The study was conducted in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and its update.[22,23]

Definition of Gastrointestinal Events

Gastrointestinal events were defined as AEs reported in each trial occurring during study participation (and therefore either during or after study treatment) and included the following categories: nausea, vomiting, diarrhea, constipation, and abdominal pain. The toxicity was reported following the Common Terminology Criteria for Adverse Events (CTCAE) grading system as follows: any grade and grade 3-4.[24]

Search Methods and Study Selection

Published results of clinicals trials regarding ADC treatment in MBC were identified by a PubMed, EMBASE, and Cochrane Library search. Moreover, references of published trials, editorials, and relevant review articles were examined for further studies or major congress abstracts. The databases were searched for articles published from inception until May 2023. Eligible articles included phase II and III studies reporting the safety (grade 1-2 and grade 3-4 toxicities) of ADCs in patients with MBC; letters, case reports, commentaries, reviews, preclinical studies, observational studies, and articles not written in English were not eligible for this analysis.

Data Extraction and Statistical Analysis

Primary endpoints were the rates of all grades and G3-4 gastrointestinal toxicities.

Overall toxicity and grade 3-4 toxicity rates from the studies analyzed were extracted for the pooled analysis. The data extraction was performed by the primary reviewer (RP) and then independently evaluated by two secondary reviewers (AG and FP) following the PRISMA guidelines.

The characteristics of the patients included median age, Eastern Cooperative Oncology Group (ECOG) performance status, number of previous lines of treatment for metastatic disease, organs involved, and type of breast cancer, as well as efficacy outcomes of interest (ie, median OS, PFS, ORR, CBR) and toxicity grades were collected and expressed as proportions (%). Overall and grade 3-4 toxicity rates are also reported. To calculate incidence, the number of patients experiencing an AE and the total number of patients evaluable for toxicity were extracted.

Quantitative analysis (meta-analysis) was performed including all data for individual treatment arms for all eligible studies. For description of the baseline population characteristics, pooled percentages were calculated for categorical variables. Student's T-test was employed for comparison of pooled weighted means if appropriate. Meta-analysis of proportions was performed for toxicity rates, employing random effects model, rather than fixed effects model, since heterogeneity between studies was expected to be present. Weights for each study in the analysis were based on the individual sample sizes. Furthermore, a sensitivity analysis was carried out

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by sequential omission of individual studies to assess the stability of the results. Between-study heterogeneity was estimated by using the $\chi 2$-based Q test and I^2 statistic. The random- or fixed-effect models were used in the presence or absence of heterogeneity. An I^2 value higher than 50% was considered to be indicative of substantial heterogeneity.[25] Patients were divided in three subgroups according to type of agent received (TDM-1, T-DXd, or SG). For each subgroup we also performed pre-specified analysis for the following variables: nausea, vomiting, diarrhea, constipation and abdominal pain.

For each gastrointestinal AEs we analyzed separately all grade toxicities and G3-G4 incidence. Publication bias was assessed using the Begg and Egger tests with funnel plots.[26,27] All analyses were performed using Comprehensive Meta-Analysis software v 3.3.070.

Results

Twenty-six publications were initially retrieved (Figure 1). Five publications were excluded because they were reviews,[3,28,29] four because they were phase I trials with different cancer types and drug doses,[11,30,31] and three were retrospective studies.[32,33]

Fourteen studies (five phase II trials[12,18-20,34] and nine phase III trials[6,13-17,35-37] involving a total of 5680 MBC patients, were included in the pooled analysis. Nine studies enrolled patients with HER2+ MBC: among them, three studies evaluated the efficacy of TDM-1, other three of T-DXd and one study compared TDM-1 and T-DXd. One study investigated the efficacy of T-DXd in HER2-low MBC. For what concern SG, four studies include TNBC, while one study enrolled patients with HR+ MBC. Overall, 761 were treated with SG, 1330 with T-DXd, and 3517 with TDM-1, respectively. Characteristics of the studies included in the current analyses are reported in Table 1 .

The dose and schedule of SG selected for the phase II and III trials were 10 mg/kg intravenously on days 1 and 8 of each 21-day cycle; those of T-DXd and T-DM1 were 5.4 and 3.6 mg/kg intravenously every 21 days, respectively.

