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ORIGINAL RESEARCH

Risk and incidence of fatal adverse events associated with immune checkpoint inhibitors: a systematic review and meta-analysis

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Background: Given the increasing use of immune checkpoint inhibitors (ICIs), a concomitant rise in adverse events is inevitable. In a recent Phase III trial of ICIs versus placebo, we found the staggering difference of incidence of fatal adverse events (FAEs). Hence, we should determine the risk of FAEs in ICIs.

Objective: To address the risks of FAEs associated with each ICI regimen, we performed a systematic review and meta-analysis of clinical trials with the Food and Drug Administration-approved ICI regimens in patients with advanced solid tumors.

Methods: Literature searching was based on PubMed before April 15, 2018. The numbers of FAEs in both study group and placebo group were collected. We assessed the risk of fatal adverse reactions associated with ICIs on Pooled Peto OR and associated 95% CI.

Results: Twelve trials were identified. OR value of FADs in all ICIs was 2.32 (95% CI: 1.33, 4.05; P=0.003). The incidence of FAE in ICI in all included studies were up to 3.2%. OR value of clinical trials of prostate cancer was 3.71 (95% CI: 1.12, 12.26; P=0.03). Among the ICI cohorts, the common FAEs were gastrointestinal toxicity (n=12, 25%), pulmonary toxicity (n=10, 20%), cardiac toxicity (n=5, 10%), and hepatic toxicity (n=5, 10%).

Conclusion: The cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors have a significantly higher risk of FAE (P=0.01), whereas programmed cell death protein 1 (PD-1) inhibitors were not. The most common CTLA-4-related FAE was gastrointestinal toxicity, and the most common PD-1-related FAE was pulmonary toxicity. Moreover, we have shown that ipilimumab has significant dose-dependent lethal toxicity.

Keywords: treatment-related mortality, immune mediated death, immune mediated mortality

Introduction

With the realization that overexpression of immune checkpoint molecules in the tumor microenvironment performs a significant function in antitumor immunity evasion, immune checkpoint inhibitors (ICIs) have expanded the scope of cancer treatment.[1,2] Monoclonal antibodies against cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein 1 (PD-1)/programmed cell death protein 1 ligand 1 (PD-L1) have shown a clinically meaningful survival benefit in a sizable subset of patients with solid cancers.[3–14] In fact, six types of drugs have been approved by the Food and Drug Administration (FDA) for the treatment of lung cancer, melanoma, renal cell carcinoma, and other tumors, including 1) CTLA-4 inhibitor, ipilimumab; 2) PD-1 inhibitors, nivolumab and pembrolizumab; and 3) PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab. In addition, clinical trials of a combination of ICIs are also ongoing.[15,16]

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Given the increasing use of ICIs, a concomitant rise in adverse events (AEs) is inevitable. Since CTLA-4 and PD-1 play a key role in maintaining autoantigen immunity and preventing autoimmune disorders,[17,18] ICIs can trigger autoimmune-like manifestations in different organ systems, commonly known as immune-related adverse events (irAEs).[19] Unlike the toxicities caused by cytotoxic or molecularly targeted agents, these irAEs were wide ranging in terms of organs affected including dermatologic, endocrine, neurologic, gastrointestinal, respiratory, and musculoskeletal toxicities, which may occur alone or in constellation, and severe adverse reactions can be life-threatening.[19] In general, the overall incidence of drug-related fatal adverse events (FAEs) was low and reported to be 0.3% in hospitalized patients in the United States.[20] However, in a recent Phase III trial of ICIs vs placebo in patients with metastatic castration-resistant prostate cancer, nine (2%) patients in the ICI arm died as a result of treatment-related AEs, compared with no treatment-related AEs reported in the placebo arm.[4] The gap was staggering; however, the risk of FAEs in ICIs was not clear.

To address the risks of FAEs associated with each ICI regimen, we performed a systematic review and meta-analysis of clinical trials with FDA-approved ICI regimens in patients with advanced solid tumors.

Methods

Search methods

We performed a systematic search of the literature using PubMed to identify relevant clinical trials of ICI that reported FAEs before April 15, 2018, including prospective trials of anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapy in solid cancer patients using ipilimumab, nivolumab, pembrolizumab, or atezolizumab either in single-agent or combination therapies. For searching, the following keywords or corresponding medical subject heading terms were used: "ipilimumab," "MDX-010," "nivolumab," "BMS-963558," "pembrolizumab," "MK-3475," "atezolizumab," "MPDL3280A," "randomized controlled trial," and "phase."

Study selection and data extraction

Our main aim was to directly explore the risk of ICI mortality; hence, our selection criteria included all clinical trials that (1) were randomized controlled trials; (2) directly comparing between the study ICI either alone or in combination with other antitumor therapies to a control arm; (3) investigated the usage of the previously mentioned ICI in advanced solid tumors; and (4) clearly reported a FAE in their safety data. We excluded trials that (1) were published in the form of news, meeting abstracts, letters, or commentaries; (2) were not published in English language; and (3) were Phase I trials. The AE leading to death is defined as FAE, the grade V AE. All treatment-related AEs were under analysis among the patients who received at least one dose of study drug and were evaluated continuously starting from the first dose of the study drug to a minimum of 70 or 90 days after the last dose. The types and grades of AEs were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 or 4.0. All FAEs should be attributed to a particular type of AE as much as possible. Any discrepancy in study selection was discussed until a consensus agreement.

