



Safety and tolerability of PD-1/PD-L1 inhibitors in the treatment of non-small cell lung cancer: a meta-analysis of randomized controlled trials

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Abstract

Background Significant improvement in survival outcome with the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors has been shown in advanced non-small cell lung cancer (NSCLC) patients compared with chemotherapy. However, the full spectrum of toxic events of PD-1/PD-L1 inhibitors was not well characterized. We conducted a comprehensive meta-analysis to state the safety profile of PD-1/PD-L1 inhibitors in NSCLC, and identify the exact incidence and relative risk (RR) of both summary and detailed AEs.

Materials and methods Electronic databases (PubMed, EMBASE and the Cochrane library databases) and major conference proceedings were systematically searched for all clinical trials in lung cancer using PD-1/PD-L1 inhibitors. Eligible studies included randomized controlled trials (RCTs) comparing PD-1/PD-L1 inhibitors with chemotherapy in NSCLC patients reporting all-grade (1–4) or high-grade (3–4) AEs [toxic symptoms, hematologic toxicities, and immune-related AEs (irAEs)], treatment discontinuation due to toxicities, or toxic deaths. The pooled incidence, RR, and corresponding 95% confidence interval (CI) of toxicity outcomes were calculated.

Results A total of 4413 patients from 8 RCTs (3 with nivolumab; 2 with atezolizumab, and 3 with pembrolizuma) were included. In terms of summary toxic events, PD-1/PD-L1 inhibitors had a significantly lower risk of any all-grade AEs (66.20 vs. 86.08%; RR 0.77) and high-grade AEs (14.26 vs. 43.53%; RR 0.32), treatment discontinuation (5.94 vs. 13.92%; RR 0.44), and toxic deaths (0.48 vs. 1.12%; RR 0.45) than chemotherapy. With regard to detailed toxic events, the risk of toxic symptoms (including all-grade fatigue, nausea, constipation, diarrhea and peripheral sensory neuropathy; high-grade fatigue, anorexia, diarrhea and peripheral sensory neuropathy) and hematologic toxicities (including all-grade and high-grade neutropenia, thrombocytopenia, and anemia) from PD-1/PD-L1 inhibitors was significantly lower than from chemotherapy. However, there was a small but significantly increased risk of irAEs, including all-grade rash, pruritus, colitis, hypothyroidism, hyperthyroidism, ALT/AST elevations and pneumonitis, as well as high-grade pneumonitis.

Conclusion PD-1/PD-L1 inhibitors are generally safer and better tolerated than chemotherapy for patients with NSCLC with regard to summary toxic events, detailed toxic symptoms and hematologic toxicities. However, PD-1/PD-L1 inhibitors can generate a unique spectrum of irAEs, and several of them can be severe and even life-threatening. Clinicians should be aware of the risk of these AEs, as they may have a potentially negative impact on the patients' quality of life and survival outcome.

Keywords PD-1 · PD-L1 · Lung cancer · Chemotherapy

Wenxin Luo and Zhoufeng Wang are the joint first authors.

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Abbreviations

AEs	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
CTCAE	The Common Terminology Criteria for Adverse Events version
CI	Confidence interval
FDA	Food and Drug Administration
irAEs	Immune-related AEs

PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
RR	Relative risk
RCTs	Randomized controlled trials

Introduction

Programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors have revolutionized the clinical management of multiple malignancies, including non-small cell lung cancer (NSCLC) over the past decade (Chae et al. 2018). PD-1 is an immune checkpoint protein expressed on the surface of T-lymphocytes. PD-L1, the ligand for PD-1, is expressed in tumor cells or tumor infiltrating immune cells at different levels. The binding of PD-L1 to PD-1 can lead to negative regulation of T-cell signaling (Buchbinder and Desai 2016). PD-1/PD-L1 inhibitors are antibodies that block immune checkpoint molecular (i.e., PD-1 and PD-L1), and serve to restore T-cell immune responses against tumor (Fay et al. 2016; Iwai et al. 2017).

To date, three PD-1/PD-L1 inhibitors have been approved by the US Food and Drug Administration (FDA) for treatment of advanced NSCLC. Pembrolizumab is the first FDA-approved PD-1 inhibitor for treatment of advanced NSCLC based on two randomized, open-label clinical trials (Pai-Scherf et al. 2017). In the phase III KEYNOTE-024 study, untreated patients with metastatic NSCLC receiving pembrolizumab had a significant improvement in progression-free survival [PFS, hazard ratio (HR) 0.50] and overall survival (OS, HR 0.60) compared with chemotherapy (Reck et al. 2016). In the KEYNOTE-010 study, patients with disease progression or following chemotherapy received pembrolizumab and also had a significantly better OS compared with chemotherapy (Herbst et al. 2016). Atezolizumab is the first FDA-approved PD-L1 inhibitor for treatment of advanced NSCLC (De Velasco et al. 2017). The approval was based on two randomized, open-label clinical trials (OAK and POPLAR), which have demonstrated that patients receiving atezolizumab had a significant improvement in OS compared with chemotherapy (Fehrenbacher et al. 2016; Rittmeyer et al. 2017).

