Original Article

Treatment-related adverse events of combination chemoimmunotherapy versus chemotherapy alone in first-line treatment for non-small cell lung cancer: a systematic review and meta-analysis of randomized clinical trials

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Background: Numerous meta-analyses have examined immunotherapy-induced adverse events (AEs) in non-small cell lung cancer (NSCLC). However, there is limited research comparing AEs from combination chemoimmunotherapy versus chemotherapy alone in the first-line NSCLC treatment, particularly regarding specific toxic symptoms and hematological toxicities associated with the addition of immune checkpoint inhibitors (ICIs).

Methods: We conducted a meta-analysis of randomized clinical trials (RCTs) comparing ICIs + non-ICIs versus non-ICIs alone as first-line therapy in NSCLC, sourced from PubMed and Scopus databases. Our objective was to assess treatment-related AEs in both regimens, focusing on identifying the more prevalent toxic symptoms and hematological toxicities with ICI treatment. We calculated the relative risks (RRs) and 95% confidence intervals (CIs), and estimated the pooled RRs and 95% CIs using common- or random-effects models.

Results: Our analysis included 10 trials with 6,008 patients. Combination chemoimmunotherapy significantly increased the risk of grade 3 or higher treatment-related AEs, treatment discontinuation, and deaths due to treatment-related AEs. Moreover, patients receiving combination chemoimmunotherapy had a significantly higher risk of certain toxic symptoms (all-grade: vomiting, diarrhea, and constipation; high-grade: fatigue and diarrhea) and pneumonitis (both all-grade and high-grade).

Conclusions: These findings offer crucial insights into the toxicity profile of combination chemoimmunotherapy, serving as a valuable resource for clinicians managing lung cancer care.

Keywords: Adverse events (AEs); chemotherapy; immunotherapy; meta-analysis; non-small cell lung cancer (NSCLC)

Submitted Oct 01, 2023. Accepted for publication Dec 01, 2023. Published online Jan 10, 2024.
doi: 10.21037/jtd-23-1532
View this article at: https://dx.doi.org/10.21037/jtd-23-1532

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Introduction

Cancer immunotherapy using anti-programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies such as nivolumab, pembrolizumab, and atezolizumab, and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies such as ipilimumab has become the mainstay of treatment for patients with advanced or recurrent non-small cell lung cancer (NSCLC). Hence, healthcare professionals need to deepen their understanding not only of its efficacy, but also of its safety and toxicity. In clinical practice, most patients with advanced or recurrent NSCLC are administered immune checkpoint inhibitors (ICIs) as first-line treatment in combination with chemotherapy. Therefore, it is very important to understand the adverse events (AEs) resulting from cancer immunotherapy combined with chemotherapy as first-line treatment, and to explore which toxic symptoms and hematological toxicities may increase with the addition of ICIs compared with conventional chemotherapy alone.

Numerous meta-analyses have addressed AEs in cancer immunotherapy (1-9). However, only a single meta-analysis has specifically examined AEs in NSCLC patients treated with combination chemoimmunotherapy versus chemotherapy alone as first-line therapy (4). This study, however, did not detail which toxic symptoms and hematologic toxicities were more prevalent with the addition of ICIs compared to conventional chemotherapy alone.

We conducted a meta-analysis of randomized clinical trials (RCTs) to investigate AEs resulting from combination chemoimmunotherapy versus chemotherapy alone in the first-line treatment of NSCLC and to determine which toxic symptoms and hematological toxicities are more frequent following the addition of ICIs compared with conventional chemotherapy alone. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1532/rc) (10).

Highlight box

Key findings

- Patients receiving combination chemoimmunotherapy had a significantly higher risk of certain toxic symptoms, including vomiting, diarrhea, fatigue, and constipation, as well as pneumonitis.

What is known and what is new?