Patients' characteristics and efficacy outcomes of the studies with ADCs selected for the current pooled analysis are reported in Tables 2A and B. Median age was 58 years and patients with an ECOG performance status of 0 were 58.4%, 38%, and 57.4% for TDM-1, SG, and T-DXd, respectively.

In all but one studies patients had received at least one prior line therapy for metastatic disease; nine of fourteen studies enrolled patients who have received ≥2 prior lines of therapy for MBC.

Visceral metastases occurred in 71.7%, 67.2%, and 75.3% of patients treated with TDM-1, T-DXd, and SG, respectively.

As reported in Table 1, gastrointestinal toxicities were the most common referred EAs.

GI toxicities were managed using standard supportive therapies (ie, antiemetics, drugs to treat constipation, and antidiarrheal medications) and/or dose reductions.

The median percentage of patients who required a dose reduction for any adverse event was 15% with TDM-1 (12.6%-22.5%), 23% with SG (16%-33%) and 23% with T-DXd (21.4%-24%).

Treatment discontinuation due to any adverse event was 10.2%, 14.8%, and 5%, respectively for TDM-1, T-DXd, and SG.

Percentage of patients who required dose reductions or who discontinued treatment for each specific gastrointestinal adverse event are not reported in trials.

Gastrointestinal Events in the Study Population

All grade toxicity and grade 3-4 toxicity were presented in Table 3 and depicted in Figure 2. Calculations were performed using a random-effect model.

The most common treatment-related gastrointestinal AE of any grade across the studies was nausea, which was reported in 75% of patients treated with T-DXd and 65.6% of those who received

Figure 1 Flow diagram of included studies and reason for exclusion.

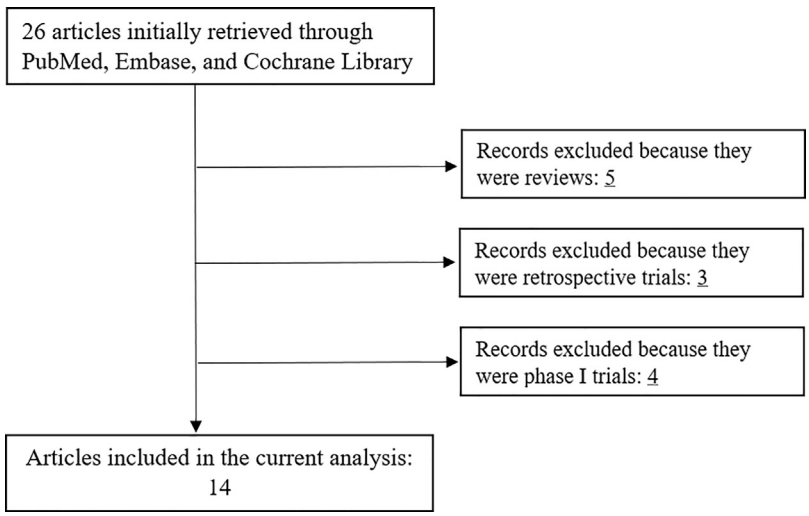

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Table 1 Characteristics of the Studies Included in the Current Pooled Analysis

