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Adverse Event Profile for Nanoparticle Albumin-Bound Paclitaxel Compared With Solvent-Based Taxanes in Solid-Organ Tumors: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is an innovative form of taxane that has superior antitumor effects; however, the safety profile between nab-paclitaxel and traditional taxanes remains controversial. **Objective:** To determine the burden of adverse events (AEs) in patients with multiple malignancies receiving nab-paclitaxel compared with that in patients receiving traditional taxanes. **Methods:** Randomized clinical trials comparing nab-paclitaxel with traditional taxanes (solvent-based paclitaxel [sb-paclitaxel] or docetaxel) in the treatment of primary solid-organ malignancies were included if AEs were reported as an outcome. Statistical analyses were conducted to calculate the summary odds ratio (OR) of the relevant adverse outcomes related to nab-paclitaxel and traditional taxanes. Prespecified subgroup analyses based on intervention and doses, primary tumor sites, and different ethnic groups were also performed. **Results:** Twelve clinical trials were included in the meta-analysis. Grade 3/4 anemia, thrombocytopenia, and neurotoxicity were more frequent with nab-paclitaxel than with traditional taxanes. Nab-paclitaxel at 100 or 125 mg/m^2/w dosage was associated with fewer or similar grade 3/4 specific AEs. Allergy was less common with nab-paclitaxel. The median recovery times of neurotoxicity were 25, 64, and 37 days in patients receiving nab-paclitaxel, sb-paclitaxel, and docetaxel, respectively. Elevated incidences of specific AEs were more common in breast cancer and non-Asian patients than in other malignancies and ethnic groups, respectively. **Conclusion and Relevance:** Nab-paclitaxel increased the risk of hematologic and non-hematologic AEs in general, but anaphylaxis was less common, and the recovery duration of neurotoxicity was shorter. Weekly administration of nab-paclitaxel at a lower dosage provided better tolerance.

Keywords

adverse events, nab-paclitaxel, taxanes, meta-analysis, neoplasm

Background

Taxanes are one of the most active and widely used cytotoxic agents for cancer treatment. The efficacy of traditional taxanes, including solvent-based paclitaxel (sb-paclitaxel) and docetaxel, has been demonstrated in multiple tumor sites.[1-3] However, certain toxicities, such as hypersensitivity reactions, prolonged sensory neuropathy, and premedications, limit their administration in some patients.[4,5] Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a solvent-free form of paclitaxel that can potentially avoid hypersensitivity reactions, thereby providing a new delivery mechanism for paclitaxel to tumors.[4-6] Nab-paclitaxel is widely approved for the treatment of metastatic breast cancer and other solid tumors on the basis of results from multiple phase II and III trials showing that it has superior antitumor effects than traditional solvent-based paclitaxel; however, safety outcomes have been reported in these trials, and the severity and type of events differed between the 2

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groups.[7-9] Yamamoto et al performed a meta-analysis demonstrating the prolonged recurrence-free and overall survival of the nab-paclitaxel group in metastatic breast cancer and a promising application in neoadjuvant and adjuvant settings.[10] However, the comparison between nab-paclitaxel and traditional taxanes remains controversial. Another meta-analysis performed by Liu et al compared nab-paclitaxel-based chemotherapy with traditional taxane-based chemotherapy and failed to demonstrate the advantages except for equivalent survival and increased sensory neuropathy in the nab-paclitaxel groups.[11] By contrary, the meta-analysis performed by Yamamoto et al suggested that the increased toxicities in the nab-paclitaxel group would be rapidly resolved after interruption of treatment and dose reduction.[10]

Immunotherapy has achieved rapid growth over the last several years, and in combination with chemotherapy, it has shown promising efficacy across many different tumor types. Chemotherapeutic drugs, in particular taxanes, may enhance tumor antigen release and anticancer activity against immune checkpoint inhibition.[12] Nab-paclitaxel is proven to be a better pairing with immunotherapy for not requiring steroid premedication, which has potential immunosuppressive effects. Rather than traditional taxanes, the improved antitumor activity of nab-paclitaxel combined with biologic therapies was approved for metastatic squamous non-small-cell lung cancer (NSCLC; in phase 1b and 3 studies) and breast cancer (in phase 1b and 3 studies).[13-18]

As the use of immunotherapy continues to expand and nab-paclitaxel is moved forward in tumor treatment algorithms, a comprehensive understanding of how the incidence of adverse events (AEs) and manifestations differ from that of traditional taxanes is crucial. We performed this systematic review and meta-analysis to evaluate the burden of AEs in patients with multiple solid-organ malignancies receiving nab-paclitaxel compared with patients receiving traditional taxanes, such as sb-paclitaxel and docetaxel.

Methods

Search Strategy and Selection Criteria

We searched PubMed Medline, Embase, Web of Science, and Cochrane CENTRAL databases from January 1, 2000, to February 26, 2020, for randomized clinical trials of nab-paclitaxel compared with solvent-based taxanes in solid-organ tumors. Reference lists from included articles and conference abstracts from the annual meetings of the American Society of Clinical Oncology and the European Society of Medical Oncology from 2014 to 2018 were cross-referenced to ensure completeness. There were no limitations regarding the publication language. After a literature search, we excluded all duplicates.

Studies that used nab-paclitaxel in the treatment arm were eligible for inclusion. The control group must have received traditional taxanes (sb-paclitaxel or docetaxel), and studies that had placebo only in the control arm were excluded. Studies evaluating patients aged $<$ 18 years or with hematologic malignancies (leukemia, lymphoma, multiple myeloma) and non-melanoma skin cancers were excluded. Published randomized phase II or III clinical trials were included, and observational studies (cohort or case-control in design), editorials, commentaries, and review articles were excluded. To prevent duplication of the patients used in our analyses, we selected the primary publication for inclusion.