- Combination chemoimmunotherapy was significantly associated with a higher risk of grade 3 or higher treatment-related adverse events (AEs) and treatment discontinuation and deaths due to treatment-related AEs.
- Combination chemoimmunotherapy was significantly associated with a higher risk of toxic symptoms (vomiting, diarrhea, fatigue, and constipation).

What is the implication, and what should change now?

- The results offer an important reference for clinicians regarding the toxicity of combination chemoimmunotherapy in the management of lung cancer care.

Methods

Literature search and study selection

We searched the PubMed and Scopus databases from the start date to February 18, 2022, to identify potentially relevant studies. The search terms were "non-small cell lung cancer or NSCLC", "immune checkpoint inhibitor or nivolumab or pembrolizumab or atezolizumab or avelumab or durvalumab or ipilimumab or tremelimumab or cemiplimab", and "study or trial".

The inclusion criteria were as follows: (I) published phase II or III RCTs in patients with advanced or recurrent NSCLC; (II) RCTs comparing ICIs + non-ICIs versus non-ICIs as first-line therapy; and (III) data available on the information of treatment-related AEs (any treatment-related AEs, grade 3 or higher treatment-related AEs, details of treatment-related AEs, treatment discontinuation due to treatment-related AEs, and death due to treatment-related AEs). The exclusion criteria were as follows: (I) not chemotherapy alone in the control arm; (II) studies not published in English; and (III) duplicated studies and single-arm phase I or II trials.

Ethical approval and informed consent for study participation were not required because this study is a systematic review and meta-analysis of RCTs.

Data extraction

Two authors (K.T. and F.M.) independently reviewed and extracted data from the published papers, including first author, journal name, year of publication, study ID and name, sample size by histology, experimental and control regimens, number of patients for analysis, the National Cancer Institute Common Terminology Criteria for AEs version, and the information of treatment-related AEs

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(any treatment-related AEs, grade 3 or higher treatment-related AEs, details of treatment-related AEs, treatment discontinuation due to treatment-related AEs, and death due to treatment-related AEs). With regards to treatment-related AEs, representative clinical symptoms (fatigue, vomiting, nausea, diarrhea, and constipation) and hematological toxicities (anemia, neutropenia, and thrombocytopenia) were included. Furthermore, treatment-related pneumonitis was also included. Any disagreements between the two authors (K.T. and F.M.) were resolved by discussion and agreement.

Statistical analysis

We conducted all statistical analyses using R software (version 3.4.0). All P values were two-sided, and P<0.05 was considered statistically significant. We calculated the relative risks (RRs) and 95% confidence intervals (CIs) based on the data from RCTs. To estimate the pooled RRs and 95% CIs, we employed either common- or random-effects models, depending on the heterogeneity observed among the included studies. Heterogeneity among studies was examined using Cochran Q and I^2 statistics (11), and it was considered low, moderate, and high for I^2 values <25%, 25–50%, and >50%, respectively (12). When there was obvious heterogeneity among the included studies (I^2 value >50%), the random-effects model was used to calculate the pooled RR. Otherwise, the common-effects model was applied (4). We assessed publication bias using funnel plots for any treatment-related AEs, grade 3 or higher treatment-related AEs, treatment discontinuation due to treatment-related AEs, and death due to treatment-related AEs.

Results

Literature search results and patients' characteristics in the included studies

We identified a total of 5,923 potentially relevant articles from PubMed and Scopus online databases through an initial search strategy. Then, a total of 11 trials involving 6,757 patients was identified after screening and reviewing the titles, abstracts, and full texts. There have been two clinical trials of anti-CTLA-4 ipilimumab, one of which used high-dose ipilimumab (10 mg/kg) (13,14). In this study, toxicity was observed, including seven treatment-related deaths in the ipilimumab 10 mg/kg combined with chemotherapy arm (13). Therefore, high-dose ipilimumab (10 mg/kg) is not used in clinical practice. We excluded the study by Govindan *et al.* from this meta-analysis (13). Finally, a total of 10 clinical trials involving 6,008 patients was included in this meta-analysis. The flow diagram of the study selection process in this meta-analysis is shown in *Figure 1*. The patients' characteristics in the included studies are summarized in *Table 1* (14-23).

