Incidence of Antibody-drug Conjugate-induced Peripheral Neuropathy in Patients with Breast Cancer: A Systematic Review and Meta-analysis

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Abstract: Background: Although ADCs have revolutionized breast cancer treatment, their risk of peripheral neuropathy has not been systematically evaluated. Methods: We systematically reviewed articles and conference abstracts published up to May 10, 2024, from Web of Science, PubMed, and Cochrane Library databases. Data were extracted independently and analyzed using a random-effects model, with heterogeneity assessed by I2 statistics and p-values. Results: Our meta-analysis found the overall incidence of any-grade peripheral neuropathy in breast cancer patients treated with ADCs to be 17.99% (95% CI, 13.73–22.65%). The incidence was 12.95% (95% CI, 9.03–17.4%) for ADC monotherapy regimens, with trastuzumab deruxtecan (T-DXd) having the highest incidence at 18.17% (95% CI, 4.96–35.89%). Conclusions: ADC-associated peripheral neuropathy is common in breast cancer treatment. The highest rate of neuropathy was seen with T-DXd, followed by T-DM1 and SG.

***Keywords*: antibody–drug conjugate, breast cancer, meta-analysis, peripheral neuropathy**

1. Introduction

Antibody-drug conjugates (ADCs) are a new therapeutic strategy for solid tumour treatment. ADCs allow the selective delivery of chemotherapeutic agents to tumour cells by combining cytotoxic drugs and monoclonal antibodies through cleavable or non-cleavable linkers[1]. Ideal therapeutic targets for breast cancer are concentrated in tumour cells rather than in the surrounding non-tumour cells. Compared to conventional systemic chemotherapy modalities, ADCs can specifically concentrate drugs around tumour cells, and drug concentrations can exceed those of conventional chemotherapy by 100–1000 times[2a glycosylphosphatidylinositol-anchored glycoprotein first identified as p97, a cell-surface marker in melanomas. L49 was conjugated via a proteolytically cleavable valine-citrulline linker to the antimitotic drug, monomethylauristatin F (vcMMAF-3], Currently, three types of ADCs have been approved by the United States food and drug administration (U.S. FDA) for use as a breast cancer treatment, trastuzumab deruxtecan (T-DXd), trastuzumab emtansine (T-DM1), and sacituzumab govitecan (SG) [4]. Additionally, the ADC, disitamab vedotin (RC48), has been approved for breast cancer treatment in China [5].

Incomplete statistics show that approximately 30–40% of patients with cancer develop chemotherapy-induced peripheral neuropathy, which is a common side effect of chemotherapy [6]. Peripheral neuropathy is extensive and can damage various parts of the nervous system, including motor nerves and sensory nerves [7]. The pathogenesis of peripheral neuropathy is not well understood and may be related to (1) the dysregulation of voltage-gated sodium channels [8-9], (2) microtubule disruption and axonal transport disorders [10without affecting that of neurofilament proteins. Actin and a large number of polypeptides cotransported with actin as minor components are also blocked by taxol, although to a lesser extent. Fast axonal transport is essentially free from the inhibitory effect of this drug. Although previous models have suggested that slow axonal transport involves the bulk movement of cytoskeletal structures,these results suggest that such transport may involve an equilibrium between polymerised and depolymerised forms of the axonal cytoskeleton.","container-title":"Cell Motility","DOI":"10.1002/cm.970110302","ISSN":"0886-1544","issue":"3","journalAbbreviation":"Cell Motil. Cytoskeleton","language":"en","page":"151-156","source":"DOI.org (Crossref-11which has no preventative therapy. We have previously shown that cisplatin induces apoptosis in dorsal root ganglion (DRG]. The main clinical symptoms of peripheral neuropathy are tingling and numbness in the hands and feet, and these symptoms usually do not subside quickly[12].

2. Methods

2.1 Search strategy and selection criteria

We searched the Enbase, Web of Science, PubMed, and Cochrane Library databases using subject-related and free terms from database establishment to May 10, 2024, which mainly included drugs and breast cancer. Specific search strategies are described in the Supplementary Information. (Table.S1)The inclusion criteria were as follows: (1) prospective clinical trials; (2) breast cancer patients treated with ADCs;(3) patients who developed peripheral neuropathy after treatment with ADCs. This study is registered with PROSPERO (No. CRD42023469145).

2.2 Data extraction

Data extraction included first author, year, NCT, trial name, drug used, trial phase, trial type, number of participants in the safety analysis, and number of participants with varying degrees of peripheral neuropathy. We referred to clinical trial websites to adjudicate the data and graded adverse reactions according to CTCAEv5.0 to determine the accuracy of our included data.