	N° Pts	Type of Study and Setting	Drug	Follow Up (Months)	Line	All AEs %	G3-G4 %	Dose Reductions for Any AEs	Discontinued Treatment for Any AEs
Bardia, 2017	69	Phase 1-2 TNBC	Sacituzumab govitecan	16.6	>1	Nausea 74% Diarrhea 59% Vomiting 51% Constipation 38% Abdominal pain 26% Anorexia 23%	Nausea 7% Diarrhea 13% Vomiting 10% Constipation 1% Abdominal pain 3% Anorexia 0%	16%-19%	4.3%
Bardia, 2019	108	Phase 1-2 TNBC	Sacituzumab govitecan	9.7	>2	Nausea 67% Diarrhea 62% Vomiting 49% Constipation 34% Abdominal pain 25% Mucositis 14%	Nausea 6% Diarrhea 8% Vomiting 6% Constipation 1% Abdominal pain 1% Mucositis 0%	34%	2.8%
Kalinsky, 2020	54	Phase 1-2 TNBC	Sacituzumab govitecan	11.5	>1	Nausea 66.7% Diarrhea 46.3% Vomiting 46.3% Decreased appetite 31.5% Constipation 25.9%	Nausea 1.9% Diarrhea 7.4% Vomiting 3.7% Decreased appetite 0% Constipation 0%	24.1%	7%
Bardia, 2021	267	Phase 3 TNBC	Sacituzumab govitecan	-	≥2	Diarrhea 59% Nausea 57% Vomiting 29%	Diarrhea 10% Nausea < 3% Vomiting < 2%	22%	5%
Tamura, 2019	115	Phase 1 HER2+	Trastuzumab deruxtecan	9.9	≥2	Nausea 79% Vomiting 52% Diarrhea 38% Constipation 37% Stomatitis 21% Dyspepsia 12% Abdominal pain 11%	Nausea 3% Vomiting 4% Diarrhea 2% Constipation 1% Stomatitis 0% Dyspepsia 0% Abdominal pain 0%	21%	11.3%
Modi, 2020	184	Phase 2 HER2+	Trastuzumab deruxtecan	11.1	≥2	Nausea 77.7% Vomiting 45.7% Constipation 35.9% Decreased appetite 31% Diarrhea 29.3% Abdominal pain 16.8%	Nausea 7.6% Vomiting 4.3% Constipation 0.5% Decreased appetite 1.6% Diarrhea 2.7% Abdominal pain 1.1%	23.4%	15.2%
Cortes, 2022	261	Phase 3 HER2+	Trastuzumab deruxtecan	16.2	≥1	Nausea 72.8% Vomiting 44% Diarrhea 23.7% Constipation 22.6%	Nausea 6.6% Vomiting 1.6% Diarrhea 0.4% Constipation 0%	21.4%	13.6
Verma, 2012	495	Phase 3 HER2+	Trastuzumab emtansine	19.1	2	Nausea 39.2% Diarrhea 23.3% Vomiting 19% Mucosal inflammation 6.7%	Nausea 0.8% Diarrhea 1.6% Vomiting 0.8% Mucosal inflammation 0.2%	16.3%	5.9%
Perez, 2016	361	Phase 3 HER2+	Trastuzumab emtansine	35	1	Nausea 47.1% Diarrhea 25.2% Vomiting 21.6%	Nausea 0% Diarrhea 0.3% Vomiting 0%	13.6%	18.3%
Krop, 2017	404	Phase 3 HER2+	Trastuzumab emtansine	30.5	pretreated	Nausea 35.7% Constipation 22.3% Vomiting 19.3% Decreased appetite 16.1% Diarrhea 12.6% Dry mouth 12.6% Abdominal pain 7.4%	Nausea 1% Constipation < 1% Vomiting 1% Decreased appetite < 1% Diarrhea 1% Dry mouth 0% Abdominal pain 1%	13%	15%

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Table 1 (*continued*)

	N° Pts	Type of Study and Setting	Drug	Follow Up (Months)	Line	All AEs %	G3-G4 %	Dose Reductions for Any AEs	Discontinued Treatment for Any AEs
Montemurro, 2019	2002	Phase 3b HER2+	Trastuzumab emtansine	20.6	≥2	Nausea 32.5% Constipation 19.8% Decreased appetite 16% Vomiting 15.2% Dry mouth 14.1% Diarrhea 12.7%	Nausea 0.7% Constipation 0.5% Decreased appetite 0.6% Vomiting 1.4% Dry mouth 0.1%) Diarrhea 0.8%	22.5%	4.3%
Cortes, 2022	263	Phase 3 HER2+	Trastuzumab emtansine	15.3	≥1	Nausea 27.6% Vomiting 5.7% Diarrhea 3.8%) Constipation 9.6%	Nausea 0.4% Vomiting 0.4% Diarrhea 0.4% Constipation 0%	12.6%	7.3%
André, 2023	404	Phase 3 HER2+	Trastuzumab deruxtecan	21.5	≥1	Nausea 73% Vomiting 38% Diarrhea 27% Constipation 35.1%	Nausea 7% Vomiting 3.7% Diarrhea 3% Constipation 0.2%	24%	18%
Modi, 2022	373	Phase 3 HER2-low	Trastuzumab deruxtecan	18.4	≥2[a]	Nausea 73% Vomiting 34% Diarrhea 22.4% Constipation 21.3%	Nausea 4.6% Vomiting 1.3% Diarrhea 1.1% Constipation 0%	22.6%	16.2%
Rugo, 2022	272	Phase 3 HR+/HER2-	Sacituzumab Govitecan	10.2	>2[b]	Nausea 55% Vomiting 19% Diarrhea 57% Constipation 18% Abdominal pain 13%	Nausea 1% Vomiting < 1% Diarrhea 9% Constipation 0% Abdominal pain 1%	33%	6%