Along with the impressive therapeutic efficacy, we have seen a wide range of adverse events (AEs) in NSCLC clinical trials. Different from chemotherapy or molecular targeted therapy, PD-1/PD-L1 inhibitors therapy can induce some special side effects termed immune-related adverse events (irAEs), which clinically manifest with autoimmune-like/inflammatory toxicities involving multiple organs and tissues (Cousin and Italiano 2016; O’Kane et al. 2017). Since the AEs may be severe and even fatal, it is important for clinicians to be familiar with these AEs to recognize them timely and manage them appropriately for patients. Therefore, we

conducted a comprehensive meta-analysis to state the safety profile of PD-1/PD-L1 inhibitors in NSCLC, and identify the exact incidence and relative risk (RR) of both summary and detailed AEs.

Materials and methods

Literature search

The present meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (Panic et al. 2013). Potentially relevant studies were identified by searching PubMed, Embase, and the Cochrane library databases. The search dates were from the inception of each database to May 1, 2018. The search terms included: “lung neoplasm”, “non-small cell lung cancer”, “nivolumab”, “atezolizumab”, “pembrolizumab”, “PD-1”, “PD-L1”, “programmed death receptor 1”, “programmed death receptor ligand”, and “immune checkpoint inhibitor”. To identify additional studies, we also searched the reference lists of relevant studies.

Study selection

The following predefined inclusion criteria were used: (a) clinical trials in patients with lung cancer; (b) random assignment of patients to single-agent PD-1/PD-L1 inhibitor treatment or chemotherapy; and (c) reporting number or rate and sample size for any all-grade (1–4) or high-grade (3–4) AEs, detailed all-grade or high-grade AEs, treatment discontinuation due to AEs, and toxic deaths. The exclusion criteria were listed as follows: (a) no chemotherapy control arm; (b) PD-1/PD-L1 inhibitors in both arms; and (c) studies not published in English.

Data extraction

The following data were extracted by two authors independently: name of first author, year of publication, trial phase, masking, histology of lung cancer, treatment arms, number of patients available for analysis, age, follow-up duration, any all-grade or high-grade AEs, detailed all-grade or high-grade AEs, treatment discontinuation due to AEs, and toxic deaths. The AEs included clinical relevant symptoms (fatigue, anorexia, nausea, constipation diarrhea, and peripheral sensory neuropathy), hematologic AEs (neutropenia and anemia), and immune-related AEs (irAEs; rash, pruritus, colitis, hypothyroidism, hyperthyroidism, hypophysitis, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations, and pneumonitis) (Naidoo et al. 2015; Reeve et al. 2014). All the included studies evaluated and graded AEs according to the National Cancer

Institute Common Terminology Criteria for Adverse Events (CTCAE) 4.0 (National Cancer Institute 2009). When multiple doses of PD-1/PD-L1 inhibitors were used for different cohort of patients in the same trial, they were extracted as separate studies. The third author assessed the data and resolved the disagreement.

Assessment of study quality and publication bias

The Cochrane Collaboration’s risk of bias tool was used to assess the methodological quality of each included study (Higgins 2011). This tool is based on the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each item was described as low risk of bias, high risk of bias, or unclear risk of bias by two independent authors. The publication bias was assessed using Funnel plot and Egger’s test (Begg and Mazumdar 1994; Egger et al. 1997).

Statistical analysis

All statistical analyses were done with R version 3.4.4. P value less than 0.05 was considered statistically significant. Pooled incidences and risk ratios (RRs) were used to evaluate the risk of AEs and 95% confidence intervals (CIs) were calculated for each estimate. Statistical heterogeneity among studies was examined using Cochran Q and I^2 statistics. Heterogeneity was considered low, moderate or high for I^2 values < 25, 25–50, and > 50%, respectively. In this analysis, the null hypothesis that the studies were homogenous

would be rejected if P for heterogeneity is less than 0.10 or $I^2 > 50\%$. When there is significant heterogeneity among the results of included study, the random effects model was used to calculate summary estimate, reported using the DerSimonian and Laird method, assuming both within-study and between-study variations (DerSimonian and Laird 1986). Otherwise, the summary estimate was calculated based on the fixed effects model, reported using the inverse variance method, assuming that the studies included in the meta-analysis have the same effect size.

Results

Search results and characteristics of the included studies

Our search retrieved 1380 potentially relevant publications from the PubMed, Embase, the Cochrane library and ASCO databases. The selection process and reasons for exclusion are presented in Fig. 1. A total of 4413 patients (2272 with PD-1/PD-L1 inhibitors; 2141 with chemotherapy) from 8 RCTs (3 with nivolumab; 2 with atezolizumab and 3 with pembrolizuma) were included. The characteristics of the included studies are shown in Table 1.

