Assessing taxane-associated adverse events using the FDA adverse event reporting system database

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Abstract

Background: Taxanes are an essential class of antineoplastic agents used to treat various cancers and are a fundamental cause of hypersensitivity reactions. In addition, other adverse events, such as bone marrow toxicity and peripheral neuropathy, can lead to chemotherapy discontinuation. This study aimed to evaluate the safety of taxanes in the real world.

Methods: Taxane-associated adverse events were identified by the Medical Dictionary for Regulatory Activities Preferred Terms and analyzed and compared by mining the US Food and Drug Administration Adverse Event Reporting System pharmacovigilance database from January 2004 to December 2019. Reported adverse events, such as hypersensitivity reaction, bone marrow toxicity, and peripheral neuropathy, were analyzed with the following signal detection algorithms: reporting odds ratio (ROR), proportional reporting ratio (PRR), multi-item gamma Poisson shrinker (MGPS), Bayesian confidence propagation neural network (BCPNN), and logistic regression methods. Adverse outcome events and death outcome rates were compared between different taxane groups using Pearson's χ^2 test, whereas significance was determined at $P < 0.05$ with a 95% confidence interval (CI).

Results: A total of 966 reports of hypersensitivity reactions, 1109 reports of bone marrow toxicity, and 1374 reports of peripheral neuropathy were analyzed. Compared with paclitaxel and docetaxel, bone marrow toxicity following the use of nab-paclitaxel had the highest ROR of 6.45 (95% two-sided CI, 6.05–6.88), PRR of 5.66, ($\chi^2 = 4342.98$), information component of 2.50 (95% one-sided CI = 2.34), and empirical Bayes geometric mean of 5.64 (95% one-sided CI = 5.34). Peripheral neuropathy following the use of nab-paclitaxel showed a higher ROR of 12.78 (95% two-sided CI, 11.55–14.14), PRR of 12.16 ($\chi^2 = 4060.88$), information component of 3.59 (95% one-sided CI = 3.25), and empirical Bayes geometric mean of 12.07 (95% one-sided CI = 11.09).

Conclusions: The results showed that bone marrow toxicity and peripheral neuropathy were the major adverse events induced by taxanes. Nab-paclitaxel exhibited the highest potential for taxane-associated adverse events. Further research in the future is warranted to explain taxane-associated adverse effects in real-world circumstances.

Keywords: Taxane; Pharmacovigilance; Bone marrow toxicity; Peripheral neuropathy

Introduction

Taxanes (paclitaxel, docetaxel, and nab-paclitaxel) represent a catalog of antineoplastic agents that interfere with microtube function, which leads to altered mitosis and cellular death. Paclitaxel was initially extracted from the Pacific yew tree (*Taxus brevifolia*). Due to paclitaxel scarcity, docetaxel was initially developed from the European yew tree (*Taxus baccata*).[1] Paclitaxel (solvent-based paclitaxel) is formulated in a mixture of the vehicle called Cremophor EL (polyoxyethylenated castor oil) and ethanol (50:50 v/v). Nab-paclitaxel is a solvent-free albumin-bound nanoparticle formulation of paclitaxel that is readily reconstituted in saline.[2] Taxanes are a class of antineoplastic agents widely used for the treatment of several types of cancers, such as breast cancer and lung cancer.[3] Although the application of chemotherapy is essential for improving patient survival, taxane-associated adverse events can lead to the discontinuation of chemotherapy. Physicians are familiar with the concept that taxanes are an indispensable cause of hypersensitivity reactions in cancer patients.[4] Other adverse events can also limit the smooth progress of chemotherapy, such as bone marrow toxicity and peripheral neuropathy. The use of taxanes can cause bone marrow toxicity, such as transient neutrophilic granulopenia.[5] The application of taxanes typically leads to microtube impairment, neuroimmune and inflammatory changes, ion channel remodeling, impaired mitochondrial function, and genetic predisposition, which might be the mechanisms of peripheral neuropathy.[6]

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The US Food and Drug Administration's (FDA's) Adverse Event Reporting System (FAERS) is the largest pharmacovigilance (PV) system available for adverse drug events reported by health professionals, consumers, and manufacturers. The purpose of the establishment of FAERS is to monitor the safety profile of postmarketing drugs and therapeutic biologics. We aimed to assess taxane-associated adverse events by investigating the FAERS due to the scarcity of knowledge following taxane administration in real-world practice.