We mainly extracted the following data from each selected study: numbers of FAEs in both study group and placebo group, numbers of total evaluable patients in both study group and placebo group. It is significant to note that the evaluable patients for adverse reactions mean that patients received at least one cycle of treatment, rather than randomization. We also extracted the following data: first author's name, year of publication, phase of the trial, types of tumor, treatment regimen in both arms, and types of FAEs.

Statistical analyses

We assessed the risk of fatal adverse reactions associated with ICIs on Pooled Peto OR and associated 95% CI based on the fixed-effect model. The range of changes in the incidence of FAE in both study group and placebo group was also collected. Subgroup analyses were conducted by classifying the kinds of ICIs, tumors, the dose of ICI, and the types of FAEs. Statistical heterogeneity between RCTs was evaluated using the Cochran Q statistic and I^2 statistics, with values greater than 50% regarded as being indicative of moderate to high heterogeneity. Risks of bias of RCTs included were assessed by using The Cochrane Collaboration tool. We evaluated the possibility of publication bias by constructing funnel plots which were assessed by using Begg's and Egger's tests, and a two-sided *P*-value cutoff of 0.05 was considered statistically significant. All statistical analyses were performed using Review Manager software (version 5.3) and Stata 12.0.

Results

Search results

A total of 609 records were identified in the PubMed search. After screening and eligibility assessment, the specific

screening process was described in Figure 1, we identified a total of 12 clinical trials. These include eight Phase III studies and four Phase II studies. Sorting by treatment, ten trials evaluated CTLA-4 inhibitor (ipilimumab, n=10), and four trials evaluated PD-1 inhibitor (nivolumab, n=3; pembrolizumab, n=1). Two trials included three cohorts, so a pairwise analysis was conducted to compare the risk of ICI drugs. Given the control group was limited to be a placebo or a blank control group, no PD-L1 or combination therapy clinical trials were selected. Sorting by cancer types, six trials evaluated melanoma, four trials evaluated non-small-cell lung cancer (NSCLC), two trials evaluated prostate cancer, and one trial evaluated gastric or gastroesophageal junction cancer, one trial evaluated small-cell lung cancer. A total of 6,390 patients were eligible for analyzing, including 3,568 in the experimental group and 2,822 in the control group. All the patients in these 12 trials had an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, cardiac, and renal functions. All the trials included in the analysis used CTCAE, version 3.0 (n=8) or 4.0 (n=4), to uniformly assess toxicity parameters (Table 1).

OR of FAEs

OR value of FADs in all ICIs was 2.01 (95% CI: 1.17, 3.44; *P*=0.01). Results were further classified according to the different treatment methods used. OR value of FADs in CTLA-4 inhibitors was 2.47 (95% CI: 1.31, 4.66; *P*=0.005), and OR value of FADs in PD-1 inhibitors was 1.06 (95% CI: 0.37, 3.05; *P*=0.92) (Figure 2).

Incidence of FAEs

For the analysis of overall incidence of ICI treatment-related death, we considered only study arms receiving ICIs. The incidence of FAE in ICI was reported in all the studies and ranged from 0% to 3.2%. The incidence of FAE in CTLA-4 trials ranged from 0% to 2.8%. The incidence of FAE in PD-1 trials ranged from 0% to 3.2% (Table 1).

Analysis based on types of tumor

In order to determine whether there is a relationship between the risk of FAE and tumor type, we conducted an analysis based on tumor type. In the included six clinical trials with melanoma, the OR value of patients with melanoma was 1.57 (95% CI: 0.65, 3.77; *P*=0.31). In the included four clinical trials with NSCLC, the OR value of patients with NSCLC was 1.85 (95% CI: 0.65, 5.25; *P*=0.25). Few clinical trials of other tumor types were included; OR value of clinical trials of prostate cancer was 3.71 (95% CI: 1.12, 12.26; *P*=0.03), OR value of clinical trials of gastric cancer was 1.24 (95% CI: 0.24, 6.45; *P*=0.80), and OR value of clinical trials of small cell lung cancer was 3.22 (95% CI: 0.13, 81.19; *P*=0.48) (Figure 3).

Analysis of FAE type

The types of FAE were described and analyzed. A total of 63 FAE cases occurred in all clinical trials, including 48 in the ICI cohort and 15 in the control cohort. Among the ICI cohorts, the common FAEs were gastrointestinal toxicity (n=12, 25%), pulmonary toxicity (n=10, 20%), cardiac toxicity