Summary of toxic events

In previous clinical trials including a trial of ipilimumab, combination chemoimmunotherapy was not significantly associated with a higher risk of any treatment-related AEs (RR: 1.03; 95% CI: 1.00–1.06; P=0.0803), but it was significantly associated with a higher risk of grade 3 or higher treatment-related AEs (RR: 1.21; 95% CI: 1.12–1.32; P<0.0001), treatment discontinuation due to treatment-related AEs (RR: 1.80; 95% CI: 1.45–2.24; P<0.0001), and death due to treatment-related AEs compared with chemotherapy alone (RR: 1.54; 95% CI: 1.06–2.24; P=0.0225) (*Table 2*).

In previous clinical trials excluding a trial using ipilimumab, the results were almost identical (any treatment-related AEs, RR: 1.03; 95% CI: 0.99–1.06; P=0.1280; grade 3 or higher treatment-related AEs, RR: 1.21; 95% CI: 1.10–1.32; P<0.0001; treatment discontinuation due to treatment-related AEs, RR: 1.71; 95% CI: 1.38–2.12; P<0.0001; death due to treatment-related AEs, RR: 1.58; 95% CI: 1.06–2.35; P=0.0243) (Table S1).

Toxic symptoms

In previous clinical trials including a trial using ipilimumab, the risk of three toxic symptoms (all-grades) was significantly higher in the combination chemoimmunotherapy group compared with the chemotherapy alone group, as follows: vomiting (RR: 1.16; 95% CI: 1.00–1.35; P=0.0499), diarrhea (RR: 1.36; 95% CI: 1.20–1.55; P<0.0001), and constipation (RR: 1.15; 95% CI: 1.01–1.31; P=0.0307) (*Table 3*). In addition, patients receiving combination chemoimmunotherapy had a significantly higher risk of two grade 3 or higher toxic symptoms compared with patients receiving chemotherapy alone, as follows: fatigue (RR: 1.67; 95% CI: 1.19–2.35; P=0.0028) and diarrhea (RR: 1.76; 95% CI: 1.20–2.57; P=0.0036) (*Table 3*).

In previous clinical trials excluding a trial using ipilimumab, the results were almost identical except for grade 3 or higher diarrhea, as follows: all-grade vomiting

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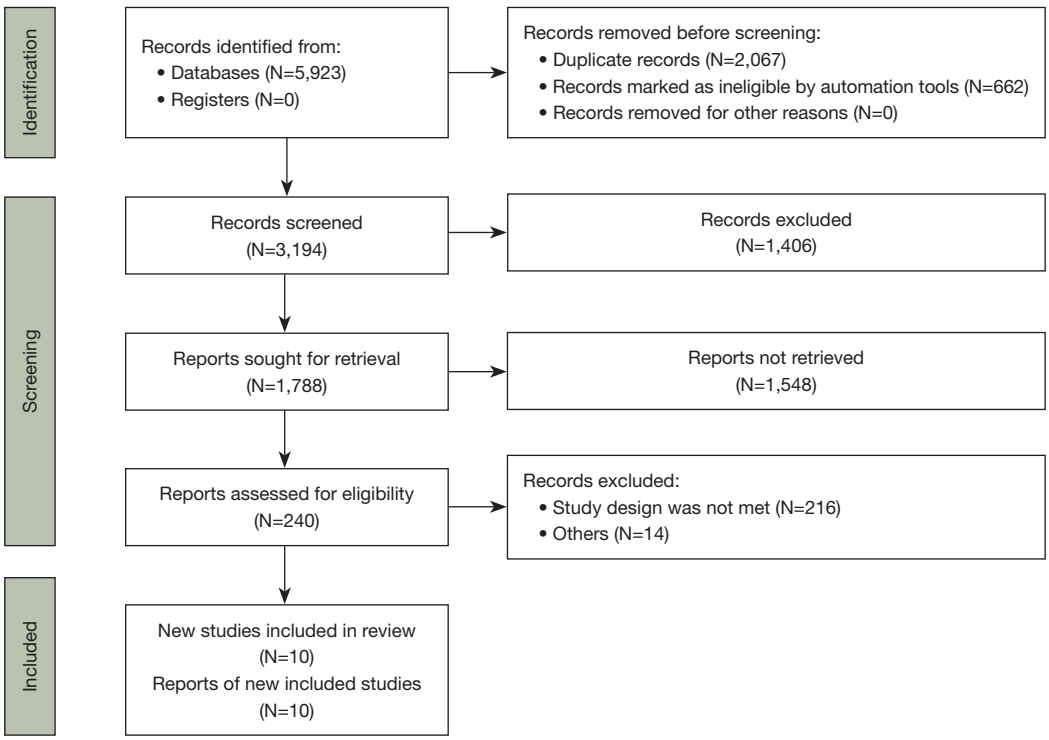