Data Extraction and Clinical Outcomes

Data extraction and analysis were conducted independently by 2 independent investigators, and any discrepancy was resolved by consensus according to the Quality of Reporting of Meta-Analyses guidelines.[19] The primary outcome was severe AEs (defined as Common Terminology Criteria for Adverse Events [CTCAE] grade $\geq$ 3). Secondary outcomes were the proportion of overall AEs, the proportion of treatment discontinuation due to AEs, and the proportion of deaths due to AEs, and the incidence rates of specific AEs were examined for both the nab-paclitaxel and traditional taxane groups. Study characteristics including first author, year of publication, trial name, underlying disease site, study design, type of therapy, line of therapy, analysis type, intervention and dose, control treatment, area, and duration of therapy were extracted. In addition, the proportion of patients experiencing AEs was also assessed. Prespecified subgroup analyses based on intervention and doses, primary tumor sites, and different ethnic groups were also performed.

Statistical Analysis

We assumed a class effect and performed a meta-analysis of nab-paclitaxel compared with traditional taxanes with ReVman Software Version 5.3 (Review Manager 5.3). The incidence of AEs was pooled in an unweighted manner. Odds ratio (OR) was used as the effect quantity, and its estimated value and 95% confidence interval (CI) value were calculated for each effect quantity. Statistical heterogeneity was identified by visual examination of forest plots and the Q test, estimated using the inverse-variance method, and quantified using the I^2 statistic, with a test level of 0.10. If there was no statistical heterogeneity ($P > 0.10$, $I^2 \leq 50\%$), the fixed-effect model was used for analysis. If statistical

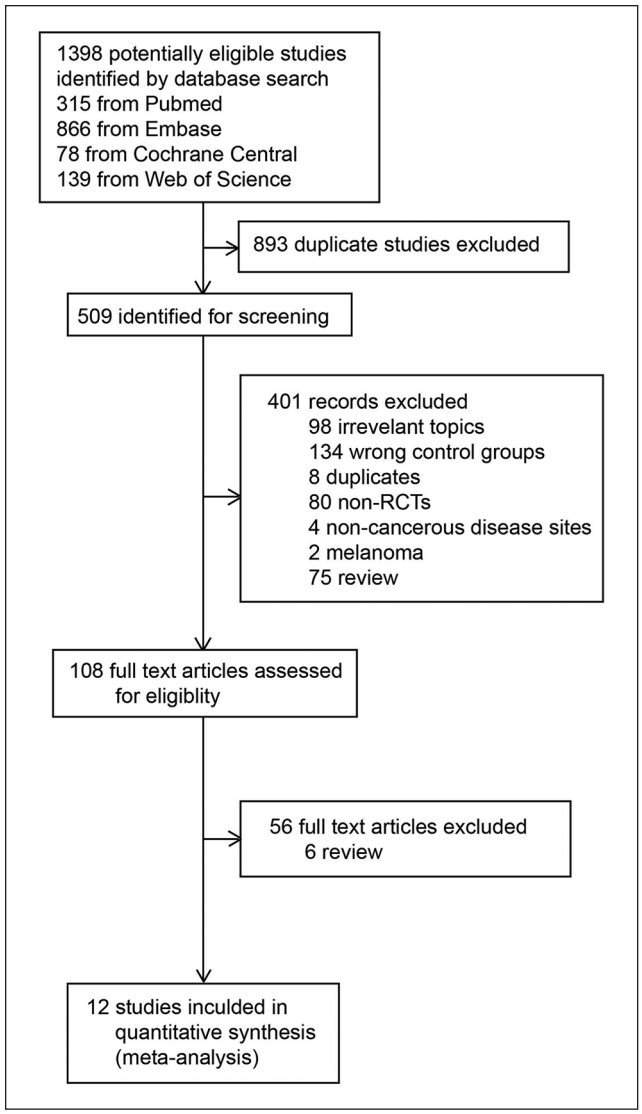


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram.
Abbreviations: RCT, randomized controlled trial.

heterogeneity existed ($P \leq 0.10$, $I^2 > 50\%$), the random effects model was used for analysis.

The Paule-Mandel technique for pooling measures of effect was used because of the rarity of some of our secondary outcomes. The fixed versus random effects models were selected for use in the meta-analyses based on clinical heterogeneity in our data.

Results

We retrieved 1400 relevant articles from our literature search. After reviewing 108 potentially eligible articles in detail, 12 trials met our inclusion criteria and were included in this study. Figure 1 lists the reasons for exclusion of the 96 papers. Of note, 4 of the excluded papers were AE subgroup analyses of previously published studies and were without intact data. We decided to use the first published available data to maintain consistency.

The main characteristics of the included trials are listed in Table 1 and a total of 5762 patients were enrolled in this meta-analysis. All 12 trials enrolled patients within the past 15 years, and safety was evaluated as a secondary endpoint, except for 1 trial focused on neurotoxicity. Nine trials (75%) were evaluated in breast cancer, 1 (8.3%) in NSCLC, 1 (8.3%) in urothelial cancer, and 1 (8.3%) in gastric cancer.[7,20-31] Most trials investigated nab-paclitaxel as a single agent; however, 2 trials combined nab-paclitaxel with other agents (bevacizumab and carboplatin). There were 4 trials investigating nab-paclitaxel monotherapy in different doses, whereas the other 6 trials investigated a single dose. The comparison arm was prescribed standard chemotherapy of traditional taxane agents, 9 trials (75%) assessed sb-paclitaxel as a comparison arm, and 3 (25%) assessed docetaxel.

Termination of therapy due to AEs was more common in patients who received nab-paclitaxel than in those who received traditional taxanes (Figure 2a, OR = 1.72, 95% CI, 1.22-2.41). Considering different dosages of nab-paclitaxel (Figure S1), treatment discontinuation was more common in the 125 and 150 mg/m^2/w and 260 mg/m^2/3w nab-paclitaxel groups than in the control groups. Treatment delay and deaths due to treatment-related AEs did not show significant differences between the 2 groups (Figures 2b and 2c, OR = 0.31, 95% CI, 0.02-4.01; OR = 0.73, 95% CI, 0.36-1.46).