[a] 1 line if recurrence during or within 6 months after completing adjuvant chemotherapy.
[b] Not more than four prior systemic chemotherapy regimen for MBC5.AEs, adverse events; pts, patients; TNBC, triple-negative breast cancer; HER2 human epidermal growth factor receptor 2.

Table 2A Patients' Characteristics and Efficacy Outcomes in the Studies With Anti-HER2 ADCs (T-DM1 and TDX-d) Selected for the Current Pooled Analysis

	Verma, 2012	Perez, 2016	Krop, 2017	Montemurro, 2019	Cortes, 2022	Tamura, 2019	Modi, 2020	Cortes, 2022	André, 2023	Modi, 2022
Drug	T-DM1	T-DM1	T-DM1	T-DM1	T-DM1	TDX-d	TDX-d	TDX-d	TDX-d	TDX-d
Number of patients	495	367	404	2002	263	115	184	261	404	373
ECOG PS 0 (%) ≥1 (%)	299 (60) 194 (39)	239 (65.1) 128 (34.9)	180 (45) 222 (55)	1110 (55.4) 890 (44.4)	175 (66.5) 87 (33.1)	72 (63) 43 (37)	102 (55.4) 89 (44.5)	154 (59) 106 (40.6)	228 (56) 178 (44%)	200 (53.6) 173
Median age (range)	53 (25-84)	52 (27-82)	53 (27-89)	55 (26-88)	54.2 (20.2-83)	55 (47-66)	55 (28-96)	54.3 (27.9-83.1)	54.2 (45.5-62-4)	57.5 (31.5-80.2)
HR positive	282 (57)	195 (53.1)	208 (51)	1232 (61.5)	134 (51)	81 (70)	97 (52.7)	131 (50.2)	238 (59%)	333 (89.3)
HER2 positive	495 (100)	367(100)	404 (100)	2002 (100)	263 (100)	11 (97)	182 (98.9)	260 (99.3)	405 (100)	0
Visceral disease	334 (67)	251 (68.4)	302 (75)	1561 (78)	185 (70.3)	-	-	184 (70.5)	316 (78%)	199 (53.3)
Median follow-up	19.1	35	30.5	20.6	15.3	9.9	11.1	16.2	21.5	18.4
PFS (median months, 95% CI)	9.6 (-)	14.1 (-)	6.2 (5.5-6.8)	6.9 (6-7.6)	6.8 (5.6-8.2)	22.1 (NE)	16.4 (12.7-NR)	NR (18.5-NE)	17.8 (14.3-20.8)	9.9 (9.0-11.3)
OS (median months, 95% CI)	30.9 (-)	-	22.7 (19.4-27.5)	27.2 (25.5-28.7)	-	-	-	-	39.2 (32.7-NE)	23.4 (20.0-24.8)
ORR (%)	43.6	59.7	31	29.3	34.2	59.5	60.9	79.7	70%	52.3%

T-DM1, trastuzumab emtansine; TDX-d, trastuzumab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group Performance status; HR, hormone receptor; HER2, Human epidermal growth factor receptor 2; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; CI, confidence interval; NE, not estimable; NR, not reached.