Quality of the included studies and publication bias

Most of the included studies had a high risk of selection bias, performance bias, and detection bias due to their open-label design (Supplementary Fig. 1). On the other

Fig. 1 Flow diagram showing identification and inclusion of studies

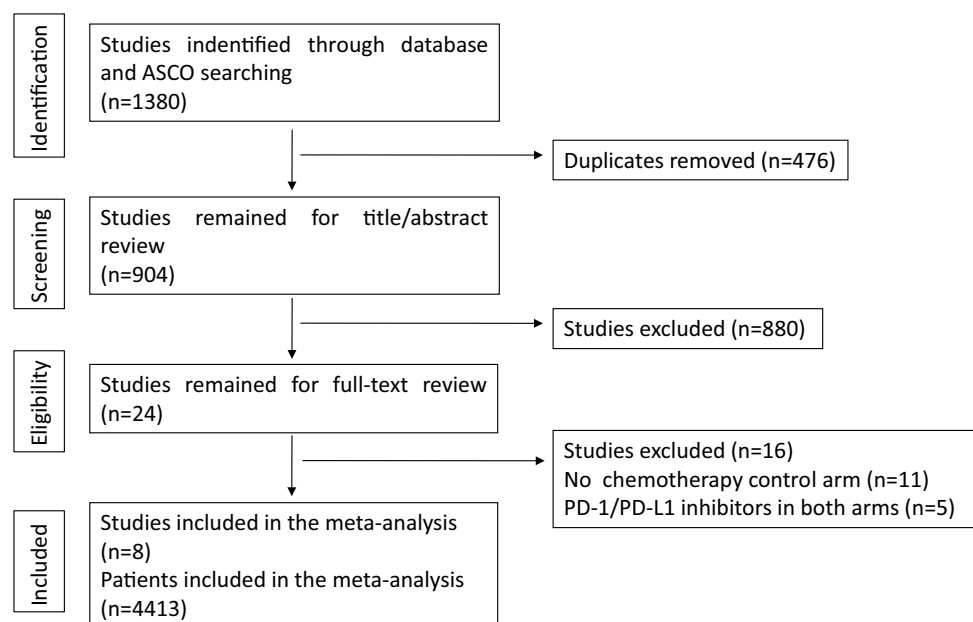


Table 1 Characteristics of studies included in the meta-analysis (PD-1/PD-L1 inhibitors vs. chemotherapy)

Reference	Author, year	Phase	Masking	Histology	Treatment arms	Number of patients available for analysis	Age in years (median)	Follow-up duration (months)	CTCAE version
1	Brahmer, 2015	III	Open-label	Squamous NSCLC	Nivolumab Docetaxel	131 129	62 64	Minimum 11	4.0
2	Borghaei, 2015	III	Open-label	Non-squamous NSCLC	Nivolumab Docetaxel	287 268	61 64	Minimum 13.2	4.0
3	Carbone, 2017	III	Open-label	NSCLC	Nivolumab Platinum-based chemotherapy	267 263	63 65	Median 13.5	4.0
4	Fehrenbacher, 2016	II	Open-label	NSCLC	Atezolizumab Docetaxel	142 135	62 62	Median; 14.8 for Atezolizumab; 15.7 for Docetaxel	4.0
5	Rittmeyer, 2017	III	Open-label	NSCLC	Atezolizumab Docetaxel	609 578	63 64	median 21	4.0
6*	Herbst, 2016 (1)	II/III	Open-label	NSCLC	Pembrolizumab 2 mg/kg Docetaxel	339 309	63 62	Median 13.1	4.0
7*	Herbst, 2016 (2)	II/III	Open-label	NSCLC	Pembrolizumab 10 mg/kg Docetaxel	343 309	63 62	Median 13.1	4.0
8	Reck, 2016	III	Open-label	NSCLC	Pembrolizumab Platinum-based chemotherapy	154 150	64.5 66	MEDIAN 11.2	4.0

*Different cohorts with different dose of PD-1/PD-L1 inhibitors in the same trial

PD-1 programmed death receptor-1, *PD-L1* programmed death ligand 1, *NSCLC* non-small cell lung cancer, *CTCAE* the Common Terminology Criteria for Adverse Events version

hand, most studies had a low risk of attrition bias, reporting bias and other bias, because all the assessments of AEs were based on the CTCAE 4.0.

Funnel plots showed some evidence of publication bias for the RRs of any high-grade AEs and treatment discontinuation (Supplementary Fig. 2). When using Egger's test to evaluate the asymmetry of funnel plots, the results suggested that there was no evidence for publication bias for the RRs of any high-grade AEs ($t = -1.585$, $P = 0.1641$), as well as treatment discontinuation ($t = -1.001$, $P = 0.3554$). This difference might be attributed to the

small number of included studies, which would affect the statistical power of Egger's test.