Methods

Data source

A retrospective PV study was conducted using data from FAERS quarterly data files dated from January 2004 to December 2019. Demographic and administrative information and the initial report image ID number, drug information from the case reports, reaction information, patient outcome information, information on the source of the reports, and a "README" file containing a description of the data files were included in the quarterly data files.

According to US FDA recommendations, the deduplication process should be performed while selecting the latest FDA_DT if the case ID is identical. A higher primary ID was assigned if the case ID and FDA_DT were the same. A total of 966 reports associated with a hypersensitivity reaction, 1109 reports of bone marrow toxicity, and 1374 reports of peripheral neuropathy were obtained from the FAERS database.

Drug and adverse event identification

We chose a list of generic and brand names of paclitaxel, docetaxel, and nab-paclitaxel using www.drugbank.ca as a dictionary for data mining. The generic and brand names of taxanes were listed in Supplementary Digital Content, Table 1, http://links.lww.com/CM9/A606. Generic names and brand names were both included as keywords for the FAERS database search. We investigated in the REAC files for comprehensive MedDRA v22.1 (International Council of Harmonization) preferred terms (PTs) related to adverse events, such as hypersensitivity reaction, bone marrow toxicity, and peripheral neuropathy. Taxane-associated adverse events and preferred terms were listed in Supplementary Digital Content, Table 2, http://links.lww.com/CM9/A606.

Data mining

Four statistical procedures were applied in the data mining process mainly based on disproportionality analysis and Bayesian analysis, such as reporting odds ratio (ROR), proportional reporting ratio (PRR), multi-item gamma Poisson shrinker (MGPS), and Bayesian confidence propagation neural network (BCPNN). These algorithms were used in combination to identify the association between a particular drug and a specific adverse event.[7-15] The major algorithms used for signal detection were summarized in Supplementary Digital Content, Table 3, http://links.lww.com/CM9/A606.

The time to onset and death outcomes due to taxane-associated adverse events were assessed. The time to onset was defined as the interval between the date of occurrence of adverse events (EVENT_DT) and the start date of taxane administration (START_DT). Input errors, such as an earlier EVENT_DT than START_DT and inaccurate date entries, should be excluded. The result of death outcome was calculated as the total number of lethal adverse events divided by the total number of taxane-associated hypersensitivity reactions, bone marrow toxicity, and peripheral neuropathy.

Statistical analysis

We used descriptive analyses to summarize the clinical characteristics of taxane-associated adverse events, such as hypersensitivity reactions, bone marrow toxicity, and peripheral neuropathy, collected from the FAERS. Given that the data were typically not normally distributed, the times to onset of hypersensitivity reaction, bone marrow toxicity, and peripheral neuropathy between different taxane administrations were compared with non-parametric tests (using the Kruskal-Wallis test when there were more than two subgroups of respondents and the Mann-Whitney test when there were dichotomous variables). Adverse outcome events and death outcome rates were compared using Pearson's χ^2 test between different taxane groups. All statistical analyses and data mining processes were performed with Statistical Analysis System v. 9.4 (SAS Institute Inc., Cary, NC, USA), whereas statistical significance was determined at $P < 0.05$ with a 95% confidence interval (CI).

Results

Clinical characteristics of the patients

Of all taxane-associated adverse reports from the FAERS database, 8721 reports of hypersensitivity reactions, 4964 reports of bone marrow toxicity, and 1374 reports of peripheral neuropathy were analyzed. Most of the hypersensitivity reaction reports and peripheral neuropathy were associated with paclitaxel (52.07% and 41.41%, respectively), whereas most of the bone marrow toxicity reports were caused by docetaxel (46.15%). The clinical characteristics of the patients are shown in Table 1.