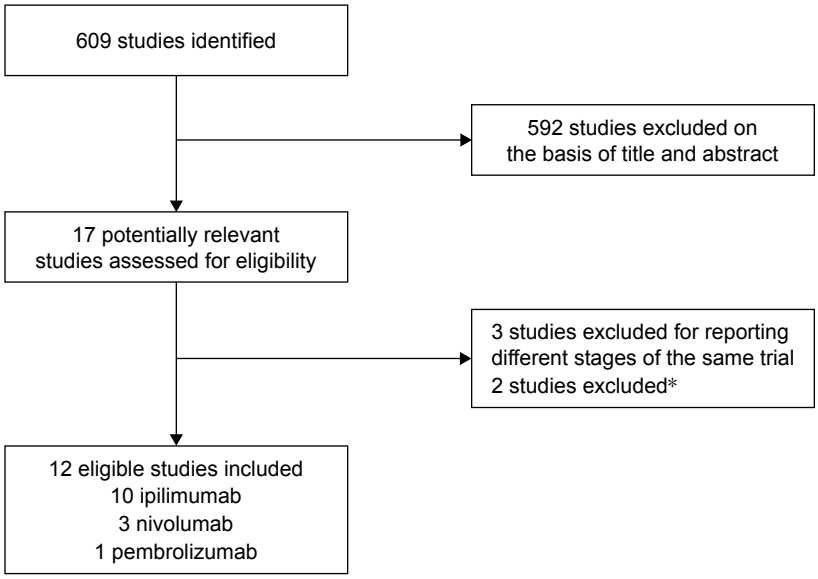

Figure 1 Flow diagram of study selection.
Note: *Two trials were excluded because FAEs did not occur in either study group or control group.
Abbreviation: FAE, fatal adverse event.

Table 1 Baseline characteristics of the included studies

Study	Phase	Cancer type	Study ICI	Arms	Dose of ICI	Numbers of patients	FAEs (%)
Beer et al,[4] 2017	III	Prostate	Ipilimumab	Arm A: ipilimumab	10 mg/kg Q3W	Arm A: 399	Arm A: 9 (2.3)
				Arm B: placebo		Arm B: 199	Arm B: 0 (0)
Eggermont et al,[7] 2015	III	Melanoma	Ipilimumab	Arm A: ipilimumab	10 mg/kg Q3W	Arm A: 471	Arm A: 5 (1.1)
				Arm B: placebo		Arm B: 474	Arm B: 0 (0)
Govindan et al,[5] 2017	III	NSCLC	Ipilimumab	Arm A: ipilimumab plus chemotherapy	10 mg/kg Q3W	Arm A: 388	Arm A: 7 (1.8)
				Arm B: placebo plus chemotherapy		Arm B: 361	Arm B: 1 (0.2)
Hodi et al,[9] 2010	III	Melanoma	Ipilimumab	Arm A: ipilimumab plus gp100	3 mg/kg Q3W	Arm A: 380	Arm A: 8 (2.1)
				Arm B: gp100		Arm B: 132	Arm B: 2 (1.5)
Kwon et al,[8] 2014	III	Prostate	Ipilimumab	Arm A: ipilimumab plus radiotherapy	10 mg/kg Q3W	Arm A: 393	Arm A: 7 (1.8)
				Arm B: placebo plus radiotherapy		Arm B: 396	Arm B: 3 (0.8)
Lynch et al,[6] 2012	II	NSCLC	Ipilimumab	Arm A: concurrent ipilimumab plus chemotherapy	10 mg/kg Q3W	Arm A: 71	Arm A: 2 (2.8)
Lynch et al,[6] 2012*	II	NSCLC	Ipilimumab	Arm B: phased ipilimumab plus chemotherapy	10 mg/kg Q3W	Arm B: 67	Arm B: 0 (0)
				Arm C: Placebo plus chemotherapy		Arm C: 65	Arm C: 1 (1.5)
Reck et al,[3] 2013	II	SCLC	Ipilimumab	Arm A: concurrent ipilimumab plus chemotherapy	10 mg/kg Q3W	Arm A: 42	Arm A: 1 (2.4)
				Arm B: placebo plus chemotherapy		Arm B: 44	Arm B: 0 (0)
Robert et al,[11] 2011	III	Melanoma	Ipilimumab	Arm A: ipilimumab plus dacarbazine	3 mg/kg Q3W	Arm A: 247	Arm A: 0 (0)
				Arm B: placebo plus dacarbazine		Arm B: 251	Arm B: 1 (0.4)
Larkin et al,[10] 2015	III	Melanoma	Ipilimumab	Arm A: ipilimumab plus nivolumab	3 mg/kg Q3W	Arm A: 313	Arm A: 0 (0)
Larkin et al,[10] 2015$	III	Melanoma	Nivolumab	Arm B: nivolumab plus placebo	1 mg/kg Q3W	Arm B: 313	Arm B: 1 (0.3)
				Arm C: ipilimumab plus placebo		Arm C: 313	Arm C: 1 (0.3)
Kang et al,[12] 2017	III	G/GJC	Nivolumab	Arm A: nivolumab	3 mg/kg Q2W	Arm A: 330	Arm A: 5 (1.5)
				Arm B: placebo		Arm B: 163	Arm B: 2 (1.2)
Langer et al,[13] 2016	II	NSCLC	Pembrolizumab	Arm A: pembrolizumab plus chemotherapy	200 mg Q3W	Arm A: 59	Arm A: 1 (1.7)
				Arm B: chemotherapy		Arm B: 62	Arm B: 2 (3.2)
Postow et al,[14] 2015	II	Melanoma	Nivolumab	Arm A: nivolumab plus ipilimumab	1 mg/kg Q3W	Arm A: 94	Arm A: 3 (3.2)
				Arm B: placebo plus ipilimumab		Arm B: 47	Arm B: 0 (0)