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Table 2B Patients' Characteristics and Efficacy Outcomes in the Studies With Sacituzumab Govitecan Selected for the Current Pooled Analysis

	Bardia, 2017	Bardia, 2019	Kalinski, 2020	Bardia, 2021	Rugo, 2020
Number of patients	69	108	54	235	272
ECOG PS **0 (%)** **>1 (%)**	 23 (33) 46 (67)	 31 (28.7) 77 (71.3)	 21 (38.9) 33 (61.1)	 108 (46) 127 (54)	116 (43%) 156 (57%)
Median age (range)	56 (31-81)	55 (31-80)	54 (33-79)	54 (29-82)	57 (29-86)
HR positive	0	0	100	0	100
TNBC	100	100	0	100	0
Metastatic site (%) Visceral	 -	 83 (76.9)	 Lung 35 (51) Liver 30 (43)	 206 (88)	259 (95) Liver 229 (84)
PFS (median months, 95% CI)	6 (5-7.3)	5.5 (4.1-6.3)	5.5 (3.6-7.6)	5.6 (4.3-6.3)	5.5 (4.2-7.0)
OS (median months, 95% CI)	16.6 (11.1-20.6)	13 (11.2-13.7)	12.0 (9.0-18.2)	12.1 (10.7-14.0)	13-9 (12.7-15.4)
Median follow-up	16.6	9.7	11.5	17.7	10.2
Clinical benefit (%)	46	45.4	44.4	45	34
ORR (%)	30	33.3	31.5	35	21

ECOG PS, Eastern Cooperative Oncology Group Performance status; HR, hormone receptor; TNBC, triple negative breast cancer; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; CI, confidence interval.

Table 3 Gastrointestinal Toxicities of the Different ADCs in MBC Patients in the Current Pooled Analysis

Gastrointestinal toxicities	Toxicity pooled % (CI 95%)	SG % (CI 95%)	TDM-1 % (CI 95%)	TDX-d % (CI 95%)	P[a]	P[b]	P[c]
Nausea							
All grades	56 (46-66)	65.6 (61-70)	36 (30-42)	75 (71-78)	< .01	< .01	< .01
G3-G4	2.2 (1.1-4.5)	4.3 (2.2-8.3)	0.7 (0.5-1.1)	6.2 (3.4-11.1)	< .01	< .01	.71
Diarrhea							
All grades	29 (19-41)	59.7 (52.4-66.6)	13 (9-21)	29 (25-32)	< .01	< .01	< .01
G3-G4	2.2 (1.1-4.5)	7.5 (4.3-12.7)	0.9 (0.6-1.6)	2.4 (1.1-4.9)	< .01	.03	.015
Vomiting							
All grades	30 (21-39)	43.7 (33.5-54.5)	15 (12-20)	45 (41-49)	< .01	< .01	NS
G3-G4	1.7 (1-2-9)	4.4 (1.7-10.8)	1.2 (0.9-1.7)	3.3 (1.8-6.1)	< .01	< .01	NS
Abdominal pain							
All grades	14.8 (9.4-22.5)	20.1 (11.9-31.8)	6.2 (4.2-9)	14.5 (9.8-21)	< .01	< .01	NS
G3-G4	1.2 (0.7-2.1)	1.3 (0.4-3.9)	1.2 (0.5-2.9)	0.9 (0.3-3.1)	NS	NS	NS
Constipation							
All grades	25 (18-33)	32.2 (18.6-49.6)	15 (10-21)	30 (22-41)	< .01	< .01[d]	NS
G3-G4	0.5 (0.3-0.9)	0.8 (0.3-2.6)	0.5 (0.3-0.9)	0.5 (0.2-1.8)	NS	NS	NS

[a] Statistically significant difference ($P < .05$) among the three ADCs.
[b] Statistically significant difference ($P < .05$) for TDM-1 versus the other two ADCs.
[c] Statistically significant difference ($P < .05$) for sacituzumab govitecan versus trastuzumab deruxtecan.
[d] This value was not significant for T-DM1 versus sacituzumab govitecan comparison.SG, sacituzumab govitecan, TDM-1, trastuzumab emtansine, TDX-d trastuzumab deruxtecan, CI, confidence interval; NS, not significant.

SG. The frequency of nausea was lower in patients who received T-DM1 (38.1%). Grade 3-4 nausea was reported in 6.2% of patients treated with T-DXd, 4.3% of patients treated with SG, and 0.7% of those treated with T-DM1. Patients who were given SG and T-DXd reported vomiting more frequently than those who were treated with T-DM1: 43.7 and 46.3, versus 17.1. Grade 3-4 vomiting were higher with SG (4.4%) compared to the other ADCs (3.3% for T-DXd and 1.2 for TMD-1).