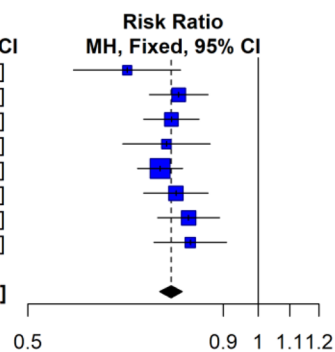
Incidence and relative risk of summary toxic events

The incidences of any all-grade AEs (66.20 vs. 86.08%), high-grade AEs (14.26 vs. 43.53%), discontinuation of treatment (5.94 vs. 13.92%), and toxic deaths (0.48 vs. 1.12%) from PD-1/PD-L1 inhibitors were lower than those from chemotherapy; PD-1/PD-L1 inhibitors also had a significantly lower risk of any all-grade AEs (RR 0.77; 95% CI: 0.74–0.80; $P < 0.0001$), high-grade AEs (RR 0.32;

a Any all-grade AEs

Study	PD-1/PD-L1 inhibitor		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		MH, Fixed, 95% CI	
Brahmer, 2015	76	131	111	129	5.9%	0.67	[0.57; 0.79]
Borghaei, 2015	199	287	236	268	12.9%	0.79	[0.72; 0.86]
Carbone, 2017	190	267	243	263	12.9%	0.77	[0.71; 0.84]
Fehrenbacher, 2016	95	142	119	135	6.4%	0.76	[0.67; 0.87]
Rittmeyer, 2017	390	609	497	578	26.9%	0.74	[0.70; 0.80]
Herbst, 2016(1)	215	339	251	309	13.8%	0.78	[0.71; 0.86]
Herbst, 2016(2)	226	343	251	309	13.9%	0.81	[0.74; 0.89]
Reck, 2016	113	154	135	150	7.2%	0.82	[0.73; 0.91]
Total (95% CI)		2272		2141	100.0%	0.77	[0.74; 0.80]

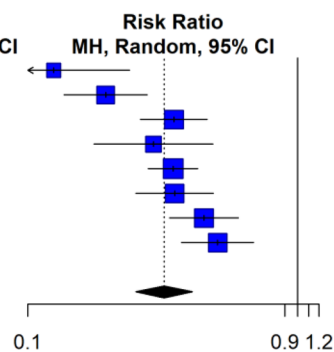
Heterogeneity: Tau² = 0; Chi² = 6.16, df = 7 (P = 0.52); I² = 0%



b Any high-grade AEs

Study	PD-1/PD-L1 inhibitor		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		MH, Random, 95% CI	
Brahmer, 2015	9	131	71	129	7.7%	0.12	[0.07; 0.24]
Borghaei, 2015	30	287	144	268	12.6%	0.19	[0.14; 0.28]
Carbone, 2017	47	267	133	263	14.0%	0.35	[0.26; 0.46]
Fehrenbacher, 2016	16	142	52	135	9.8%	0.29	[0.18; 0.49]
Rittmeyer, 2017	90	609	247	578	15.3%	0.35	[0.28; 0.43]
Herbst, 2016(1)	40	339	104	309	13.1%	0.35	[0.25; 0.49]
Herbst, 2016(2)	52	343	104	309	13.8%	0.45	[0.34; 0.61]
Reck, 2016	40	154	77	150	13.5%	0.51	[0.37; 0.69]
Total (95% CI)		2272		2141	100.0%	0.32	[0.25; 0.41]

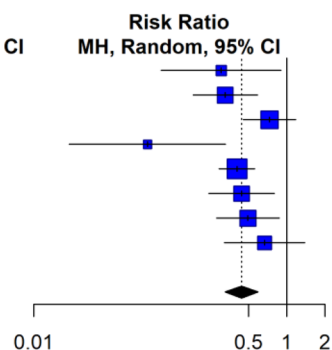
Heterogeneity: Tau² = 0.0880; Chi² = 29.45, df = 7 (P < 0.01); I² = 76%



c Treatment discontinuation due to AEs

Study	PD-1/PD-L1 inhibitor		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		MH, Random, 95% CI	
Brahmer, 2015	4	131	13	129	5.9%	0.30	[0.10; 0.90]
Borghaei, 2015	14	287	40	268	13.8%	0.33	[0.18; 0.59]
Carbone, 2017	26	267	35	263	16.7%	0.73	[0.45; 1.18]
Fehrenbacher, 2016	2	142	24	135	3.8%	0.08	[0.02; 0.33]
Rittmeyer, 2017	46	609	108	578	21.7%	0.40	[0.29; 0.56]
Herbst, 2016(1)	15	339	31	309	13.5%	0.44	[0.24; 0.80]
Herbst, 2016(2)	17	343	31	309	14.1%	0.49	[0.28; 0.87]
Reck, 2016	11	154	16	150	10.6%	0.67	[0.32; 1.40]
Total (95% CI)		2272		2141	100.0%	0.44	[0.33; 0.59]