Notes: *In the annotated study, Arm B was compared with the control group; $In the annotated study, Arm B was compared with the control group.
Abbreviations: FAE, fatal adverse event; G/GJC, gastric or gastroesophageal junction cancer; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

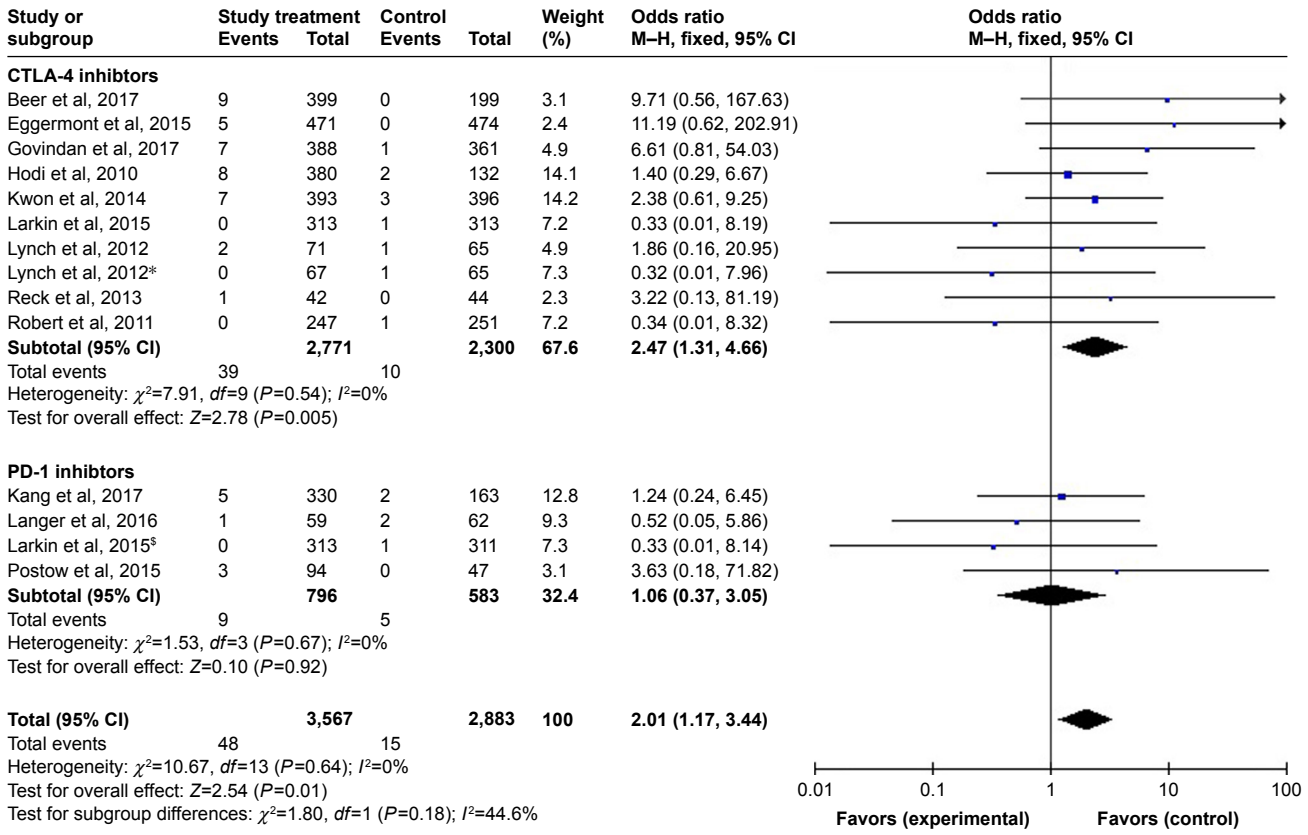

Figure 2 Forest plots of odds ratios of FAEs with ICIs compared with controls (subgrouped by the types of ICIs).
Notes: *In the annotated study, Arm B was compared with the control group; $In the annotated study, Arm B was compared with the control group.
Abbreviations: FAE, fatal adverse event; ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; PD-1, programmed cell death protein 1.

(n=5, 10%), and hepatic toxicity (n=5, 10%). Based on the different regimes, we have realized that CTLA-4 inhibitors have a higher risk of FAE of pulmonary toxicity (OR =3.48, 95% CI: 0.78, 15.61, *P*=0.10), gastrointestinal toxicity (OR =2.52, 95% CI: 0.75, 8.52, *P*=0.14), and hepatic toxicity (OR =2.80, 95% CI: 0.45, 17.42, *P*=0.27). PD-1 inhibitors had a higher risk of FAE of pulmonary toxicity (OR =1.51, 95% CI: 0.16, 14.61, *P*=0.72), cardiac toxicity (OR =0.88, 95% CI: 0.16, 4.79, *P*=0.88), and hepatic toxicity (OR =1.49, 95% CI: 0.06, 36.74, *P*=0.81). The difference was not significant (Table 2).