Figure 1 Flow diagram of the study selection process in this meta-analysis.

(RR: 1.22; 95% CI: 1.04–1.44; P=0.0158), all-grade diarrhea (RR: 1.31; 95% CI: 1.14–1.50; P<0.0001), all-grade constipation (RR: 1.20; 95% CI: 1.05–1.38; P=0.0066), and grade 3 or higher fatigue (RR: 1.53; 95% CI: 1.08–2.17; P=0.0162) (Table S2).

Hematological toxicities

In previous clinical trials including a trial using ipilimumab, no statistically significant differences were found between the combination chemoimmunotherapy group and the chemotherapy alone group for three hematological toxicities (all-grade and grade 3 or higher): anemia, neutropenia, and thrombocytopenia (*Table 3*).

In previous clinical trials excluding a trial using ipilimumab, the results were almost identical, although the combination chemoimmunotherapy group had a significantly higher risk of all-grade neutropenia than the chemotherapy alone group (RR: 1.12; 95% CI: 1.01–1.23; P=0.0297) (Table S2).

Pneumonitis

Data of treatment-related pneumonitis were not available for the clinical trial using ipilimumab. The combination chemoimmunotherapy group had a significantly higher risk of all-grade and grade 3 or higher pneumonitis than the chemotherapy alone group (all-grade, RR: 3.67; 95% CI: 2.49–5.42; P<0.0001; grade 3 or higher, RR: 1.89; 95% CI: 1.09–3.29; P=0.0234) (*Table 4*).

Publication bias

The funnel plots showed some asymmetry, indicating that evidence of publication bias for the RRs of any treatment-related AEs, grade 3 or higher treatment-related AEs, treatment discontinuation due to treatment-related AEs, and death due to treatment-related AEs might exist (Figures S1,S2).

Discussion

The addition of ICIs to chemotherapy regimens may increase the incidence of immune-related AEs. However, the specific toxic symptoms and hematological toxicities that occur more frequently with ICIs, as compared to conventional chemotherapy alone, remain unclear. In our meta-analysis, the combination chemoimmunotherapy was significantly

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Table 1 Characteristics of RCTs included in the meta-analysis