Heterogeneity: Tau² = 0.0793; Chi² = 13.22, df = 7 (P = 0.07); I² = 47%



d Toxic deaths

Study	PD-1/PD-L1 inhibitor		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		MH, Fixed, 95% CI	
Brahmer, 2015	0	131	3	129	13.7%	0.14	[0.01; 2.70]
Borghaei, 2015	1	287	1	268	4.0%	0.93	[0.06; 14.85]
Carbone, 2017	2	267	3	263	11.7%	0.66	[0.11; 3.90]
Fehrenbacher, 2016	1	142	3	135	12.0%	0.32	[0.03; 3.01]
Rittmeyer, 2017	0	609	1	578	6.0%	0.32	[0.01; 7.75]
Herbst, 2016(1)	3	339	5	309	20.3%	0.55	[0.13; 2.27]
Herbst, 2016(2)	3	343	5	309	20.4%	0.54	[0.13; 2.24]
Reck, 2016	1	154	3	150	11.8%	0.32	[0.03; 3.09]
Total (95% CI)		2272		2141	100.0%	0.45	[0.23; 0.90]

Heterogeneity: Tau² = 0; Chi² = 1.39, df = 7 (P = 0.99); I² = 0%

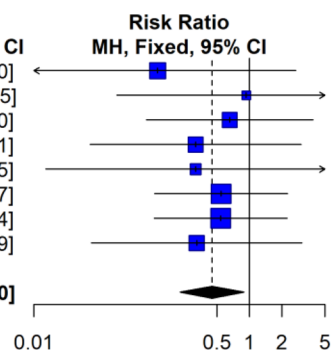


Fig. 2 Forest plots of the relative risks of any all-grade AEs, any high-grade AEs, treatment discontinuation and toxic deaths associated with PD-1/PD-L1 inhibitors vs. chemotherapy

Table 2 Incidence and RR of summary toxic events

Summary toxic events	Number of trials	Incidence (%; 95% CI)		Effect estimate		Heterogeneity	
		PD-1/PD-L1 inhibitor	Control	RR (95% CI)	<i>P</i>	<i>P</i>	<i>I</i> ² (%)
Any all-grade AEs	8	66.20 (64.21; 68.14)	86.08 (84.54; 87.52)	0.77 (0.74; 0.80)	<0.0001	0.5215	0.0
Any high-grade AEs	8	14.26 (12.85; 15.77)	43.53 (41.42; 45.66)	0.32 (0.25; 0.41)	<0.0001	0.0001	76.2
Treatment discontinuation	8	5.94 (5.01; 6.99)	13.92 (12.48; 15.46)	0.44 (0.33; 0.59)	<0.0001	0.067	47.0
Toxic deaths	8	0.48 (0.24; 0.86)	1.12 (0.71; 1.66)	0.45 (0.23; 0.90)	0.0229	0.9858	0.0

AEs adverse events, RR relative risk, CI confidence interval, PD-1 programmed death receptor-1, PD-L1 programmed death ligand 1

95% CI: 0.25–0.41; $P < 0.0001$), treatment discontinuation (RR 0.44; 95% CI: 0.33–0.59; $P < 0.0001$), and toxic deaths (RR 0.45; 95% CI: 0.23–0.90; $P = 0.0229$) from PD-1/PD-L1 inhibitors (Fig. 2; Table 2).

Toxicity-related death was rare from PD-1/PD-L1 inhibitors and occurred in 0.48% (11/2272) of cases. The most common cause for treatment-related deaths was pneumonitis (36.4%, 4/11), other causes included: two from pneumonia, one from encephalitis, one from cardiac failure, one from myocardial infarction, one from multiorgan failure, and another from unknown cause.

Incidence and relative risk of toxic symptoms

Patients receiving PD-1/PD-L1 inhibitors had a significantly lower risk for five evaluated all-grade toxic symptoms when compared with chemotherapy (Table 3): fatigue (18.75 vs. 30.83%; RR 0.61; 95% CI: 0.55–0.68; $P < 0.0001$), nausea (12.54 vs. 25.69%; RR 0.45; 95% CI: 0.31–0.65; $P < 0.0001$), constipation (6.34 vs. 8.08%; RR 0.49; 95% CI: 0.26–0.94; $P = 0.031$), diarrhea (10.61 vs. 19.85%; RR 0.51; 95% CI: 0.37–0.72; $P < 0.0001$), and peripheral sensory neuropathy (1.32 vs. 6.31%; RR 0.13; 95% CI: 0.05–0.34; $P < 0.0001$). The risk of four high-grade toxic symptoms was significantly lower from PD-1/PD-L1 inhibitors therapy than chemotherapy: fatigue (1.58 vs. 4.06%; RR 0.39; 95% CI: 0.27–0.57; $P < 0.0001$), anorexia (0.35 vs. 1.26%; RR 0.30; 95% CI: 0.14–0.64; $P = 0.0018$), diarrhea (0.75 vs. 1.77%; RR 0.44; 95% CI: 0.25–0.76; $P = 0.0034$), and peripheral sensory neuropathy (0.00 vs. 0.61%; RR 0.10; 95% CI: 0.02–0.53; $P = 0.0068$).