Adverse events associated with taxanes were mainly reported by healthcare professionals. Female patients experienced more adverse events, such as hypersensitivity reactions, bone marrow toxicity, and peripheral neuropathy.

Signal detection

Paclitaxel exhibited a positive signal in ROR associated with hypersensitivity reactions, whereas docetaxel and nab-paclitaxel showed a negative signal. Nab-paclitaxel showed the highest signal associated with bone marrow

Table 1: Clinical characteristics of patients with taxane-associated hypersensitivity reaction, bone marrow toxicity, and neuropathy peripheral.

Characteristics	Hypersensitivity reaction (N=8721)			Bone marrow toxicity (N =4964)			Neuropathy peripheral (N =1374)		
	Paclitaxel (N=4543)	Docetaxel (N=3215)	Nab-paclitaxel (N=966)	Paclitaxel (N=1564)	Docetaxel (N=2291)	Nab-paclitaxel (N=1109)	Paclitaxel (N=569)	Docetaxel (N=407)	Nab-paclitaxel (N=398)
Reporting region									
Africa	6 (0.13)	30 (0.93)	0	1 (0.06)	41 (1.79)	0	0	1 (0.25)	0
Asian	264 (5.81)	430 (13.37)	167 (17.29)	241 (15.41)	391 (17.07)	209 (18.85)	64 (11.25)	18 (4.42)	74 (18.59)
Europe	2337 (51.44)	1397 (43.45)	331 (34.27)	781 (49.94)	1012 (44.17)	439 (39.59)	261 (45.87)	247 (60.69)	146 (36.68)
North America	1388 (30.55)	994 (30.92)	417 (43.17)	372 (23.79)	617 (26.93)	427 (38.50)	196 (34.45)	124 (30.47)	170 (42.71)
Oceania	35 (0.77)	27 (0.84)	17 (1.76)	10 (0.64)	12 (0.52)	21 (1.89)	3 (0.53)	2 (0.49)	7 (1.76)
South America	96 (2.11)	38 (1.18)	27 (2.80)	7 (0.45)	18 (0.79)	12 (1.08)	6 (1.05)	4 (0.98)	1 (0.25)
Country not specified	417 (9.18)	299 (9.30)	7 (0.72)	157 (10.04)	210 (9.17)	1 (0.09)	39 (6.85)	11 (2.70)	0
Reporters									
Healthcare professional	3768 (82.94)	2760 (85.85)	874 (90.48)	1260 (80.56)	2027 (88.48)	1067 (96.21)	443 (77.86)	309 (75.92)	359 (90.20)
Non-healthcare professional	775 (17.06)	455 (14.15)	92 (9.52)	304 (19.44)	264 (11.52)	42 (3.79)	126 (22.14)	98 (24.08)	39 (9.80)
Patient gender									
Female	3337 (73.45)	1998 (62.15)	508 (52.59)	1027 (65.66)	1192 (52.03)	487 (43.91)	430 (75.57)	277 (68.06)	158 (39.70)
Male	951 (20.93)	1144 (35.58)	297 (30.75)	388 (24.81)	1001 (43.69)	392 (35.35)	75 (13.18)	113 (27.76)	88 (22.11)
Unknown	255 (5.61)	73 (2.27)	161 (16.67)	149 (9.53)	98 (4.28)	230 (20.74)	64 (11.25)	17 (4.18)	152 (38.19)
Patient age groups (years)									
<18	12 (0.26)	4 (0.12)	2 (0.21)	15 (0.96)	7 (0.31)	2 (0.18)	2 (0.35)	1 (0.25)	0
18–44	516 (11.36)	357 (11.10)	61 (6.31)	183 (11.70)	255 (11.13)	45 (4.06)	39 (6.85)	49 (12.04)	18 (4.52)
45–64	1885 (41.49)	1427 (44.39)	315 (32.61)	512 (32.74)	843 (36.80)	353 (31.83)	224 (39.37)	174 (42.75)	99 (24.87)
65–74	1036 (22.80)	677 (21.06)	240 (24.84)	377 (24.10)	574 (25.05)	287 (25.88)	114 (20.04)	62 (15.23)	77 (19.35)
75–84	345 (7.59)	286 (8.90)	84 (8.70)	148 (9.46)	228 (9.95)	137 (12.35)	43 (7.56)	35 (8.60)	21 (5.28)
≥85	30 (0.66)	11 (0.34)	3 (0.31)	328 (20.97)	384 (16.76)	285 (25.70)	10 (1.76)	0	0
Unknown	719 (15.83)	453 (14.09)	261 (27.02)	1 (0.06)	0	0	137 (24.08)	86 (21.13)	183 (45.98)