2.3 Quality assessment

The studies included randomised and non-randomised controlled trials, and the quality of the studies was evaluated using the Cochrane Literature Quality Assessment Tool and MINORs scale.(Table S2)

2.4 Statistical analysis

Stata (version 17.0) was used for the statistical analyses. A random-effects model was used to draw forest plots, that visualised the prevalence and weights of each study. We used the I2 statistic and p-value to assess the study heterogeneity; the larger the I2 value, the higher the heterogeneity. We considered I2 > 50% or P < 0.1 to indicate the presence of heterogeneity. Finally, publication bias was evaluated using funnel plots and Egger's test. (Fig.S4-S7)

3. Results

3.1 Study selection and characterization

We selected 33 articles that we considered appropriate by inclusion exclusion criteria and 31 studies by careful reading of the full study reports. (Fig. S1) Finally, 7,549 patients from 31 studies were included in our analysis, and we summarised the characteristics of these studies to compare the incidence of peripheral neurotoxicity among four ADC drugs.[13pharmacokinetics, and preliminary activity of T-DM1 in patients with advanced HER2-positive breast cancer. Patients and Methods Successive cohorts of patients who had progressed on trastuzumab-based therapy received escalating doses of T-DM1. Outcomes were assessed by standard solid-tumor phase I methods.\nResults Twenty-four patients who had received a median of four prior chemotherapeutic agents for metastatic disease received T-DM1 at 0.3 mg/kg to 4.8 mg/kg on an every-3-weeks schedule. Transient thrombocytopenia was dose-limiting at 4.8 mg/kg; the maximum-tolerated dose (MTD-43an epithelial antigen expressed in breast cancer.\nMETHODS: In this global, randomized, phase III study, SG was compared with physician's choice chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine] (Table 1)

Table 1. The number of antibody–drug conjugate–related peripheral neuropathy for breast cancer in all studies included in this meta-analysis.

First author	Years	NCT	Study	Drug	Phase	Arm	No. of patients: No. of treated patients	No. of patients: All-grade	No. of patients: Grade≥ 3
R.Bartsch	2022	NCT04752059	TUXEDO-1	T-DXd	II	single-arm	15	2	0
T.Doi	2017	NCT02564900	T.Doi，2017	T-DXd	I	single-arm	12	3	0
A.Bardia	2021	NCT01631552	IMMU-132-01	SG	I/II	single-arm	108	20	0
H.SRugo	2022	NCT03901339	TROPiCS-02	SG	III	RCT	268	23	3
J.OShaughnessy	2022	NCT02574455	ASCENT	SG	III	RCT	235	9	0
J.Watanabe	2017	NA	JO29317	T-DM1	II	single-arm	232	18	1
M.Kashiwaba	2016	NA	JO22997	T-DM1	II	single-arm	73	8	1
D.A.Yardley	2015	NCT01120561	(TDM4884g)T-PAS	T-DM1	NA	single-arm	215	28	5
K.D.Miler	2014	NCT00875979	K.D.Miler，2014	T-DM1	IbIIa	single-arm	64	12	2
I. E. Krop	2012	NA	TDM4374g	T-DM1	II	single-arm	110	20	0
M.Beeram	2012	NCT00932373	TDM3569g	T-DM1	I	single-arm	28	3	0
I.E.Krop	2010	NA	I.E.Krop，2010	T-DM1	I	single-arm	24	3	0
F.MOntemurro	2020	NCT01702571	KAMILLA	T-DM1	III	single-arm	2002	205	0
A. G. Waks	2022	NCT03032107	A. G. Waks，2022	T-DM1	Ib	single-arm	20	3	0
D.Ji	2020	NCT03153163	D.Ji，2020	T-DM1	I	single-arm	11	4	0
Y.Kojima	2019	NA	UMIN000018383	T-DM1+S-1	Ib	single-arm	12	3	0
S.Jain	2018	NA	S.Jain，2018	T-DM1+Alpelisib	I	single-arm	17	2	0
S. Jenkins	2023	NCT03190967	S. Jenkins ，2023	T-DM1+TMZ	I	single-arm	12	6	0
H. K. Ahn	2022	NCT3881878	Neo-PATH (KCSG BR18-23)	T-DM1+atezolizumab	II	single-arm	67	39	1
H. Wildiers	2022	NA	EORTC 75111-10114	T-DM1	II	RCT	40	2	0
S. M. Tolaney	2021	NCT01853748	ATEMPT	T-DM1	I	RCT	383	42	0
E. P. Mamounas	2021	NCT01772472	KATHERINE	T-DM1	III	RCT	740	239	12
V.Dieras	2017	NA	EMILIA	T-DM1	III	RCT	490	59	9
I. E. Krop	2022	NCT01966471	KAITLIN	A +T-DM1+ P	III	RCT	912	--	22
N.Masuda	2020	NA	Neopeaks	T-DM1+P/+P+TCbPH	II	RCT	153	39	0
E.A.Perez	2019	NA	MARIANNE	T-DM1+PBO / +P	III	RCT	727	121	0
S.A.Hurvitz	2017	NA	KRISTINE	TDM-1 + P	III	RCT	223	17	2
Tejal A. Patel	2016	NA	TEAL	T-DM1 + lapatinib + nab-PTX	II	RCT	14	3	0
L.A.Emens	2020	NCT02924883	KATE2	TDM1 + atezolizumab/ +PBO	II	RCT	200	25	3
I. E. Krop	2016	NCT00951665	TDM4652g	TDM-1 + PTX/+P	IIA	RCT	44	40	8
M.Martin	2016	NCT00934856	BP22572	T-DM1 + DTX /+P	IBIIA	RCT	98	21	0