Incidence and relative risk of hematologic toxicities

Patients receiving PD-1/PD-L1 inhibitors were at a significantly lower risk of all-grade neutropenia (0.70 vs. 18.68%; RR 0.03; 95% CI: 0.01–0.08; $P < 0.0001$), thrombocytopenia (0.09 vs. 2.57%; RR 0.04; 95% CI: 0.01–0.16; $P < 0.0001$), and anemia (5.59 vs. 23.26%; RR 0.19; 95% CI: 0.10–0.34; $P < 0.0001$) when compared with chemotherapy. A significantly lower risk of high-grade neutropenia (0.13 vs. 14.53%; RR 0.02; 95% CI: 0.01–0.04; $P < 0.0001$), thrombocytopenia

(0.04 vs. 1.40%; RR 0.05; 95% CI: 0.01–0.25; $P = 0.0003$), and anemia (1.01 vs. 6.03%; RR 0.17; 95% CI: 0.07–0.42; $P = 0.0001$) was also observed in PD-1/PD-L1 inhibitors (Table 3).

Incidence and relative risk of immune-related AEs

The most frequently reported all-grade irAEs from PD-1/PD-L1 inhibitors therapy included rash (5.77%), hypothyroidism (4.89%), and pneumonitis (3.21%), while the most frequently observed high-grade irAE was pneumonitis (1.45%), ALT/AST elevations (0.57%) and colitis (0.40%).

Compared to chemotherapy, PD-1/PD-L1 inhibitors therapy was associated to a significantly increased risk of seven all-grade irAEs: rash (5.77 vs. 2.76%; RR 2.07; 95% CI: 1.54–2.80; $P < 0.0001$), pruritus (2.16 vs. 0.51%; RR 4.15; 95% CI: 2.20–7.81; $P < 0.0001$), colitis (0.70 vs. 0.00%; RR 5.44; 95% CI: 1.42–20.80; $P = 0.013$), hypothyroidism (4.89 vs. 0.23%; RR 17.59; 95% CI: 7.74–39.98; $P < 0.0001$), hyperthyroidism (2.11 vs. 0.37%; RR 5.27; 95% CI: 2.56–10.86; $P < 0.0001$), ALT/AST elevations (1.85 vs. 0.89%; RR 2.15; 95% CI: 1.31–3.51; $P = 0.002$), and pneumonitis (3.21 vs. 0.65%; RR 3.83; 95% CI: 2.20–6.68; $P < 0.0001$). There was also a small, but significantly increased risk of high-grade pneumonitis from PD-1/PD-L1 inhibitors compared with chemotherapy (1.45 vs. 0.19%; RR 3.78; 95% CI: 1.43–10.03; $P = 0.007$) (Table 3).

Subgroup analysis

There was no significant heterogeneity among studies for RRs of any all-grade AEs ($P = 0.5215$; $I^2 = 0.0\%$) and toxic deaths ($P = 0.9858$; $I^2 = 0.0\%$). However, significant heterogeneity existed among studies for RRs of any high-grade AEs ($P = 0.0001$; $I^2 = 76.2\%$) and treatment discontinuation ($P = 0.067$; $I^2 = 47.0\%$).

We conducted subgroup analysis with regard to summary AEs stratified by types of PD-1/PD-L1 inhibitors (nivolumab vs. atezolizumab vs. pembrolizumab) (Supplementary Fig. 3; supplementary Table 1). The results showed that only the difference in RR of any high-grade AEs between patients treated with nivolumab and