Analysis based on the dose of ipilimumab

We conducted subgroup analysis according to different doses of ipilimumab, and the results were as follows: OR value of 3 mg/kg group was 0.86 (95% CI: 0.27, 2.78; *P*=0.80), and the OR value of 10 mg/kg group was 3.63 (95% CI: 1.65, 7.99; *P*=0.001), so the subgroup difference was significant (Figure 4).

Quality of the included studies

Figure 5 shows the risk of bias across all included studies. The possibility of publication bias was presented by constructing funnel plots in Figure 6. Begg's and Egger's tests indicated no publication bias among included articles regarding the OR value (Begg's test: *P*=0.063 and Egger's test *P*=0.373) (Figures 7 and 8). And we did pre-sensitivity analyses to evaluate the robustness of the risk we get by exchanging analysis model (random-effect model), exchanging alternative effect measure (relative risk, RR), and repetitive analysis after excluding pairwise analysis study. The results were reliable. Any disagreements in quality assessing were resolved by consensus.

Discussion

This is the first meta-analysis to comprehensively probe into the ICI-related FAE. We found that the use of ICI increased the risk of FAE, among which the risk of FAE caused by CTLA-4 inhibitor was significantly higher than that caused by the PD-1 inhibitor (*P*=0.01). This is similar to another phenomenon observed in the inclusion trials:[3–14] the incidence of AE above grade 3 of CTLA-4 inhibitor is higher than that of PD-1 inhibitor. The exact reason for the difference is not clear and may be related to the differences

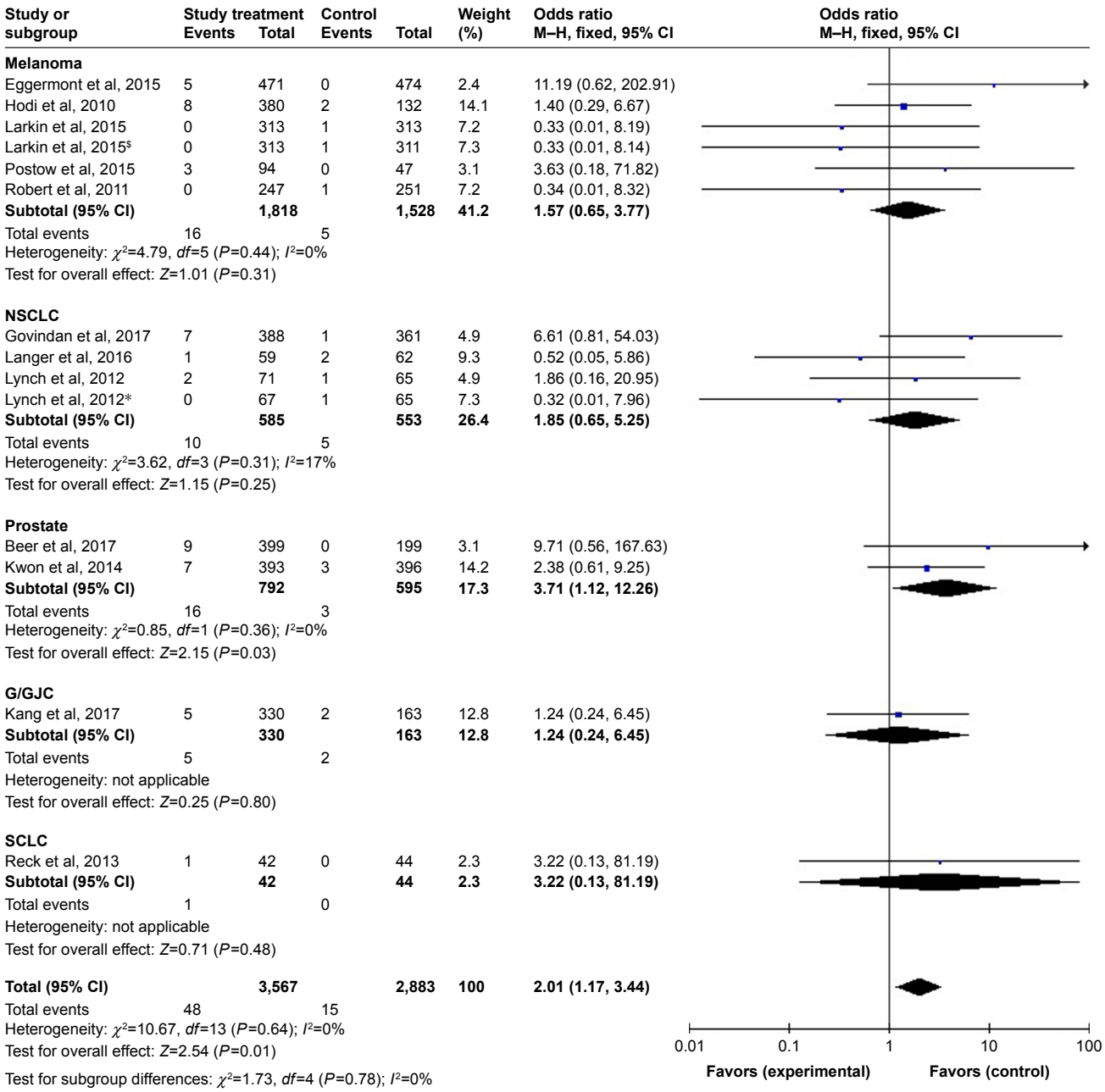

Figure 3 Forest plots of odds ratios of FAEs with ICIs compared with controls (subgrouped by the types of tumors).
Notes: *In the annotated study, Arm B was compared with the control group; §In the annotated study, Arm B was compared with the control group.
Abbreviations: FAE, fatal adverse event; ICI, immune checkpoint inhibitor; G/GJC, gastric or gastroesophageal junction cancer; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