Abbreviations: T-DM1: trastuzumab emtansine; T-DXd: trastuzumab deruxtecan; SG: sacituzumab govitecan; S-1: Teysuno; TMZ: Temozolomide; A: anthracycline chemotherapy; P: pertuzumab; TCbPH: paclitaxel+ carboplatinum+ trastuzumab+ pertuzumab; PBO: placebo; nab-PTX: nab-paclitaxel; PTX: paclitaxel; DTX: docetaxel; NA: not available.

a Includes patients receiving Antibody-Drug Conjugate monotherapy regimens and combination regimens, and excludes patients not using

Antibody-Drug Conjugate medications.

b The number of peripheral neuropathies includes the number of peripheral sensory neuropathy, peripheral motor neuropathy, peripheral neuropathy, neuropathy, Hypoaesthesia.

3.2 Incidence of ADC-associated peripheral neuropathy

The incidence rates of ADC-associated peripheral neuropathy of any grade and grades ≥ 3 in 31 studies are summarised in Fig. 2. Since the KAITLIN study only reported the incidence of grade 3–5 peripheral neuropathy, we analysed the total incidence of any grade for only 30 studies (n = 6,637 patients). The overall incidence of patients with breast cancer with any-grade peripheral neuropathy was 17.99% (95% CI, 13.73–22.65%) (Figure 1).

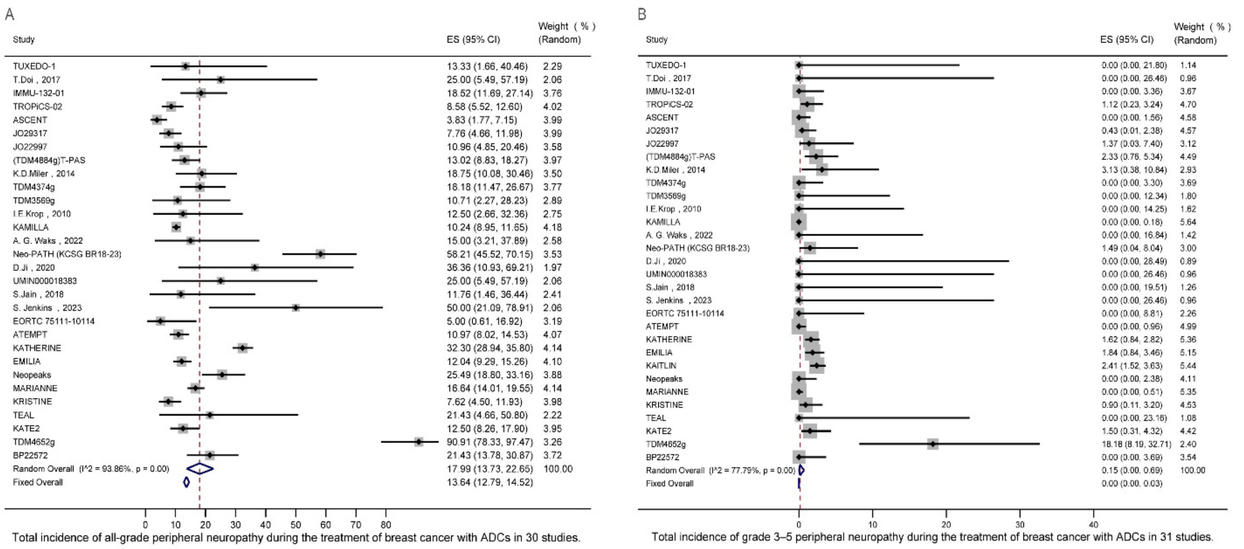

Figure 1. Forest plot of the total incidence of ADC drug-induced peripheral neuropathy. (A) Total incidence of all-grade peripheral neuropathy during the treatment of breast cancer with ADCs in 30 studies. (B) Total incidence of grade 3–5 peripheral neuropathy during the treatment of breast cancer with ADCs in 31 studies.