Table 3 Incidence and RR of detailed adverse events

	Number of trials	Incidence (%; 95% CI)		Effect estimate		Heterogeneity		
		PD-1/PD-L1 inhibitor	Control	RR (95% CI)	<i>P</i>	<i>P</i>	<i>I</i> ² (%)	
All-grade clinically relevant symptoms								
Fatigue	8	18.75 (17.16; 0.41)	30.83 (28.87; 32.83)	0.61 (0.55; 0.68)	< 0.0001	0.1233	38.4	
Anorexia	8	14.83 (13.40; 16.36)	20.27 (18.59; 22.04)	0.67 (0.50; 0.89)	0.0054	0.0002	74.8	
Nausea	8	12.54 (11.21; 13.98)	25.69 (23.85; 27.60)	0.45 (0.31; 0.65)	< 0.0001	< 0.0001	85.0	
Constipation	6	6.34 (5.37; 7.42)	8.08 (6.96; 9.32)	0.49 (0.26; 0.94)	0.031	< 0.0001	80.8	
Diarrhea	8	10.61 (9.37; 11.95)	19.85 (18.18; 21.60)	0.51 (0.37; 0.72)	< 0.0001	< 0.0001	76.7	
Peripheral sensory neuropathy	5	1.32 (0.89; 1.88)	6.31 (5.31; 7.42)	0.13 (0.05; 0.34)	< 0.0001	0.0435	59.3	
All-grade hematologic AEs								
Neutropenia	8	0.70 (0.40; 1.14)	18.68 (17.05; 20.40)	0.03 (0.01; 0.08)	< 0.0001	0.0723	46.1	
Thrombocytopenia	2	0.09 (0.01; 0.32)	2.57 (1.94; 3.33)	0.04 (0.01; 0.16)	< 0.0001	0.6952	0.0	
Anemia	8	5.59 (4.68; 6.62)	23.26 (21.48; 25.11)	0.19 (0.10; 0.34)	< 0.0001	< 0.0001	86.2	
All-grade irAEs								
Rash	5	5.77 (4.84; 6.80)	2.76 (2.10; 3.54)	2.07 (1.54; 2.80)	< 0.0001	0.1128	46.5	
Pruritus	3	2.16 (1.60; 2.84)	0.51 (0.26; 0.92)	4.15 (2.20; 7.81)	< 0.0001	0.6361	0.0	
Colitis	7	0.70 (0.40; 1.14)	0.00 (0.00; 0.17)	5.44 (1.42; 20.80)	0.013	0.992	0.0	
Hypothyroidism	6	4.89 (4.04; 5.85)	0.23 (0.08; 0.54)	17.59 (7.74; 39.98)	< 0.0001	0.815	0.0	
Hyperthyroidism	4	2.11 (1.56; 2.79)	0.37 (0.16; 0.73)	5.27 (2.56; 10.86)	< 0.0001	0.9204	0.0	
Hypophysitis	3	0.13 (0.03; 0.39)	0.00 (0.00; 0.17)	2.79 (0.44; 17.62)	0.276	0.9993	0.0	
ALT/AST elevations	5	1.85 (1.34; 2.49)	0.89 (0.54; 1.38)	2.15 (1.31; 3.51)	0.002	0.6884	0.0	
Pneumonitis	8	3.21 (2.53; 4.02)	0.65 (0.36; 1.10)	3.83 (2.20; 6.68)	< 0.0001	0.4492	0.0	
High-grade clinically relevant symptoms								
Fatigue	7	1.58 (1.11; 2.19)	4.06 (3.27; 4.99)	0.39 (0.27; 0.57)	< 0.0001	0.2906	18.2	
Anorexia	7	0.35 (0.15; 0.69)	1.26 (0.83; 1.83)	0.30 (0.14; 0.64)	0.0018	0.7358	0.0	
Nausea	7	0.44 (0.21; 0.81)	0.75 (0.43; 1.21)	0.62 (0.29; 1.32)	0.211	0.5023	0.0	
Constipation	5	0.09 (0.01; 0.32)	0.14 (0.03; 0.41)	0.67 (0.13; 3.39)	0.6314	0.2359	28.8	
Diarrhea	7	0.75 (0.44; 1.20)	1.77 (1.26; 2.43)	0.44 (0.25; 0.76)	0.0034	0.1823	32.2	
Peripheral sensory neuropathy	4	0.00 (0.00; 0.16)	0.61 (0.32; 1.04)	0.10 (0.02; 0.53)	0.0068	0.9103	0.0	
High-grade hematologic AEs								
Neutropenia	7	0.13 (0.03; 0.39)	14.53 (13.06; 16.09)	0.02 (0.01; 0.04)	< 0.0001	0.8763	0.0	
Thrombocytopenia	2	0.04 (0.001; 0.25)	1.40 (0.95; 1.99)	0.05 (0.01; 0.25)	0.0003	0.8892	0.0	
Anemia	7	1.01 (0.64; 1.52)	6.03 (5.05; 7.12)	0.17 (0.07; 0.42)	0.0001	0.0201	60.1	
High-grade irAEs								
Rash	5	0.22 (0.07; 0.51)	0.14 (0.03; 0.41)	1.33 (0.42; 4.22)	0.626	0.6944	0.0	
Pruritus	3	0.00 (0.00; 0.16)	0.05 (0.00; 0.26)	0.33 (0.01; 8.02)	0.4946	NA	NA	
Colitis	7	0.40 (0.18; 0.75)	0.00 (0.00; 0.17)	3.95 (1.00; 15.64)	0.051	0.9928	0.0	
Hypothyroidism	6	0.00 (0.00; 0.16)	0.00 (0.00; 0.17)	NA	NA	NA	NA	
Hyperthyroidism	4	0.04 (0.00; 0.24)	0.00 (0.00; 0.17)	2.70 (0.11; 66.11)	0.5421	NA	NA	
Hypophysitis	3	0.13 (0.03; 0.39)	0.00 (0.00; 0.17)	2.79 (0.44; 17.62)	0.276	0.9993	0.0	
ALT/AST elevations	5	0.57 (0.31; 0.98)	0.19 (0.05; 0.48)	1.84 (0.59; 5.74)	0.291	0.3731	0.0	
Pneumonitis	8	1.45 (1.00; 2.03)	0.19 (0.05; 0.48)	3.78 (1.43; 10.03)	0.007	0.9768	0.0	

AEs adverse events, RR relative risk, CI confidence interval, PD-1 programmed death receptor-1, PD-L1 programmed death ligand 1, ALT alanine aminotransferase, AST aspartate aminotransferase, NA no available data

pembrolizumab reached statistical significance (0.21 vs. 0.43; $P = 0.0217$). In addition, we performed subgroup analyses with regard to detailed AEs based on different PD-1/PD-L1 inhibitors and found the RRs of several

detailed AEs among these three subgroups were statistically different (Supplementary Table 2).