in the CTLA-4 and PD-1 pathways.[21–23] This may provide some guidance for the clinical application of ICIs. Although the adverse reaction rate of ICI drugs is far lower than that of traditional treatment methods such as chemotherapy and radiotherapy, it still has a certain risk of drug-related death. Moreover, adverse reactions of ICI drugs tend to last for a long time, and they would not disappear immediately after drug withdrawal;[24,25] therefore, the management of ICI-related AEs is of great importance. In addition, although we did not include clinical trials of combined immunotherapy for comparison, we found that the incidence of AE above grade 3 in combination therapy was often higher in literature.[26] With the combination of immunotherapy in clinical promotion, further studies are needed to explore the risk of FAE in combination therapy.

Besides OR value as the outcome, we analyzed the incidence of FAEs. The two drug incidences of FAE were up to 2.8% (CTLA-4) and 3.2% (PD-1) of patients, respectively,

Table 2 Characteristics of FAE type

	Numbers of cases (%)	OR (95% CI)
CTLA-4 inhibitors		
Gastrointestinal toxicity	10 (25.6)	2.52 (0.75, 8.52)
Pulmonary toxicity	8 (20.5)	3.48 (0.78, 15.61)
Hepatic toxicity	4 (10.3)	2.80 (0.45, 17.42)
Cardiac toxicity	3 (7.7)	2.73 (0.30, 24.97)
Others	14 (35.9)	
Total	39	
PD-1 inhibitors		
Pulmonary toxicity	2 (22.2)	1.51 (0.16, 14.61)
Cardiac toxicity	2 (22.2)	0.88 (0.16, 4.79)
Hepatic toxicity	1 (11.1)	1.49 (0.06, 36.74)
Others	4 (44.4)	
Total	9	

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein-4; FAE, fatal adverse event; PD-1, programmed cell death protein 1.

among the included clinical trials. Unfortunately, we did not see a significant difference. In one of the other literature, treatment-related deaths occured in up to 2% of patients and varied by ICI.[24] In the included trials, most of the experimental groups used ICI in combination with other types of treatment methods, such as chemotherapy and vaccines. Therefore, the pure rate value cannot accurately reflect the risk of FAEs. In further study, we will reinclude the single-arm trials only using ICI to calculate the precise total incidence of FAE.

ICI is now approved by the FDA for eight types of tumors, including lung cancer, melanoma, renal cell cancer, and so on, and an increasing number of clinical trials of other tumor types are ongoing. We wondered whether the toxicity varied with the type of tumor. A total of five types of tumors were studied in the included literature, among which the most high-risk type of FAE was prostate cancer, significantly higher than other types of tumors (P=0.03), and there was no difference between the other four types of tumors. Searching in Medline database, we found this tumor type dependence was not properly explained, so further studies are needed to investigate the associations. The interpretation of these findings may be hampered by the low number of events and limited RCTs in some subgroups, and we must acknowledge that bias is inevitable because of the limited number of trials included.

In this meta-analysis, we collected all the FAEs that occurred in included trials. The most common FAEs are gastrointestinal toxicity, cardiotoxicity, hepatotoxicity, and pulmonary toxicity. It is not the same as the total occurrence of AE observed in clinical practice, where the most common are fatigue, pruritus, rash, endocrine adverse reactions, and so on.[26] The occurrence of FAE types changes with the types