Trial	Study ID	Study	Number of patients for analysis	Histology, number		Experimental arm [number]	Control arm [number]	CTCAE version
				Non-squamous	Squamous			
IMpower130	NCT02367781	West *et al.*, *Lancet Oncol*, 2019, (14)	705	705	0	Atezolizumab + chemotherapy [473]	Chemotherapy [232]	4
IMpower131	NCT02367794	Jotte *et al.*, *J Thorac Oncol*, 2020, (15)	668	0	668	Atezolizumab + chemotherapy [334]	Chemotherapy [334]	4
IMpower132	NCT02657434	Nishio *et al.*, *J Thorac Oncol*, 2021, (16)	565	565	0	Atezolizumab + chemotherapy [291]	Chemotherapy [274]	4
IMpower150	NCT02366143	Socinski *et al.*, *J Thorac Oncol*, 2021, (17)	787	787	0	Atezolizumab + bevacizumab + chemotherapy [393]	Bevacizumab + chemotherapy [394]	4
KEYNOTE-21	NCT02039674	Awad *et al.*, *J Thorac Oncol*, 2021, (18)	121	121	0	Pembrolizumab + Chemotherapy [59]	Chemotherapy [62]	4
KEYNOTE-189	NCT02578680	Rodríguez-Abreu *et al.*, *Ann Oncol*, 2021, (19)	607	607	0	Pembrolizumab + chemotherapy [405]	Placebo + chemotherapy [202]	4
KEYNOTE-407	NCT02775435	Paz-Ares *et al.*, *J Thorac Oncol*, 2020, (20)	558	0	558	Pembrolizumab + chemotherapy [278]	Placebo + chemotherapy [280]	4
TASUKI-52	NCT03117049	Sugawara *et al.*, *Ann Oncol*, 2021, (21)	548	548	0	Nivolumab + bevacizumab + chemotherapy [273]	Placebo + bevacizumab + chemotherapy [275]	4
CheckMate 227	NCT02477826	Paz-Ares *et al.*, *J Thorac Oncol*, 2022, (22)	742	NA	NA	Nivolumab + chemotherapy [172]	Chemotherapy [570]	4
CheckMate 9LA	NCT03215706	Reck *et al.*, *ESMO Open*, 2021, (23)	707	NA	NA	Nivolumab + ipilimumab + chemotherapy [358]	Chemotherapy [349]	4

RCT, randomized clinical trial; CTCAE, Common Terminology Criteria for Adverse Events; NA, not available.

Table 2 Summary of RRs of treatment-related AEs in clinical trials including a trial using ipilimumab

Treatment-related AEs	Number of studies	Effect estimate		Heterogeneity	
		RR (95% CI)	P value	P value	I^2 (%)
Any treatment-related AEs	9	1.03 (1.00–1.06)	0.0803	<0.0001	82.0
Treatment-related AEs ≥ grade 3	10	1.21 (1.12–1.32)	<0.0001	0.0008	68.3
Treatment discontinuation due to treatment-related AEs	9	1.80 (1.45–2.24)	<0.0001	0.0014	68.3
Deaths due to treatment-related AEs	10	1.54 (1.06–2.24)	0.0225	0.9438	0.0

RR, relative risk; AEs, adverse events; CI, confidence interval.

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Table 3 Summary of RRs of the details of treatment-related AEs in clinical trials including a trial using ipilimumab

Treatment-related AEs	Number of studies	Effect estimate		Heterogeneity	
		RR (95% CI)	P value	P value	I^2 (%)
Representative clinical symptoms (all-grade)					
Fatigue	8	1.12 (0.96–1.30)	0.1494	0.0443	51.4
Vomiting	7	1.16 (1.00–1.35)	0.0499	0.2397	24.8
Nausea	8	1.03 (0.91–1.15)	0.6636	0.0419	52.0
Diarrhea	8	1.36 (1.20–1.55)	<0.0001	0.2418	23.5
Constipation	8	1.15 (1.01–1.31)	0.0307	0.3567	9.5
Representative hematological toxicities (all-grade)					
Anemia	8	0.92 (0.80–1.07)	0.2956	0.0001	76.2
Neutropenia	7	1.07 (0.90–1.26)	0.4614	0.0111	63.7
Thrombocytopenia	4	1.13 (0.98–1.30)	0.0982	0.3954	0.0
Representative clinical symptoms (≥ grade 3)					
Fatigue	7	1.67 (1.19–2.35)	0.0028	0.1600	35.1
Vomiting	6	1.00 (0.59–1.69)	0.9879	0.5392	0.0
Nausea	7	1.42 (0.89–2.29)	0.1452	0.8152	0.0
Diarrhea	7	1.76 (1.20–2.57)	0.0036	0.3374	12.1
Constipation	7	0.82 (0.32–2.11)	0.6751	0.7400	0.0
Representative hematological toxicities (≥ grade 3)					
Anemia	7	0.99 (0.87–1.14)	0.9323	<0.0001	78.8
Neutropenia	7	1.08 (0.95–1.23)	0.2208	0.2379	25.0
Thrombocytopenia	4	1.24 (0.94–1.64)	0.1307	0.9132	0.0

