Immune-related adverse events associated with PD-1/PD-L1 Inhibitors used as first-line treatment for advanced non-small cell lung cancer: a Bayesian network meta-analysis of randomized clinical trials

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Research

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Abstract

Background

In recent years programmed cell death receptor 1 (PD-1) and its ligand, programmed cell death ligand-1 (PD-L1), have opened a new era of advanced non-small cell lung cancer (NSCLC) treatment, while yielding higher rates of immune-related adverse events (irAEs) than platinum-based chemotherapy. This network meta-analysis indirectly compared the incidences of irAEs of PD-1/PD-L1 inhibitor + chemotherapy, PD-1/PD-L1 inhibitor alone, and dual PD-1/PD-L1 inhibitor combinations.

Methods

We found 12 phase II or III randomized clinical trials (RCTs) including 8,453 patients with NSCLC by searching Pubmed, Embase, and the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov. Summary risk ratios (RRs) and 95% confidence interval were used to compare the rate of irAEs for different ICI-based treatments using pairwise and network meta-analysis with random effects.

Results

In addition to platinum-based chemotherapy, in terms of dermatologic irAEs, durvalumab had the lowest rate compared to pembrolizumab + platinum, nivolumab, atezolizumab + platinum, nivolumab, pembrolizumab, nivolumab + ipilimumab. In terms of gastrointestinal irAEs, pembrolizumab had the lowest rate compared to nivolumab, nivolumab + ipilimumab, durvalumab, atezolizumab + platinum, and pembrolizumab + platinum. For endocrine irAEs, pembrolizumab + platinum had the lowest rate compared to pembrolizumab, atezolizumab + platinum, durvalumab, nivolumab, and nivolumab + ipilimumab. For pneumonitis, atezolizumab had the lowest rate compared to durvalumab, nivolumab, atezolizumab + platinum, pembrolizumab + platinum, and pembrolizumab. For liver irAEs, durvalumab had the lowest rate compared to pembrolizumab, nivolumab, atezolizumab + platinum, pembrolizumab + platinum.

Conclusions

These findings suggested that, for patients with advanced NSCLC at high risk of irAEs, durvalumab for patients with dermatologic and liver irAEs, pembrolizumab for patients with gastrointestinal irAEs, pembrolizumab + platinum for patients with endocrine irAEs, and atezolizumab for patients with pneumonitis may be the preferred treatment regimens rather than other immune-based therapies.

Simple Summary

In recent years PD-1/PD-L1 Inhibitors, which constitute an inhibitory pathway detected in a variety of malignant tumors, have opened a new era of cancer treatment, while yielding higher rates of irAEs than platinum-based chemotherapy. Here, to help clinicians improve early management and identification of irAEs, we indirectly compared the incidences of irAEs by PD-1/PD-L1 inhibitor + chemotherapy, PD-1/PD-L1 inhibitor alone and dual PD-1/PD-L1 inhibitors combinations. Compared to previous studies, first, more patients with advanced NSCLC were included in this study, and all data were up to date. Second, this study only looked at NSCLC, and immune-related treatment regimens were more specific to each treatment regimen, which will help clinicians make better treatment choices based on patients' specific conditions. Third, all of the control experiments in our study were platinum-based chemotherapy, excluding docetaxel-based chemotherapy and others, which would reduce bias and increase credibility. Fourth, some conclusions this study drew were innovative compared to previous studies, which will have some significance for guiding clinical treatment and subsequent studies.

1. Background

According to the latest statistics, lung cancer is still the leading cause of cancer deaths, although the incidence of cancer has declined in recent years^[1–2]. Nearly 70% of patients with lung cancer are diagnosed with locally advanced or metastatic disease^[4], and the 5-year survival rate is only 5%^[5–6]. However around 80–85% of lung cancer cases are classified as NSCLC^[3]. Platinum-based chemotherapy remains the standard first-line treatment for NSCLC without target gene mutations, with a response rate of only 15%^[7–8].