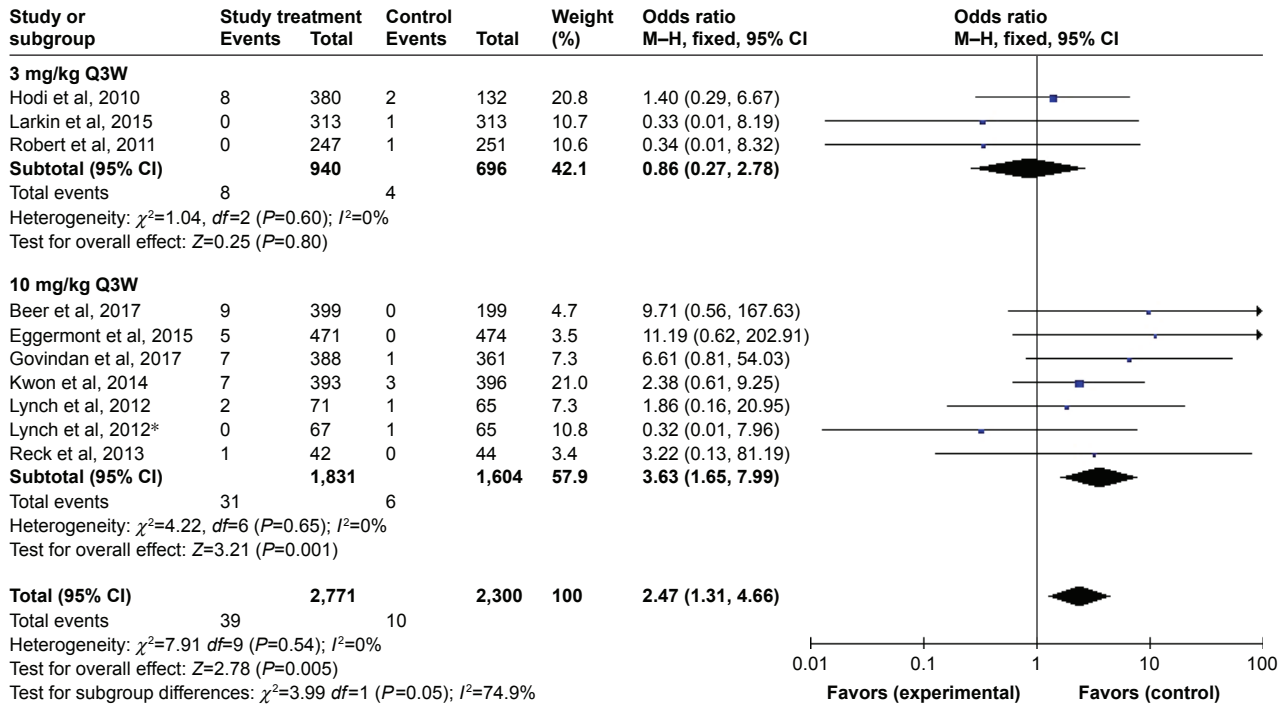

Figure 4 Forest plots of odds ratios of FAEs with ipilimumab compared with controls (subgrouped by the dose of ipilimumab).
Note: *In the annotated study, Arm B was compared with the control group.
Abbreviation: FAE, fatal adverse event.

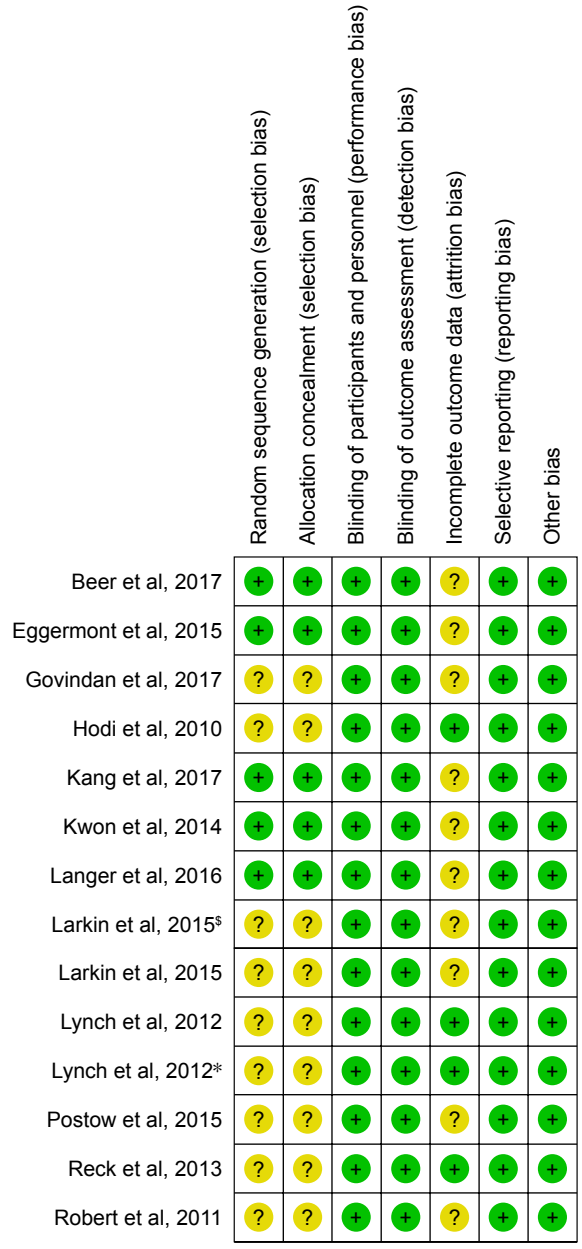

Figure 5 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.
Notes: *In the annotated study, Arm B was compared with the control group; $In the annotated study, Arm B was compared with the control group.

of ICIs. Gastrointestinal FAE has the higher risk among the trials using CTLA-4 inhibitors, and the immediate cause of death from gastrointestinal toxicity is often perforation of the stomach and intestine induced by colitis.[3–11] A large number of cases of gastrointestinal AEs have also been reported in many individual ipilimumab-related reports.[27] Occasionally steroids do not control immune-related gastrointestinal AEs. The NCCN guidelines recommend infliximab, which may successfully treat colitis.[25] In clinical trials involving PD-1 inhibitors, the highest risk of FAE was pulmonary toxicity. The direct causes of death were dyspnea and hypoxia induced by

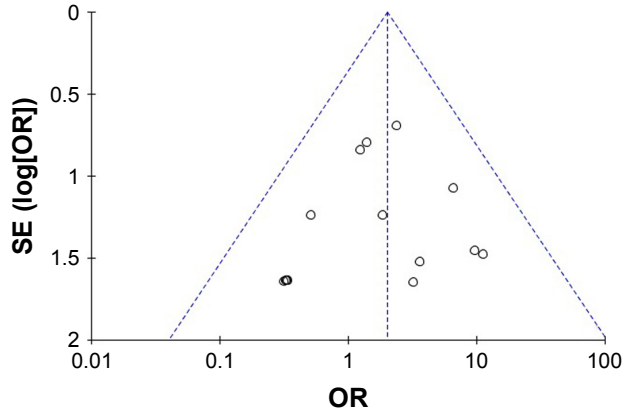

Figure 6 Funnel plot of publication bias.