Also, diarrhea was more prevalent in SG treated patients (59.7%) than those treated with T-DXd (30.2%) and TDM-1 (17.5%).

Grade 3-4 diarrhea was reported in 7.5% of patients treated with SG, 2.4% of patients treated with T-DXd, and 0.9% of those treated with T-DM1.

Abdominal pain of any grade was reported in 20.1% of patients treated with SG, in 14.5% of those treated with T-DXd, and in 6.2% of patients treated with T-DM1.

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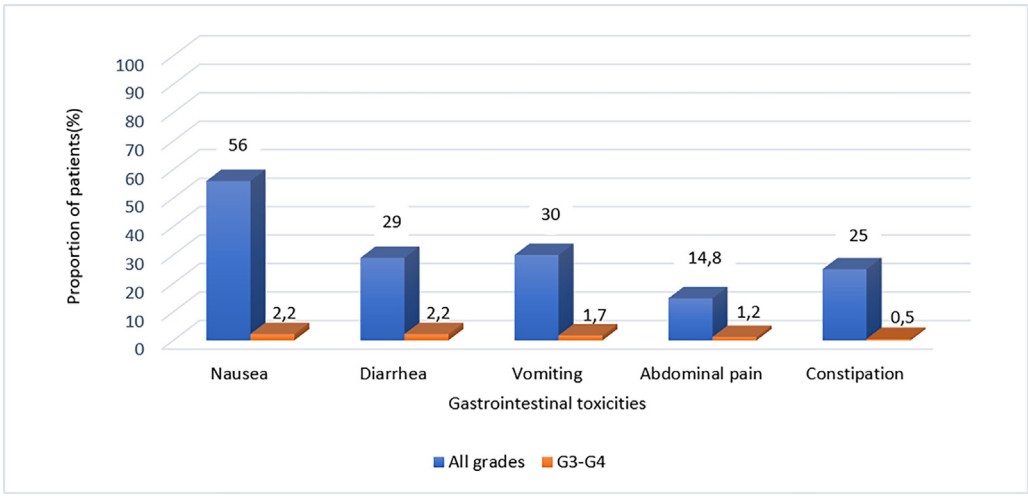
Figure 2 Pooled incidence rates of gastrointestinal toxicities.



Grade 3-4 of abdominal pain were reported in 1.3%, 1.2%, 0.9% of patients treated with, respectively, SG, T-DXd, and TDM-1.

Constipation of any grade was reported in more than 30% of patients treated with SG or with T-DXd and in only 18% of patients treated with T-DM1, with grade 3-4 reported in <1% for all three.

Discussion

Gastrointestinal toxicities are one of the most common non-hematological toxicities associated with the use of the novel ADCs, whose incidence and severity depend on the characteristics of either the payload or the patient.[38-40] Additionally, the overall potency of ADCs is influenced by the drug-to-antibody ratio, which means the number of cytotoxic molecules linked to each antibody, which determines the quantity of antibody capable of reaching the tumor site.[40]

Since ADC therapies are generally given until disease progression or toxicity occurrence and since gastrointestinal toxicity is closely associated to nutritional impairment, the management of these AEs is relevant to maintain high levels of treatment adherence, prevent premature treatment discontinuation and avoid worsening of quality of life.[3,41] Additionally, severe gastrointestinal toxicities can be potentially life threatening especially in elderly and frailer patients, as vomiting and diarrhea can lead to dehydration, malnutrition, electrolyte imbalance, enterocolitis, sepsis and multiorgan failure.