Neurotoxicity was specifically investigated in this study (Figure 3). Any grade neurotoxicity was reported more commonly in patients who received nab-paclitaxel compared with traditional taxanes (Figure 3a, OR = 1.96, 95% CI, 1.45-2.66), and severe grade 3/4 neurotoxicity was also reported to be more common in the nab-paclitaxel group (Figure 3b, OR = 2.44, 95% CI, 1.30-4.57). Fractional dosage analyses provide consistent information that nab-paclitaxel is more likely to develop neurotoxicity events (any grade or grade 3/4) when compared with traditional taxanes. However, the average median recovery time of neurotoxicity (Figure 3c) was 24.75 days in patients who received nab-paclitaxel, and 64 days and 37 days in the sb-paclitaxel and docetaxel groups, respectively.

We also examined specific symptoms and disease-related AEs. In hematologic AEs, neutropenia (any grade) was reported in 10 studies, and rates were higher among patients who received nab-paclitaxel (Figure 4a, OR = 1.70, 95% CI, 1.05-2.76). There was no significant difference in severe neutropenia (grade 3/4) between nab-paclitaxel and traditional taxane groups (OR = 0.84, 95% CI, 0.48-1.47). There was no significant difference in any grade of leukopenia between the 2 groups reported in 9 studies (Figure 4b, OR = 1.27, 95% CI, 0.95-1.70). Anemia of any grade was reported to be more common in patients who received nab-paclitaxel than in the control group (Figure 4c,

Table 1. Characteristics of the 12 Trials Included in the Meta-Analysis.

No.	Source	Trial name	Disease site	Type of study	Line of therapy	Analysis type	Intervention and dose (n)	Control treatment(n)	Area	Median time on intervention	Median time on control	Median no. of intervention doses	Median no. of control doses
1	William J. Gradishar, 2005	No name	BC	Phase III	>1	As treated	NAB-P 260 mg/m^2 Q3weeks (229)	SB-P 175 mg/m^2 Q3weeks (225)	The United States	18 weeks (range: 3-54)	18 weeks (range: 3-54)	6 (range: 1-18)	5 (range: 1-18)
2	William J. Gradishar, 2009	No name	BC	Phase II	1	As treated	NAB-P 100 mg/m^2 Qweek (76); 150 mg/m^2 Qweek (74); 300 mg/m^2 Q3weeks (76)	DOC 100 mg/m^2 Q3weeks (74)	The United States	N/A	N/A	N/A	N/A
3	Zhong-Zhen GUAN, 2009	No name	BC	Phase III	1	As treated	NAB-P 260 mg/m^2 Q3weeks (104)	SB-P 175 mg/m^2 Q3weeks (106)	China	18 weeks (range: 3-33)	18 weeks (range: 3-30)	6 (range: 1-11)	6 (range: 1-11)
4	Mark A. Socinski, 2012	CA 031	NSCLC	Phase III	1	As treated	CBP (AUC 6) Q3weeks + NAB-P 100 mg/m^2 Qweek (514)	CBP (AUC 6) Q3weeks + SB-P 200 mg/m^2 Q3weeks (524)	The United States/ Japan	18 weeks (range: 1-85)	18 weeks (range: 1-90)	15 (range: 1-85)	6 (range: 1-30)
5	Hope S. Rugo, 2015	Alliance	BC	Phase III	1	As treated	BEV + NAB-P 150 mg/m^2 Qweek (267)	BEV + SB-P 90 mg/m^2 Qweek (275)	The United States	20 weeks	N/A	15	N/A
6	Kohei Shitara, 2017	ABSOLUTE	GC	Phase III	>1	As treated	NAB-P 260 mg/m^2 Q3weeks (244); 100 mg/m^2 Qweek (241)	SB-P 80 mg/m^2 Qweek (243)	Japan	2.4M (range: 0.9-5.0), 3.7M (range: 1.9-6.7)	3.3M (range: 1.5-5.4)	4;12	14
7	Jenny Furlanetto, 2017	GBG 69	Triple(-) BC	Phase III	Neoadjuvant	As treated	NAB-P 150 mg/m^2 Qweek (229); 125 mg/m^2 Qweek (377)	SB-P 80 mg/m^2 Qweek (226); 80 mg/m^2 Qweek (374)	The United States	12 weeks	12 weeks	12	12
8	Kenji Tamura, 2017	No name	HER-2(-) BC	Phase II	1	As treated	NAB-P 150 mg/m^2 Qweek (100)	DOC 75 mg/m^2 Q3weeks (100)	Japan	N/A	N/A	N/A	N/A
9	Luca Gianni, 2018	ETNA	HER-2(-) BC	Phase III	Neoadjuvant	As treated	NAB-P 125 mg/m^2 Qweek (337)	SB-P 90 mg/m^2 Qweek (335)	Italy	16 weeks	16 weeks	12	12
10	Takashi Kuwayama, 2018	No name	HER-2(-) BC	Phase II	Neoadjuvant	As treated	NAB-P 100 mg/m^2 Qweek (74)	DOC 75 mg/m^2 Q3weeks (77)	Japan	16 weeks	16 weeks	12	4
11	EVA CIRUELOS, 2019	No name	HER-2(-) BC	Phase II	1	As treated	NAB-P 100 mg/m^2 Qweek (16); 150 mg/m^2 Qweek (14); 150 mg/m^2 Q2weeks (16)	SB-P 80 mg/m^2 Qweek (14)	Spain	N/A	N/A	N/A	N/A
12	Sridhar, 2018	NCT02033993	Urothelial	Phase II	>1	As treated	NAB-P 260 mg/m^2 Q3weeks (100)	SB-P 175 mg/m^2 Q3weeks (100)	Canada/ Australia	N/A	N/A	N/A	N/A

Abbreviations: AUC, area under the curve; BC, breast cancer; CBP, carboplatin; DOC, docetaxel; GC, gastric cancer; NAB-P, nanoparticle albumin-bound paclitaxel; NSCLC, non-small-cell lung cancer; SB-P, solvent-based paclitaxel.