3.3 Incidence of patients with breast cancer receiving ADCs monotherapy treatments

In 19 studies of ADC monotherapy treatments, the overall incidence of any grade peripheral neuropathy in patients with breast cancer was 12.95% (95% CI, 9.03–17.4%); among the ADCs, the incidence of any-grade peripheral neuropathy was 13.76% (95% CI, 9.14–19.09%) for T-DM1, 18.17% (95% CI, 10.17–22.31%) for T-DXd,and 9.22 % (95% CI, 3.25–17.68%) for SG (Fig. S2)

3.4 Incidence of breast cancer patients treated with ADC combination therapy

There were 11 studies of T-DM1 combination therapy. However, the KAITLIN study only reported the incidence of grade 3-5 peripheral neuropathy; therefore, we did not include it in the study of the incidence of any grade of peripheral neuropathy, which was 29.11% (95% CI, 17.61- 42.05%) in 11 studies (Fig. S3).

4. Discussion

The first ADC, Mylotarg (gemtuzumab ozogamicin), was approved in 2000 [44], and as of August 2023, there are a total of 15 ADCs on the global market. After entering the human bloodstream, ADCs can continue to maintain their own stability, accurately recognise tumour cell surface antigens through antibodies, and release cytotoxic drugs to precisely destroy cancer cells1. Thus the side effects of ADCs are similar to their cytotoxic load [45].

In general, the prevalence of CIPN due to different antineoplastic agents and doses varies significantly, with reported prevalence ranging from 19% to over 85% [46diagnosis and treatment. CIPN is caused by several widely-used chemotherapeutics including paclitaxel, oxaliplatin, bortezomib. Severe CIPN may require dose reduction, or cessation, of chemotherapy, impacting on patient survival. While CIPN often resolves after chemotherapy, around 30% of patients will have persistent problems, impacting on function and quality of life. Early assessment and diagnosis is important, and we discuss tools developed for this purpose. There are no effective strategies to prevent CIPN, with limited evidence of effective drugs for treating established CIPN. Duloxetine has moderate evidence, with extrapolation from other neuropathic pain states generally being used to direct treatment options for CIPN. The preclinical perspective includes a discussion on the development of clinically-relevant rodent models of CIPN and some of the potentially modifiable mechanisms that have been identified using these models. We focus on the role of mitochondrial dysfunction, oxidative stress, immune cells and changes in ion channels from summary of the latest literature in these areas. Many causal mechanisms of CIPN occur simultaneously and/or can reinforce each other. Thus, combination therapies may well be required for most effective management. More effective treatment of CIPN will require closer links between oncology and pain management clinical teams to ensure CIPN patients are effectively monitored. Furthermore, continued close collaboration between clinical and preclinical research will facilitate the development of novel treatments for CIPN.","container-title":"British Journal of Anaesthesia","DOI":"10.1093/bja/aex229","ISSN":"1471-6771","issue":"4","journalAbbreviation":"Br J Anaesth","language":"eng","note":"PMID: 29121279","page":"737-749","source":"PubMed","title":"Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN]. It is estimated that CIPN occurs in about 70% of patients receiving chemotherapy within the first month of treatment, and in about 20-30% of these patients, CIPN may transform into a chronic, persistent, and highly resistant form, which can be observed 6 months or even longer after treatment cessation [47-48].

In patients treated with ADC, close attention should be paid to the development of peripheral neuropathy prior to administration of the drug. Peripheral neuropathy can be prevented by taking oral vitamin B or by supplementing with acupuncture, massage, and foot baths while the patient is taking the medication[49]. In addition, medications such as duloxetine, a norepinephrine reuptake inhibitor, can be used for treatment [50].

The incidence of peripheral neuropathy with the T-DXd monotherapy treatment was 18.17% (95% CI, 4.96– 35.89%). This is consistent with the results of a previous study on the incidence of adverse effects of ADCs [51]. This may be related to the cleavable linker and greater pharmacoresistance ratio; T-DXd combines IgG1 of trastuzumab to a novel topoisomerase I inhibitor, the camptothecin derivative (DX-8951; derivative (DXd)), via a specific, cleavable tetrapeptide linker [52]. Because the linker is cleavable the payload is prone to premature shedding and non-therapeutic toxicities. Furthermore, the drug/antibody ratio (DAR) of T-DXd is 8:1, and studies have shown that a higher DAR often leads to increased toxicity[53].

There are some limitations to this study. Firstly, some of the enrolled population had been treated with other chemotherapeutic agents in neoadjuvant therapy prior to the use of ADCs drugs, which may have biased the results of the study due to the different research objectives of the included studies. Second, peripheral neuropathy is influenced by the subjective wishes of patients.

5. Conclusion

In conclusion, our study found a higher overall incidence of any grade of CIPN. Compared with other ADCs, T-DXD had the highest incidence of peripheral neuropathy, T-DM1 the next highest, and SG the lowest.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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