Data are presented as n (%).

Table 2: Signal detection.

Adverse events	Generic name	*N*	ROR (95% two-sided CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Hypersensitivity reaction	Paclitaxel	4540	2.41 (2.33–2.50)	1.99 (2626.20)	0.99 (0.96)	1.99 (1.93)
	Docetaxel	3215	0.51 (0.49–0.53)	0.55 (1407.30)	−0.87 (0)	0.55 (0.53)
	Nab-paclitaxel	966	0.82 (0.77–0.88)	0.85 (31.46)	−0.24 (0)	0.85 (0.80)
Bone marrow toxicity	Paclitaxel	1561	4.32 (4.10–4.56)	3.98 (3559.58)	1.99 (1.89)	3.97 (3.80)
	Docetaxel	2289	2.36 (2.26–2.46)	2.28 (1672.37)	1.18 (1.13)	2.27 (2.19)
	Nab-paclitaxel	1108	6.45 (6.05–6.88)	5.66 (4342.98)	2.5 (2.34)	5.64 (5.34)
Neuropathy peripheral	Paclitaxel	568	8.99 (8.26–9.78)	8.69 (3836.77)	3.1 (2.85)	8.6 (8.01)
	Docetaxel	407	2.43 (2.20–2.68)	2.42 (336.22)	1.27 (1.15)	2.4 (2.21)
	Nab-paclitaxel	398	12.78 (11.55–14.14)	12.16 (4060.88)	3.59 (3.25)	12.07 (11.09)

CI: Confidence interval; EBGM: Empirical Bayesian geometric mean; EBGM05: The lower 95% one-sided CI of EBGM; IC: Information component; IC025: The lower limit of the 95% two-sided CI of the IC; PRR: Proportional reporting ratio; ROR: Reporting odds ratio.

toxicity and peripheral neuropathy, although all taxane agents had positive signals in ROR, PRR, BCPNN, and MGPS. The results of signal detection were shown in Table 2.

Time to onset of taxane-associated hypersensitivity reaction, bone marrow toxicity, and peripheral neuropathy

The time to onset of the hypersensitivity reaction with nab-paclitaxel (45.91 days) was significantly later than that with docetaxel (35.10 days), $P < 0.0001$, and that for docetaxel was significantly later compared with paclitaxel (23.76 days), $P < 0.0001$. The time to onset of bone marrow toxicity by nab-paclitaxel (46.54 days) was significantly later than docetaxel (40.20 days), $P < 0.0001$, and that of paclitaxel (45.32 days) was significantly later than docetaxel, $P < 0.0001$. It can be concluded that the time to onset of neuropathy peripherally with nab-paclitaxel (91.49 days) was significantly later than that with docetaxel (34.82 days), $P < 0.0001$, and significantly later than that with paclitaxel (61.19 days), $P = 0.0019$. The times to onset of taxane-associated adverse events are shown in Figure 1.

Outcome due to taxane-associated adverse events

To evaluate the adverse effect of taxanes, we assessed both death and non-death outcomes following paclitaxel, docetaxel, and nab-paclitaxel, and the results are shown in Table 3. Although paclitaxel required more intervention to prevent permanent impairment (4.35%), it showed a lower death rate (9.77%) caused by hypersensitivity reaction. Nab-paclitaxel showed a cautious higher death rate (31.05%) caused by neuropathy peripheral.