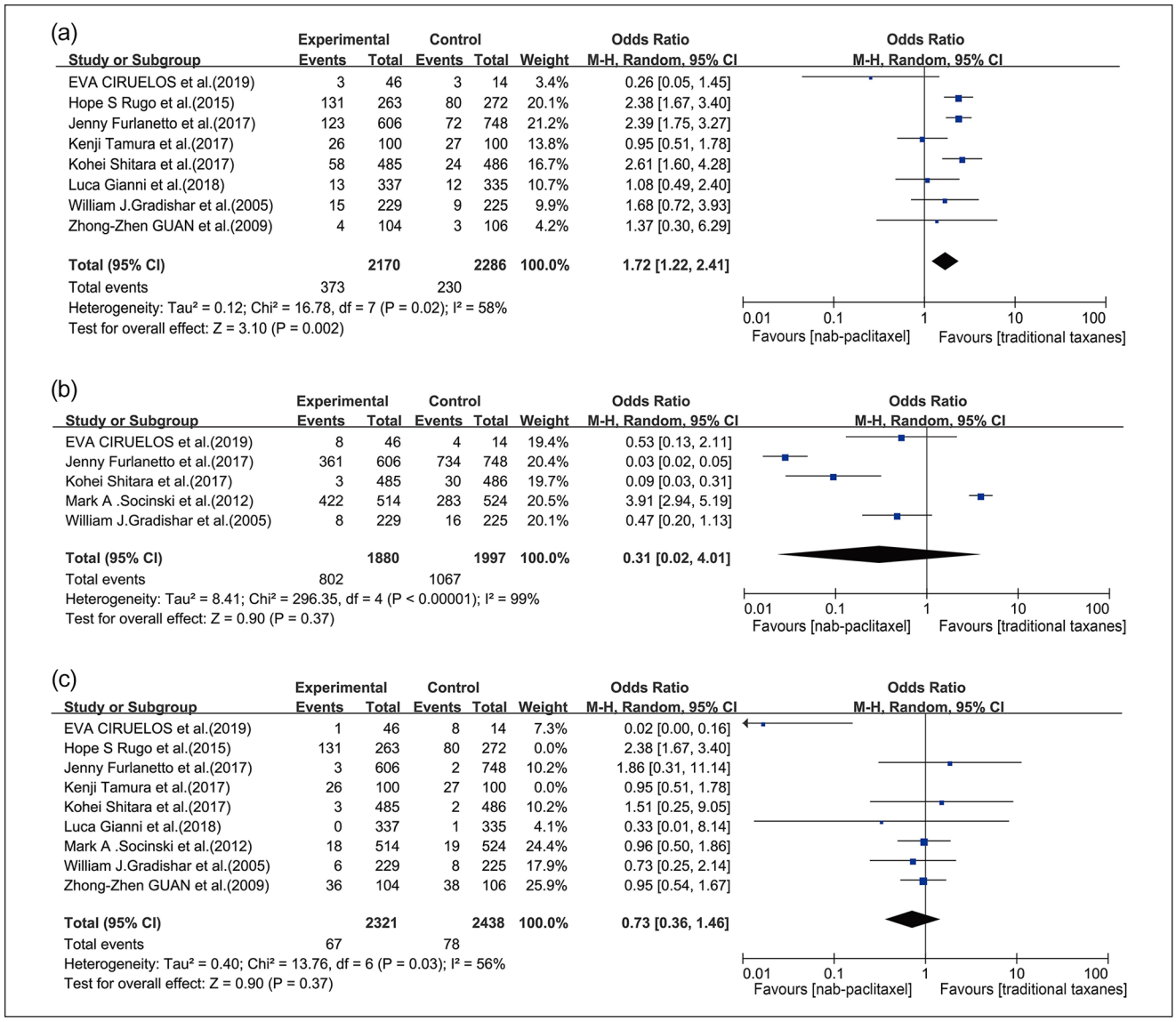


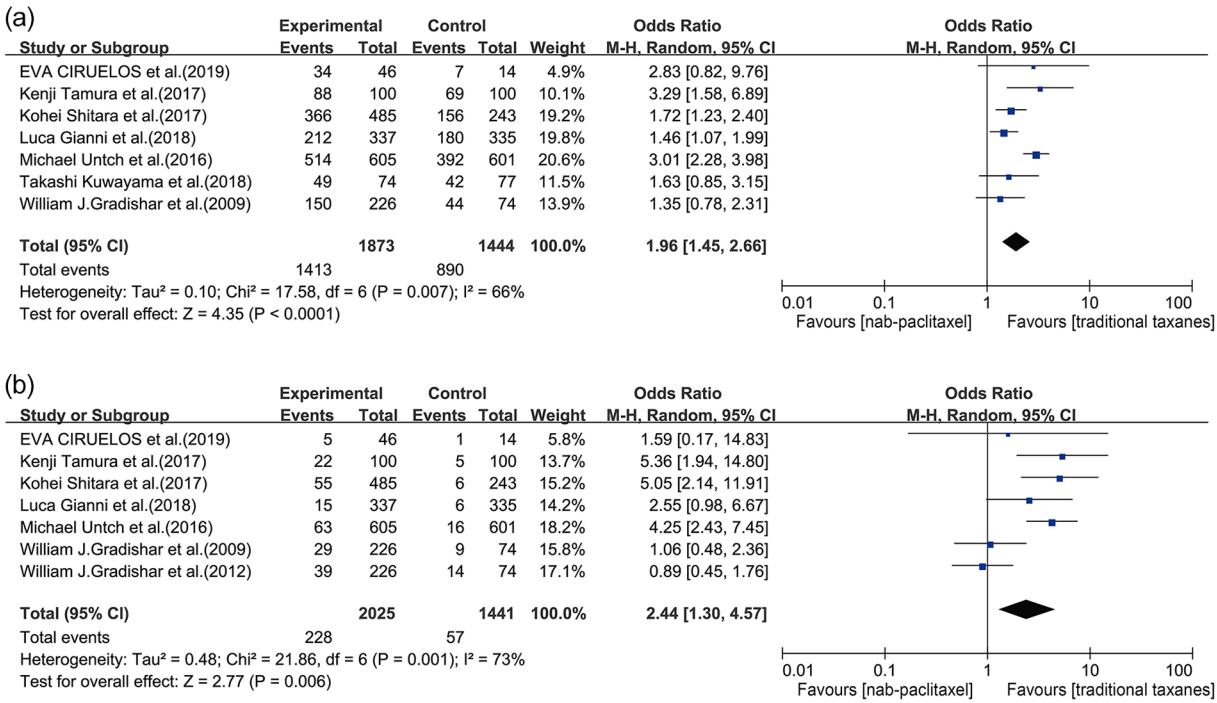
Figure 2. Forest plot of odds ratios of treatment discontinuation due to adverse events: (a) Forest plot of ORs of treatment termination due to AEs, (b) Forest plot of ORs of treatment delay due to AEs, and (c) Forest plot of ORs of deaths due to treatment-related AEs.

Abbreviations: AE, adverse event; CI, confidence interval; OR, odds ratio.

OR = 1.58, 95% CI, 1.25-2.01), which was also reported in patients with severe anemia (OR = 2.12, 95% CI, 1.06-4.27). Severe thrombocytopenia (grade 3/4) was reported to be more common in the nab-paclitaxel group (Figure 4d, 3 studies, OR = 2.09, 95% CI, 1.47-2.99).

Fractional dosage analyses provide additional information. A nab-paclitaxel dose of 100 mg/m^2/w tended to result in higher rates of neutropenia, leukopenia, and anemia, but a lower rate of severe neutropenia (grade 3/4) when compared with the sb-paclitaxel group (OR = 0.03, 95% CI, 0.01-0.08). Interestingly, the dosage of 150 mg/m^2/w led to a higher rate of severe neutropenia or leukopenia than in the sb-paclitaxel group (OR = 6.89, 95% CI, 3.98-11.92; OR = 3.43, 95% CI, 1.49-7.88), but a lower rate when compared with the docetaxel group (OR = 0.07, 95% CI, 0.03-0.16; OR = 0.15, 95% CI, 0.07-0.33).

Emesis and diarrhea (any grade) were reported in 9 studies, and rates were higher among patients who received nab-paclitaxel (Figure 4e, OR = 1.24, 95% CI, 1.07-1.44), but the rates of grade 3/4 did not show statistical significance (OR = 1.21, 95% CI, 0.65-2.25; OR = 1.18, 95% CI, 0.70-2.00). Rash was reported in 6 studies and rates were higher among patients who received nab-paclitaxel (Figure 4f, OR = 1.48, 95% CI, 1.08-2.04), and pruritus was reported in 3 studies, and rates



(c)

	Experimental	Control	