RR, relative risk; AEs, adverse events; CI, confidence interval.

Table 4 RR of treatment-related pneumonitis

Treatment-related pneumonitis	Number of studies	Effect estimate		Heterogeneity	
		RR (95% CI)	P value	P value	I^2 (%)
Pneumonitis (all-grade)	7	3.67 (2.49–5.42)	<0.0001	0.5248	0.0
Pneumonitis (≥ grade 3)	6	1.89 (1.09–3.29)	0.0234	0.6776	0.0

RR, relative risk; CI, confidence interval.

associated with a higher risk of grade 3 or higher treatment-related AEs, treatment discontinuation due to treatment-related AEs, and death due to treatment-related AEs, compared to chemotherapy alone. Furthermore, patients on combination chemoimmunotherapy were at a significantly greater risk of certain toxic symptoms (all-grade: vomiting, diarrhea, and constipation; high-grade: fatigue and diarrhea) than those on chemotherapy alone. However, no statistically significant differences were found between the combination chemoimmunotherapy group and the chemotherapy alone group for hematological toxicities (all-grade and grade 3 or higher).

Several previous meta-analyses showed that cancer immune monotherapy was significantly associated with

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a lower risk of treatment-related AEs than conventional chemotherapy in patients with cancers such as NSCLC (1,2). Although there are several treatment options for first-line therapy in the management of NSCLC without oncogenic driver alterations, including ICI monotherapy, combination chemoimmunotherapy, and chemotherapy alone, the previous and current meta-analyses indicated that patients treated with combination chemoimmunotherapy had the highest risk of treatment-related AEs among patients treated with ICI monotherapy, combination chemoimmunotherapy, and chemotherapy alone (1,2). The current study showed that combination chemoimmunotherapy was significantly associated with a higher risk of not only grade 3 or higher treatment-related AEs, but also treatment discontinuation due to treatment-related AEs and death due to treatment-related AEs than chemotherapy alone. Therefore, although many patients with advanced or recurrent NSCLC might be administered combination chemoimmunotherapy as a first-line therapy based on the results of many RCTs, the above findings should be considered when determining a treatment regimen (13-23).

With regards to treatment-related AEs, representative clinical symptoms (fatigue, vomiting, nausea, diarrhea, and constipation) and hematological toxicities (anemia, neutropenia, and thrombocytopenia) were included in this study, and our results indicated that the addition of ICIs to chemotherapy increased the incidence of gastrointestinal symptoms. These clinical symptoms are observed not only in patients treated with conventional chemotherapy but also in patients administered cancer immune monotherapy (1,2). Cancer immunotherapy can also cause specific AEs such as gastrointestinal and endocrine issues, so-called "immune-related AEs", which are often accompanied by gastrointestinal symptoms. Thus, gastrointestinal symptoms such as vomiting, diarrhea, and constipation are likely to increase. These clinical symptoms can affect the quality of life of patients with cancer (24,25). Therefore, we need to be attentive to the appearance of such gastrointestinal symptoms and manage them appropriately. According to the above, concomitant use of probiotics may be effective in reducing AEs in cancer patients undergoing cancer immunotherapy. Regarding probiotics, several reports have focused on probiotics in relation to the therapeutic efficacy of cancer immunotherapy (26,27), and probiotics may be a critical drug in both increasing therapeutic efficacy and reducing AEs.