Discussion

To the best of our knowledge, this is a novel study describing the connection between taxane-associated adverse events in the real-world setting based on the FAERS PV database.

In our study, bone marrow toxicity and neuropathy peripheral events following paclitaxel, docetaxel, and nab-

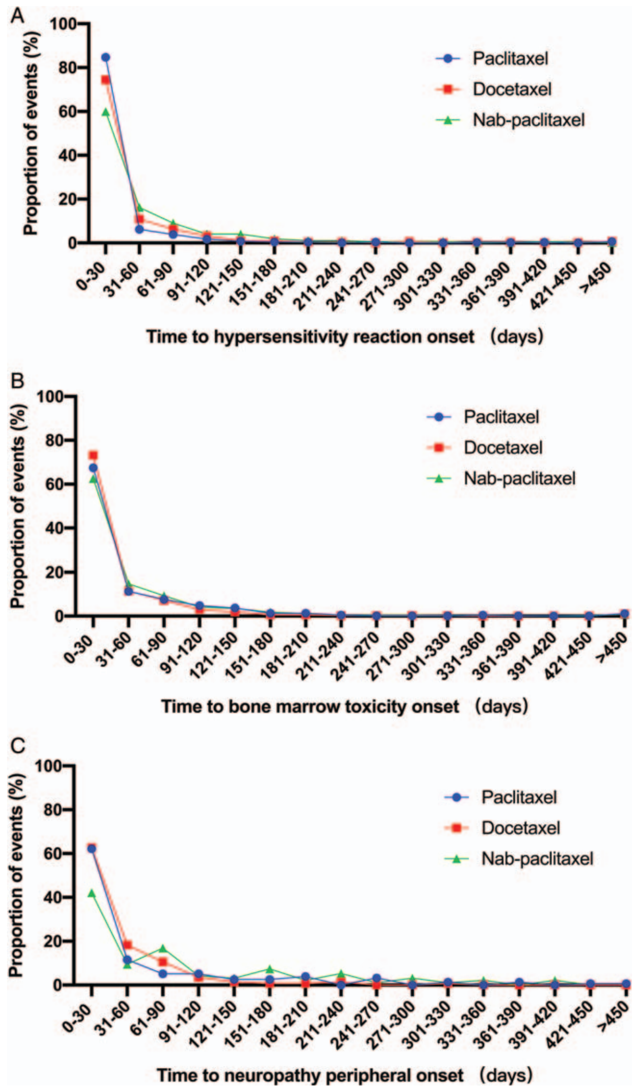

Figure 1: Proportion of adverse events *vs.* time to taxane-associated adverse reaction onset. (A) The time to onset of the hypersensitivity reaction with nab-paclitaxel was significantly later than that with docetaxel, and that for docetaxel was significantly later compared with paclitaxel. (B) The time to onset of bone marrow toxicity by nab-paclitaxel was significantly later than docetaxel, and that of paclitaxel was significantly later than docetaxel. (C) The time to onset of neuropathy peripherally with nab-paclitaxel was significantly later than that with docetaxel and that with paclitaxel.

Table 3: Outcome of taxane-associated adverse events.