Recovery time of neurotoxicity (days)	Nab-paclitaxel	Sb-paclitaxel	Docetaxel
Jenny Furlanetto et al. (2017)	17	9	
William J.Gradishar et al. (2005)	22	79	
Mark A.Socinski et al. (2002)	38	104	
William J.Gradishar et al. (2009)	22		37
Average Median time (days)	24.75	64	37

Figure 3. (a) Neurotoxicity-specific forest plot, (b) severe neurotoxicity (Grade 3/4)-specific forest plot, and (c) recovery time of neurotoxicity.
Abbreviations: CI, confidence interval; OR, odds ratio.

were higher in patients who received nab-paclitaxel (Figure 4g, OR = 2.37, 95% CI, 1.43-3.93). It is worth noting that allergy was reported to be less common in patients who received nab-paclitaxel (Figure 4h, 3 studies, OR = 0.35, 95% CI, 0.13-0.99). For different dosages, 100 mg/m^2/w and 150 mg/m^2/w of nab-paclitaxel were also reported to have lower rates of allergy events than the sb-paclitaxel group (OR = 0.15, 95% CI, 0.03-0.66; OR = 0.64, 95% CI, 0.41-1.00). Fatigue events were investigated with different dosages, and lower rates of any grade fatigue and severe fatigue were reported in the 100 mg/m^2/w nab-paclitaxel group than in the docetaxel control group. However, fatigue events were reported more commonly in the 125 and 150 mg/m^2/w nab-paclitaxel groups than in the sb-paclitaxel group.

Evaluation of primary malignancy sites as a subgroup revealed some significant changes in the OR for AEs (Figure S2). Among patients with gastric cancer, any grade of anaphylaxis (1 study, OR = 0.15, 95% CI, 0.05-0.46) and alopecia (1 study, OR = 0.01, 95% CI, 0.00-0.15) were less common in patients who received nab-paclitaxel than in those who received traditional taxanes. Severe neutropenia (grade 3/4) was reported to be less common in NSCLC patients who received the nab-paclitaxel regimen (1 study, OR = 0.64, 95% CI, 0.50-0.82).