Discussion

In the present meta-analysis of all published RCTs comparing PD-1/PD-L1 inhibitors therapy and chemotherapy in patients with NSCLC, we found PD-1/PD-L1 inhibitors therapy had a significantly lower risk of summary toxic events. More specifically, a significantly lower risk of toxic symptoms and hematologic toxicities was observed in patients treated with PD-1/PD-L1 inhibitors therapy. There was a small, but significantly increased rise in the risk of several irAEs from PD-1/PD-L1 inhibitors therapy. To our knowledge, this is the most comprehensive meta-analysis to provide an evaluation of the full spectrum of toxic events from the PD-1/PD-L1 inhibitors in patients with NSCLC.

For decades, cytotoxic chemotherapy has been used as the first-line therapy for advanced NSCLC; however, toxic events are frequently reported in patients receiving chemotherapy (Li et al. 2017). Our analysis of summary toxic events revealed that compared to chemotherapy, PD-1/PD-L1 inhibitors was associated with a lower risk of any all-grade AEs, any high-grade AEs, treatment discontinuation due to AEs, and toxic deaths. Notably, the absolute difference in risk of any high-grade AEs (14.26 vs. 43.53%; RR 0.32) was more substantial than for any all-grade AEs (66.20 vs. 86.08%; RR 0.77). Furthermore, through subgroup analysis stratified by types of PD-1/PD-L1 inhibitors (nivolumab vs. atezolizumab vs. pembrolizumab), we found only the difference in the risk of any high-grade AEs between patients treated with nivolumab and pembrolizumab reached statistically significance, indicating that the risk of summary toxic events appeared to be consistent among these three PD-1/PD-L1 inhibitors, except for any high-grade AEs between nivolumab and pembrolizumab. Overall, PD-1/PD-L1 inhibitors therapy is safer than chemotherapy for NSCLC patients.

With regard to detailed toxic symptoms and hematologic toxicities, PD-1/PD-L1 inhibitors also appeared to be better tolerated than traditional chemotherapy according to our analysis. However, PD-1/PD-L1 inhibitors can lead to a unique spectrum of irAEs, included dermatologic (rash, pruritus), gastrointestinal (colitis), hepatic (ALT/AST elevations), endocrine (hypothyroidism, hyperthyroidism, and hypophysitis), and pulmonary events (pneumonitis) (Michot et al. 2016). In our analysis, the use of PD-1/PD-L1 inhibitors was associated with a significantly increased risk of several irAEs, including all-grade rash, pruritus, colitis, hypothyroidism, hyperthyroidism, ALT/AST elevations, and high-grade pneumonitis, compared with chemotherapy.

The irAEs are considered as a possible cause for treatment discontinuation and treatment-related deaths in

PD-1/PD-L1 inhibitor treatment. Immune-mediated pneumonitis, which is defined as a focal or diffuse inflammation of the lung parenchyma, can be serious and even life-threatening (O’Kane et al. 2017). Our analysis showed that high-grade immune-related pneumonitis occurred in 1.45% (33/2272) of patients treated with PD-1/PD-L1 inhibitors, and accounted for the most frequently reported cause for treatment-related deaths (36.4%, 4/11). It is reported that immune-related pneumonitis occurs more commonly in NSCLC than with other malignancies (O’Kane et al. 2017). Immune-related hepatic toxicity, which is most frequently observed as asymptomatic ALT/AST elevations in serum, is another uncommon but potentially severe irAE of PD-1/PD-L1 inhibitors. The patients can then develop severe hepatitis if they are not recognized and managed properly (O’Kane et al. 2017). In our analysis, ALT/AST elevations are the second most frequently reported high-grade irAE (0.57%). Clinicians should be aware of the risk of these unique AEs, recognize them timely, and manage them appropriately (Thompson 2018).

Our study had several limitations. For calculating the RR of toxic events, we only included RCTs and excluded several single-arm trials. As a result, the number of studies for the present meta-analysis was limited. In addition, there was some heterogeneity among studies for RRs of high-grade AEs and treatment discontinuation. We minimized the heterogeneity using the random effects model to calculate RRs and conducted exploratory subgroup analysis stratified by the types of PD-1/PD-L1 inhibitors.

Our meta-analysis has demonstrated that PD-1/PD-L1 inhibitors are generally safer and better tolerated than chemotherapy for patients with NSCLC with regard to summary toxic events, detailed toxic symptoms and hematologic toxicities. However, PD-1/PD-L1 inhibitors can generate a unique spectrum of irAEs, and several of them can be severe and even life-threatening. Clinicians should be aware of the risk of these AEs, as they may have a potentially negative impact on the patients’ quality of life and survival outcome.

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Compliance with ethical standards


Conflict of interest The authors declare that they have no conflict of interest regarding the present study.

Ethical approval The article does not contain any studies with human participants performed by any of the authors.

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