In this meta-analysis, the combination chemoimmunotherapy group had a significantly higher risk of all-grade and grade 3 or higher pneumonitis than the chemotherapy alone group. This difference might be due to pneumonitis as an immune-related AE. Pneumonitis as an immune-related AE is one of the most alarming AEs for clinicians who use ICIs because it can sometimes be fatal. Therefore, as mentioned above, we should pay attention not only to gastrointestinal symptoms but also to respiratory symptoms.

The current meta-analysis had several limitations. First, this meta-analysis was based on the results of RCTs; patients enrolled in RCTs have clinical characteristics that differ from those in actual clinical practice. Indeed, even patients with a relatively poor general condition who receive cancer immunotherapy as a first-line therapy may be treated in clinical practice. Therefore, the patient selection process in the RCTs assessed in this meta-analysis may have biased the analysis. Second, this meta-analysis did not use patient-level data. The standard treatment for patients with NSCLC expressing high PD-L1 is cancer immunotherapy, and not chemotherapy. Therefore, not only the efficacy but also the safety profile of cancer immunotherapy according to PD-L1 expression is very important. However, we could not obtain safety profile data according to PD-L1 expression from published papers and could not conduct the analysis. Moreover, data on the association between individual AEs and treatment efficacy could not be obtained from the published papers and we could not conduct the analysis, although we would like to analyze the association. These issues will be addressed in future work. Third, the RR analysis of treatment-related AEs in this meta-analysis showed heterogeneity among the studies. Therefore, when heterogeneity between the studies was evident, a random-effects model was used to minimize this and RRs were calculated. Fourth, in this meta-analysis, we only integrated the results of a mere 10 clinical trials, and if we exclude anti-CTLA-4 antibody, it comes down to nine trials. While differences in drugs such as anti-PD-1 antibody and anti-PD-L1 antibody may affect the outcomes, the number of trials would be further reduced when conducting the analysis, so we have only analyzed the combined data of anti-PD-1 and anti-PD-L1 antibodies this time. It has been reported that there are particularly differences in the incidence rates of drug-induced pneumonitis between anti-PD-1 antibody and anti-PD-L1 antibody, so caution is needed when interpreting the results (3).

There are other similar meta-analyses focusing on other tumor types. For example, with regards to esophageal cancer, several meta-analyses investigated the safety of ICIs plus chemotherapy versus chemotherapy alone as a first-line

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treatment in advanced esophageal cancer (28,29). Li *et al.* showed that the incidence of grade 3 or higher treatment-related AEs was 60.4% with ICIs plus chemotherapy and 56.3% with chemotherapy alone (odds ratio: 1.19; 95% CI: 0.90–1.57) (28), while Lu *et al.* revealed that PD-1 inhibitor plus chemotherapy had a significantly higher incidence of treatment-related AEs (odds ratio: 1.85; P<0.01), but there was no significant difference in grade 3 or higher treatment-related AEs (odds ratio: 1.24; P=0.05) (29).

Conclusions

In our meta-analysis focusing on NSCLC, there were obvious differences in the safety between the chemoimmunotherapy combination therapy group and the chemotherapy alone group. These results provide an important reference for the toxicity of chemoimmunotherapy combination therapy when managing lung cancer treatment.

Acknowledgments

We thank H. Nikki March, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript. This study was presented at IASLC 2022 Asia Conference on Lung Cancer in October 2022.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1532/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1532/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1532/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Takada K, Takamori S, Mizuki F, Miura N, Shikada Y, Shimokawa M. Treatment-related adverse events of combination chemoimmunotherapy versus chemotherapy alone in first-line treatment for non-small cell lung cancer: a systematic review and meta-analysis of randomized clinical trials. J Thorac Dis 2024;16(1):430-438. doi: 10.21037/jtd-23-1532

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