Racial differences in nab-paclitaxel toxicity were analyzed in detail. Among Asian people, receipt of nab-paclitaxel regimen, rather than traditional taxanes, was associated with increased rates of any grade AEs (Figure S3A, 4 studies, OR

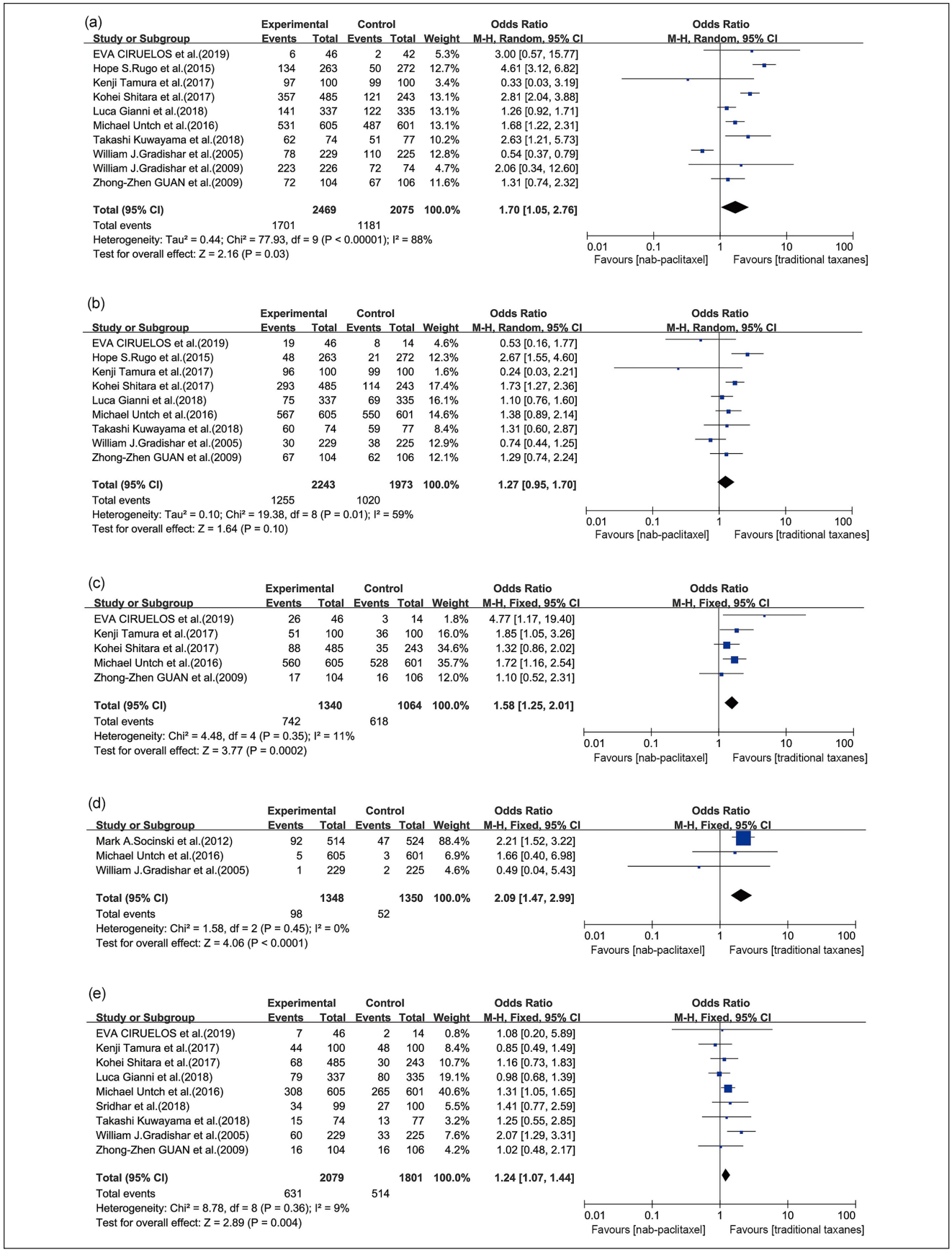


Figure 4. *(continued)*

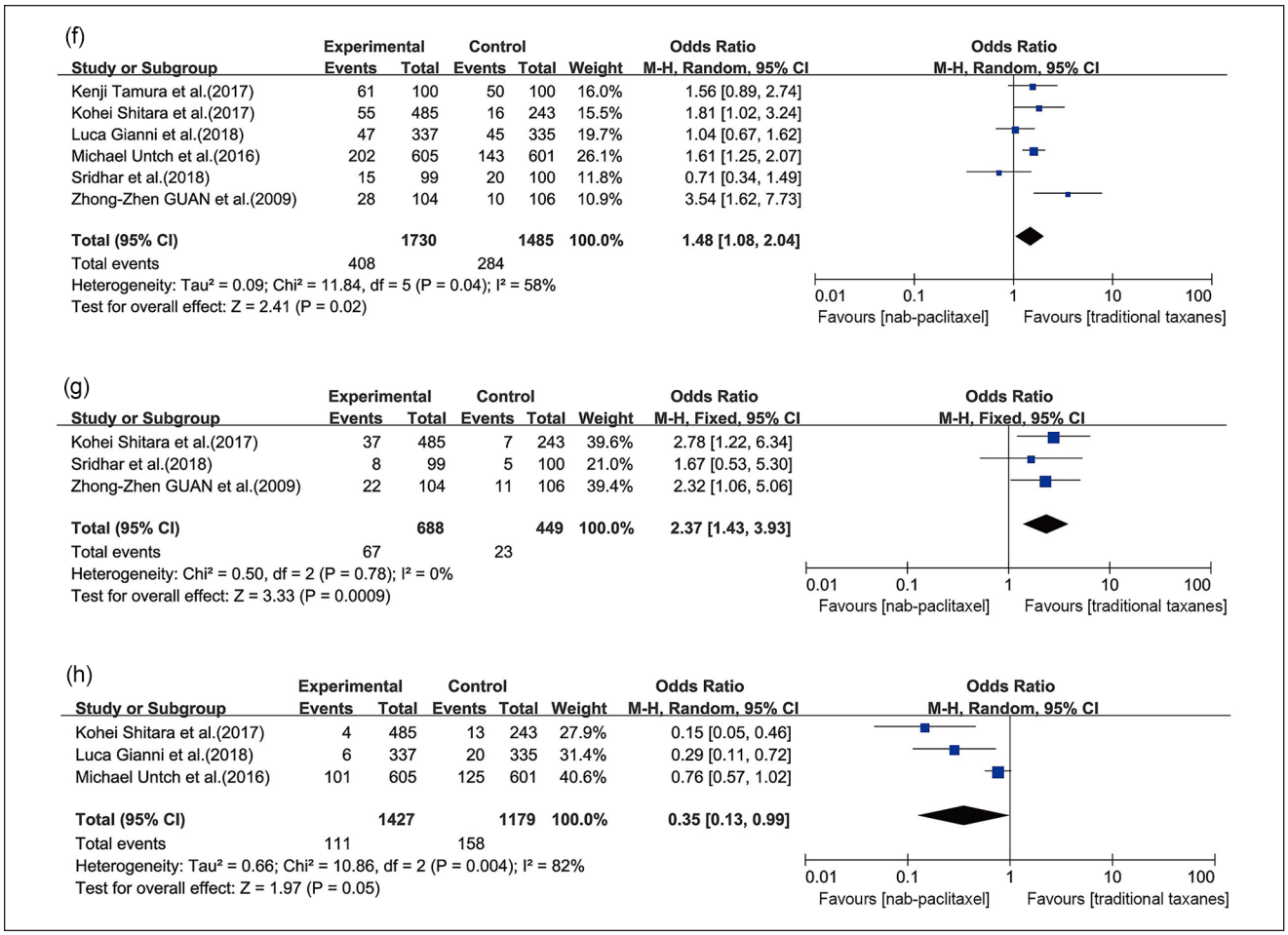


Figure 4. Symptom and disease-specific forest plots: (a) neutropenia, (b) leukopenia, (c) anemia, (d) severe thrombocytopenia (grade 3/4), (e) emesis and diarrhea, (f) rash, (g) pruritus, (h) allergy.
Abbreviations: CI, confidence interval; OR, odds ratio.

= 1.73, 95% CI, 1.34-2.22), especially severe AEs (Figure S3B, 3 studies, OR = 3.35, 95% CI, 1.37-8.23). Any grade of neutropenia (OR = 1.95, 95% CI, 1.11-3.42) and leukopenia (OR = 1.52, 95% CI, 1.18-1.96) were reported more commonly in 4 studies among Asians who received nab-paclitaxel regimen compared with those who received traditional taxanes. A higher incidence of anemia (any grade) was also reported in nab-paclitaxel groups among Asian people (3 studies, OR = 1.41, 95% CI, 1.04-1.92). Neurotoxicity was specifically investigated, and a higher incidence of any grade neurotoxicity events was reported in nab-paclitaxel groups than in traditional groups among both Asian people (OR = 1.73, 95% CI, 1.34-2.22; OR = 3.35, 95% CI, 1.37-8.23) and other ethnic groups (3 studies, OR = 1.47, 95% CI, 1.14-1.91). Other non-hematologic AEs were reported more commonly in other ethnic groups who received nab-paclitaxel than in those who received traditional taxanes (Figure S3C, 4 studies, OR = 2.19, 95% CI, 1.81-2.64), among which a higher incidence of diarrhea was reported in 5 studies (OR = 1.31, 95% CI, 1.11-1.55).

Discussion

To the best of our knowledge, this is the largest and most comprehensive meta-analysis that compared the risk of AEs with nab-paclitaxel with traditional taxanes across multiple primary solid-organ malignancies. The toxicities of nab-paclitaxel compared with traditional taxanes have been proven in multiple clinical trials and meta-analyses; however, controversy remains. To better guide clinicians in the use of nab-paclitaxel in the clinic, the present meta-analysis focused on the risk of AEs. The methodology of our study allows us to make comparisons between nab-paclitaxel and traditional taxanes. In summary, patients in the nab-paclitaxel group were more likely to develop AEs and severe AEs (grade > 3) compared with those receiving traditional taxane regimens,