Overall, our pooled analysis confirms that T-DM1, the first ADC approved for solid tumors, was well tolerated and its related toxicities were easy to handle. As regards as nausea and vomiting, in our pooled analysis these symptoms occurred in 38.1% and 17.1% of T-DM1 treated patients, respectively. The prevalence of gastrointestinal toxicities, however, was significantly higher with newer ADCs. Concerning SG, our pooled analysis shows that the frequency of nausea and vomiting was 65.6% and 43.7%, respectively. It was reportedly of low intensity (Grade 1 or 2) in the majority of patients, although grade 3-4 was observed in almost 10% of them.[40]

SG should be held for G3-G4 gastrointestinal toxicities and should be restarted only once back to grade 1, considering a 25% dose reduction. Treatment should be definitely discontinued if grade 3-4 toxicity lasted more than three weeks.[42,43]

It should be noted, however, that the duration of nausea and vomiting as well as the percentage of patients requiring a dose reduction or interruption due to this side effect were not reported in the randomized SG trials. The absence of these data is a significant drawback of published studies, due to the impact of these side effects on health-related quality of life (HRQoL). As a matter of fact, in an exploratory analysis of ASCENT clinical trial, SG was associated with greater improvements in HRQoL than treatment of physicians' choice (TPC), except for greater worsening of nausea and vomiting.[44]

As regards as T-DXd, in our pooled analysis the prevalence of nausea and vomiting reached 75% and 46.6%, respectively and their severity was mainly of grade 1-2. Again, data about the duration of nausea and vomiting, as well as dose reduction or interruptions due to these symptoms, were not reported.

It should be noted that in clinical trials testing SG[14,15,19,34] or T-DXd,[16,17,37] supportive therapies were not mandated and were left up to the investigator's discretion, due to the lack of information on the frequency and severity of these side effects. Moreover, the majority of study protocols require approval from a medical monitor for any premedication, particularly steroids, before administering it.

Based on the results of the registrative studies, the international guidelines have produced recommendations on the antiemetics treatment to be associated with these drugs.[38,39,45]

Accordingly, NCCN antiemesis guidelines classified TDM-1 as a low emetogenic chemotherapy (LEC) requiring the prescription of an antiemetic therapy on an individual basis.[39]

Conversely, International Guidelines classifies SG as a high emetogenic chemotherapy (HEC) which require triple combination of NK1 receptors antagonist (eg, Netupitant), 5-HT3 recep-

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tors antagonist (eg, Palonosetron), and corticosteroid (Dexamethasone).[39,45,46]

T-DXd was previously categorized as moderately emetogenic (MEC) based on clinical trial data.[47] However, recently, it was re-categorized as highly emetogenic (HEC) due to clinical experience of experts and institutional retrospective data showing that the addition of an NK1 receptors antagonist was required for a number of patients due to poor control of the symptom using antiemesis prophylaxis for MEC in the first cycle.[39]

The recommendations provided by the international guidelines, however, are mainly based on expert opinion instead of clinical evidence, therefore the frequency of these symptoms after adopting an accurate antiemetic prophylaxis should be evaluated in prospective studies.

Moreover, recent evidences from a Cochrane network meta-analysis determined the combination netupitant/palonosetron (NEPA) to be the most efficacious approach in patients treated with HEC,[48] since palonosetron inhibits serotonin signaling involved in acute emesis (0-24 hours after therapy) while netupitant disrupts signaling responsible of delayed emesis (24-120 hours after therapy).[49,50]

Studies investigating NEPA as antiemetic prophylaxis in patients treated with SG and T-DXd are needed to confirm the potential benefit of this combination as first antiemetic choice.

Even with prophylaxis, breakthrough nausea or vomiting may occur and need to be treated with metoclopramide along with or without dexamethasone. Uncontrolled nausea or vomiting after rescue therapy is defined as refractory and can be treated with olanzapine.[42,51]

Patients with nausea and vomiting during first cycles may develop anticipatory nausea: these patients may benefit from the addiction of anxiolytics such as Lorazepam as well as relaxing measures (eg, yoga or acupuncture).[51]

In our pooled analysis, the frequency of patients reporting diarrhea during SG treatment was 59.7% which was superior to that reported with T-DXd (30.2%) and TDM-1 (17.5%).

The novel anti-Trop-2 ADC SG is conjugated with SN-38, the active metabolite of single agent irinotecan (CPT-11)[52-54] and SN-38 metabolite could be responsible for the acute and secretory diarrhea associated with CPT-11 administration with mucosal damage leading to malabsorption of water and electrolytes.[55,56]

Diarrhea impacts with HRQoL and social functioning, so preventive and supportive measures are highly recommended for patients receiving SG.