PD-1-related pneumonitis.[10,12–14] PD-1-related pneumonitis is a type of noninfectious lung inflammation characterized by interstitial and alveolar infiltration, whose presentation is always complicated and unpredictable, and the disease tends to occur later than other irAEs.[28] Since different kinds of pneumonia are similar in their early stages, careful multidisciplinary consultation should be conducted in each case of suspected fatal pneumonia. Workup for infections and timely discontinuation of immunotherapy are required for serious immune-related pneumonia, and high-dose steroids are advised with a taper over 6 weeks or longer. If there is no improvement after 48 hours, infliximab, mycophenolate mofetil, or intravenous immunoglobulin should be considered.[29]

According to the results of subgroup analysis classifying dosage of CTLA-4 inhibitor, we found that the occurrence of ipilimumab-related FAE was dose related. The risk of FAE was significantly lower in the group with dosage of 3 mg/kg than in the group with dosage of 10 mg/kg (P=0.005).

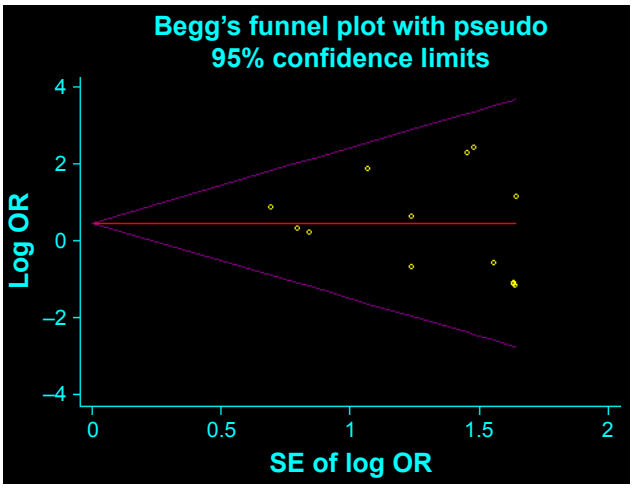

Figure 7 Begg's funnel plot for publication bias testing.

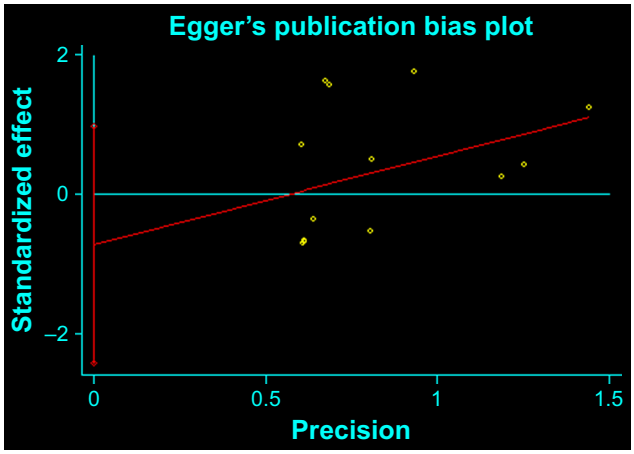

Figure 8 Egger's funnel plot for publication bias testing.

This dose-dependence has also been demonstrated in other trials.[30,31] Although it was not analyzed in this paper, this phenomenon does not seem to exist in PD-1 drugs. The toxicities of PD-1 blockade with nivolumab are similar at doses ranging from 0.3 to 10 mg/kg.[32–34]

The limitations of this article should be taken into account. One of the limitation was that when comparing different types of tumors for subgroup analysis, the number of RCTs in each subgroup is deficient, and the conclusion may be biased. In future studies, we need more suitable included RCTs to determine the relationship between FAE occurrence and cancer types. The other limitation was that we did not include appropriate clinical trials of PD-L1 inhibitor drugs or combined immunotherapy, which may hinder us to recognize the risk of FAE of PD-L1 drugs and ICIs combined immunotherapy.

Conclusion

This meta-analysis shows that ICIs are associated with a high risk of FAEs and that the CTLA-4 inhibitors have a significantly higher risk of FAE (P=0.01), whereas PD-1 inhibitors were not. Compared with other tumor types, there may be a higher correlation between prostate cancer and the occurrence of treatment-related FAE in ICIs. The most common CTLA-4-related FAE was gastrointestinal toxicity, and the most common PD-1-related FAE was pulmonary toxicity. Moreover, we have shown that ipilimumab has significant dose-dependent lethal toxicity. Additional studies are needed to get an accurate mortality incidence of ICIs and an optimal treatment plan of serious AE management.

Disclosure

The authors report no conflicts of interest in this work.

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