which was consistent with the known safety profiles of each agent. Furthermore, patients receiving nab-paclitaxel were also more likely to experience therapy termination due to treatment-related AEs.

In our analysis of specific AEs, patients who received nab-paclitaxel were more likely to develop disease-related AEs in general, except for allergy events that were reported to be less common in patients who received nab-paclitaxel than in those who received traditional taxanes. Immunotherapy, including immune checkpoint inhibitors and chimeric antigen receptor-T cell therapy, is becoming a vital component of cancer treatment because of its dramatic efficacy and has garnered first- and later-line Food and Drug Administration (FDA) approval in a variety of melanoma and solid tumors. Immune-related adverse events (irAEs) are increasingly reported, which are unique and different from traditional cancer therapies due to nonspecific immune activation in normal organs.[32-34] Previous studies and reviews have demonstrated that the most frequent irAEs are cutaneous complications, which are mostly mild to moderate, but severe cutaneous AEs may also occur, which may lead to therapy discontinuation and even fatal outcomes.[34,35] As taxanes have proven to be promising partners in immunotherapy, the improved antitumor efficacy of the combination regimen has been demonstrated previously. Meanwhile, nab-paclitaxel is preferred over traditional taxanes for not requiring steroid premedication. The lower incidence of developing allergy events of nab-paclitaxel, reported in our analysis, also makes nab-paclitaxel more compatible with immunotherapy than traditional taxanes. Hypersensitivity resulting from allergy events may exacerbate the immune response produced by immunotherapy, thus worsening irAEs. Further studies are required to better understand the synergistic effects of reducing irAEs in cancer patients receiving immunotherapy combined with nab-paclitaxel. On the contrary, although neurotoxicity was more common in patients who received nab-paclitaxel, the median recovery time from neurotoxicity was shorter in patients who received nab-paclitaxel compared with sb-paclitaxel or docetaxel groups, which was consistent with the conclusion of Yamamoto et al.[10] It has been suggested that nab-paclitaxel is preferred for patients with a higher risk of developing neurotoxicity, which will facilitate recovery from this adverse toxicity.