As for nausea and vomiting, data about duration of diarrhea, dose reduction or interruption for diarrhea were lacking in published studies and need to be explored in future.

An updated safety analysis of ASCENT trial revealed a higher rate of G3-G4 diarrhea in patients with the homozygous presence of the UGT1A1*28 polymorphism.[57] Therefore, this variant should be exploited before starting SG to identify earlier patients at higher risk of developing diarrhea.

Patients with G1-G2 uncomplicated diarrhea can be managed with hydration and oral loperamide at an initial orally dose of 4 mg, followed by 2 mg every additional episode until 16 mg of maximum dose.[42,43,51,58] In case of G3-G4 diarrhea i.v route should be preferred for fluid replacement associated, if necessary, to electrolyte corrections.[58] For persistent diarrhea (not resolved after 48 hours from loperamide assumption), the somatostatin analogue octreotide or tincture of iodium should be considered, while antibiotic are indicated only in presence of red flags (eg, fever, peritoneal signs, bloody diarrhea etc).[43,51,58]

Nutritional counselling and diet modifications with high-fiber intake, oral supplements and probiotics could be considered as prophylactic management strategies.[58]

For patients suffering from diarrhea during earlier coursed atropine-based prophylaxis can be considered for subsequent administration of SG, especially in presence of concurrent symptoms as abdominal pain, sweating, and salivation.[43,51]

Again, the efficacy of recommended strategies in the management of diarrhea associated with SG needs to be checked in a prospective study.

Constipation and abdominal pain were reported less frequently during treatment with ADCs. The prevalence of constipation in cancer patients ranges between 40% and 90%[59,60] and it is more common in the opioid-treated population.[61] Constipation of any grade was reported in more than 30% of patients treated with SG and with T-DXd, while only in 18% with TDM-1.

Abdominal pain was reported in 20.1% of patients treated with SG, 14.5% of those treated with T-DXd, and in 6.2% of patients treated with T-DM1.

Common factors contributing these symptoms in cancer patients may include disruption of normal motility induced by drugs such as opioids, 5-HT3 antagonist antiemetics, iron, antidepressants, advanced age, poor food and/or fluid intake.[62]

Prevention and management of constipation include increasing of fluid intakes and mobility.

If laxatives are needed the preferred choices are osmotic (eg, PEG or lactulose) or stimulant (eg, senna, cascara). If digital rectal exam identifies full rectum or fecal impaction suppositories and enemas could be considered as first line therapy.

A prophylaxis with laxatives should be offered to all patients receiving concomitant opioid analgesics, unless contraindicated.[62]

Data about duration of abdominal pain and constipation or when they required dose reduction or interruption are lacking, as well as information about patients' home therapy.

These data should be investigated in phase IV studies to evaluate the efficacy of strategies for prevention and self-care management of these side effects, as recommended by guidelines.

Ongoing clinical trials are assessing the efficacy and safety of each ADCs with modified dose schedules. This could allow the detection of novel predictive biomarkers as well as creation of new diagnostic tools.[63]

In addition to the design and conduction of phase IV studies, we advocate the collection of new real-life data regarding the safety of these drugs, how side effects are managed and the efficacy of the supportive measures adopted in the routine clinical practice.

Ethical Approval

This article does not contain any studies with human participants performed by any of the authors.

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CRediT authorship contribution statement

Rebecca Pedersini: Conceptualization, Data curation, Supervision, Writing – original draft. **Martina Buffoni:** Funding acquisition, Validation, Writing – review & editing, Project administration, Supervision. **Fausto Petrelli:** Data curation, Formal analysis, Methodology. **Antonio Ghidini:** Supervision. **Pierluigi di Mauro:** Conceptualization, Data curation, Resources, Writing – original draft. **Vito Amoroso:** Visualization, Supervision. **Maria Chiara Parati:** Visualization. **Lara Laini:** Visualization. **Deborah Cosentini:** Visualization. **Greta Schivardi:** Visualization. **Giuseppe Ippolito:** Visualization. **Alfredo Berruti:** Conceptualization, Data curation, Resources, Writing – review & editing, Writing – original draft. **Marta Laganà:** Validation, Visualization.

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