	Hypersensitivity reaction			Bone marrow toxicity			Neuropathy peripheral		
Outcome	Paclitaxel	Docetaxel	Nab-paclitaxel	Paclitaxel	Docetaxel	Nab-paclitaxel	Paclitaxel	Docetaxel	Nab-paclitaxel
Congenital anomaly	1 (0.02)	0	1 (0.11)	6 (0.39)	3 (0.13)	1 (0.09)	0	0	0
Death	409 (9.77)	650 (20.95)	244 (26.38)	327 (21.47)	629 (27.82)	340 (31.11)	40 (8.25)	21 (5.33)	118 (31.05)
Disability	76 (1.81)	122 (3.93)	11 (1.19)	22 (1.44)	50 (2.21)	27 (2.47)	40 (8.25)	44 (11.17)	32 (8.42)
Hospitalization-initial or prolonged	1677 (40.04)	1768 (56.98)	553 (59.78)	781 (51.28)	1499 (66.3)	577 (52.79)	148 (30.52)	125 (31.73)	87 (22.89)
Life-threatening	721 (17.22)	384 (12.38)	101 (10.92)	118 (7.75)	276 (12.21)	151 (13.82)	20 (4.12)	12 (3.05)	12 (3.16)
Other serious (important medical event)	2193 (52.36)	1375 (44.31)	379 (40.97)	876 (57.52)	995 (44.01)	583 (53.34)	372 (76.7)	298 (75.63)	285 (75.00)
Required intervention to prevent permanent impairment/damage	182 (4.35)	45 (1.45)	4 (0.43)	20 (1.31)	16 (0.71)	1 (0.09)	10 (2.06)	4 (1.02)	1 (0.26)

Data are presented as n (%).

paclitaxel were confirmed by the positive signals of ROR, PRR, BCPNN, and MGPS. Among them, nab-paclitaxel shows the highest signal. Cremophor is not used as the vehicle in nab-paclitaxel, and no infusion reactions were observed in phases I, II, and III studies of nab-paclitaxel omission of routine premedication.[16-18] We should focus on avoiding bone marrow toxicity and neuropathy peripheral events, although nab-paclitaxel is always considered safer.[19]

Paclitaxel shows a positive ROR signal, whereas docetaxel and nab-paclitaxel show a negative hypersensitivity reaction signal. There is evidence that both the taxane component and the vehicles used to solubilize these agents can cause various infusion reactions.[20] Among the proposed mechanisms underlying paclitaxel, infusion reactions are complement activation, direct mast cell/basophil activation, and classic immunoglobulin E-mediated anaphylaxis due to Cremophor and docetaxel infusion reactions due to polysorbate 80.[21-23] Based on the FAERS data, there is no evidence that taxane use produces a strong positive signal related to the hypersensitivity reaction, which is different from our past cognition. As clinical experience has generally adopted predosing treatment for patients using taxane, the incidence of hypersensitivity reaction is low, which also suggests that we need to understand the limitations of the FAERS data mining method correctly.[24]

Nab-paclitaxel exhibits an increased rate of death-related outcomes compared with paclitaxel and docetaxel, which is another surprising discovery since nab-paclitaxel is always considered to be a safer taxane by design.[25-27] The safety of nab-paclitaxel should be further explored in future clinical applications. In general, the adverse events related to paclitaxel that clinicians are concerned about are mainly infusion reactions because this may affect the smooth progress of the patient's treatment.[28] Using premedication before taxane administration can avoid the impact of reducing infusion-related reactions, including hypersensitivity reactions, but there is insufficient preparation for adverse events, such as bone marrow toxicity and peripheral neuropathy.[24] Late-onset adverse events may also cause drug withdrawal, life-threatening events, and death, which need to be taken seriously.[29]

Although the data mining techniques showed many advantages, they cannot solve all the problems by detecting and analyzing adverse event signals based on spontaneous reporting systems alone.[30] Furthermore, this study has voidable limitations. Analysis of the FAERS database found that the data of taxane-associated adverse events are mainly reported in Europe and North America. However, the taxane is widely used globally, so it is necessary to consider whether regional data are missing.

Conclusions

Our FAERS database analysis study identified positive signals for hypersensitivity reaction, bone marrow toxicity, and neuropathy peripheral events associated with taxanes in a real-world setting. The most important finding from this study is that nab-paclitaxel showed the highest signal in signal detection. The time to onset of nab-paclitaxel-associated adverse events was significantly later than that of paclitaxel and docetaxel. More research is needed in the future to explain the safety of nab-paclitaxel for better taxane application.

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Conflicts of interest

None.

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