Dosage fractional analyses were specifically performed in the present meta-analysis, which provides us with some special points and a better view of the clinical use of nab-paclitaxel. In previous studies, the superior antitumor activity of weekly nab-paclitaxel was confirmed, and the administered dosage exceeded those typically for traditional taxanes.[36,37] Compared with 150 and 125 mg/m^2/w dosage, nab-paclitaxel at 100 mg/m^2/w dosage was less toxic and comparable with that of traditional taxanes. It should be noted that lower incidences of alopecia and fatigue were reported when compared with docetaxel groups, and a lower incidence of allergy was reported when compared with the sb-paclitaxel group. Moreover, although nab-paclitaxel was more likely to develop hematologic AEs than the sb-paclitaxel group as mentioned above, most hematologic AEs at 100 mg/m^2/w dosage were grade 1 or 2, and severe neutropenia (grade $>$ 3) were less likely to occur. Meanwhile, most hematologic toxicities can be treated or prevented by colony-stimulating factors and supportive care. Although nab-paclitaxel was reported to be more effective at higher dosages, a better safety profile associated with 125 and 100 mg/m^2/w dosage of nab-paclitaxel provides a more tolerable method of drug administration for some patients.

For patients who can tolerate AEs and pursue better efficacy, the 125 or 150 mg/m^2/w dosage of nab-paclitaxel remains the first choice. Furlanetto et al demonstrated that 125 mg/m^2/w dosage of nab-paclitaxel was associated with a better safety profile and compliance without compromising the efficacy when compared with 150 mg/m^2/w dosage.[24] In the present meta-analysis, the incidence of neurotoxicity and hematology-related AEs was relatively higher but acceptable in the 125 and 150 mg/m^2/w nab-paclitaxel groups when compared with traditional taxanes. It is expected that relatively similar incidences of nonhematologic AEs were observed in the 125 and 150 mg/m^2/w nab-paclitaxel groups, and a lower incidence of allergy was reported in the 150 mg/m^2/w nab-paclitaxel group than in the sb-paclitaxel control group.

With respect to different administration intervals of nab-paclitaxel, the incidence of neurotoxicity was higher in 260 mg/m^2/3w nab-paclitaxel groups, but generally similar incidences of hematology-related AEs were observed in patients who received 260 mg/m^2/3w nab-paclitaxel when compared with traditional taxanes. This suggests that patients with a higher risk of developing neurotoxicity could be recommended with weekly nab-paclitaxel instead of q3w dosage.

The strengths of this meta-analysis include the unique perspective of conducting a comprehensive safety analysis between nab-paclitaxel and traditional taxanes, and a rigorous, up-to-date search strategy. Our methodology allowed us to compare specific AEs of interest and how they are affected by the administration of different dosages of nab-paclitaxel, which better guide clinical practice. Moreover, the subgroup analyses in this meta-analysis compared the safety profile of nab-paclitaxel versus traditional taxanes in specific tumor sites and different ethnic groups, which has not been previously reported to the best of our knowledge. Our methodology allowed comparisons of specific AEs of interest at multiple solid-organ sites. Among gastric cancer patients, anaphylaxis and alopecia are less likely to develop in patients who received nab-paclitaxel, while neurotoxicity events were more likely to develop. Moreover, severe neutropenia (grade $>$ 3) was less common in NSCLC patients who received the

nab-paclitaxel regimen. Furthermore, this particular meta-analysis compared the toxicities of nab-paclitaxel and traditional taxanes in different ethnic groups in detail. Exposure to nab-paclitaxel in Asian cancer patients increased the risk of treatment-related AEs, especially severe AEs (grade > 3), compared with traditional taxanes. Based on our results, patients receiving nab-paclitaxel were more likely to develop hematologic AEs than traditional taxanes in Asians, and patients receiving nab-paclitaxel were more likely to develop non-hematologic AEs compared with traditional taxanes in non-Asians. These findings may be helpful in the prevention and management of AEs associated with nab-paclitaxel in different ethnic populations. As taxanes remain the first-line choice of systemic chemotherapy for multiple tumors, to better guide clinical practice in certain scenarios, safety profiles between nab-paclitaxel and traditional taxanes in hierarchical subgroups deserve further exploration.

This meta-analysis had several limitations. First, it relied on the available data of AEs from published clinical trials in which the granularity varied. For example, all AEs occurring in any incidence were reported in some studies, but in some others, AEs were only reported if 10% of patients experienced the symptoms or if severe symptoms ($>$ grade 3) occurred. Therefore, the accounting methodology for specific AEs cannot be consistent, especially for rare symptoms. Second, the total number of included clinical trials was limited. Although there were 12 trials included, the hierarchical methodology of this meta-analysis led to a small number of trials in each subgroup analysis, which reduced statistical significance in general.

Conclusion and Relevance

This comprehensive meta-analysis evaluated the risk of AEs associated with nab-paclitaxel compared with traditional taxanes across multiple primary solid-organ malignancies. In comparison, although nab-paclitaxel increased the risk of hematologic and non-hematologic AEs in general, anaphylaxis was significantly less common and the recovery duration of neurotoxicity was shorter. A slight difference was detected between the ethnic groups. Weekly administration of nab-paclitaxel at a lower dosage provided better tolerance compared with every 3 weeks and traditional taxanes.

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