In recent years PD-1/PD-L1 inhibitors, which constitute an inhibitory pathway detected in a variety of malignant tumors, have opened a new era of cancer treatment^[9–10]. Treatment with PD-1/PD-L1 inhibitor alone or in combination makes longer survival possible^[11–12].

Data from a series of randomized clinical trials suggest that PD-1/PD-L1 inhibitors alone or in combination as first-line treatment for advanced NSCLC patients provides better clinical benefits and fewer side effects than conventional platinum-based chemotherapy[13–26]. However, PD-1/PD-L1 inhibitors enhance self immune functions against cancer cells through a unique mechanism that blocks negative regulators expressed on immune or tumor cells, while yielding higher rates of irAEs than platinum-based chemotherapy[26]. Immune-related adverse events may involve a number of organs or systems: dermatologic irAEs (pruritus and rash), gastrointestinal irAEs (diarrhea and constipation), endocrine irAEs (hypothyroidism and hyperthyroidism), pneumonitis and liver irAEs (increased alanine aminotransferase, increased aspartate aminotransferase level and hepatitis). These irAEs have attracted the attention of clinicians as they invoke a high rate of drug withdrawal and mortality. The occurrence of grade 3 or higher irAEs varied from 8–10% among patients with advanced NSCLC receiving PD-1/PD-L1 inhibitors. If not properly treated and managed in clinical practice, irAEs will lead to treatment termination, failure, and may even be life-threatening.

Here, to help clinicians improve early management and identification of irAEs, a Bayesian network meta-analysis was conducted to compare the incidences of irAEs and rank the safety of PD-1/PD-L1 inhibitor + chemotherapy, PD-1/PD-L1 inhibitor alone, and dual PD-1/PD-L1 inhibitor combinations.

2. Methods

2.1 Data sources and searches

This network meta-analysis (NMA) was based entirely on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) [27–28] and PRISMA extended guidelines for an NMA. RCTs on PD-1/PD-L1 inhibitors versus platinum-based chemotherapy as the first-line treatment of advanced NSCLC from 2015 to 2020 were searched in PubMed, Embase, the Cochrane Library, and Web of Science databases. To search for data not explicitly given in the RCTs, the National Institutes of Health ongoing Trial Registry (Clinicaltrials.gov) was also searched. A combination of MeSH and free-text words was searched according to the PICOS principle. Search terms and their combinations used in the search strategy included: (PD-1 OR PD-L1 OR nivolumab OR pembrolizumab OR durvalumab OR atezolizumab OR ipilimumab) AND (Non-Small-Cell Lung Carcinoma OR Non-Small Cell Lung Cancer) AND chemotherapy AND (randomized controlled trial). Two independent reviewers (Jingjing Gu and Weidong Zhang) conducted a preliminary screening of the searched topics and abstracts, and if they did not meet the criteria, further read the full text, and all references were evaluated as potentially relevant articles.

2.2 Inclusion and exclusion criteria

Inclusion criteria for RCTs of this NMA were as follows: (1) study type: only Phase II or III double blind RCTs for advanced NSCLC; (2) participants: included patients that were pathologically diagnosed as advanced NSCLC; (3) experimental group: patients were treated with immunotherapy alone or an immune-based combination as first-line treatment, control group: patients were treated with only platinum-based chemotherapy as first-line treatment; (4) outcome indicators: there was at least one irAE in the RCTs or searched on Clinicaltrials.gov.

Exclusion criteria: non-English articles, studies without valid data, reviews, meta-analyses, editorials, commentary letters, repeat studies.

2.3. Data extraction

By reading the titles, abstracts and full texts, the two authors screened out the articles that met the predetermined inclusion criteria. 1) Trial information, including first author, study year, trial id; 2) Stage information, study endpoint, and sample size of treatment; 3) Patient characteristics at baseline included median age, sex, and the numbers of patients with dermatologic irAEs, gastrointestinal irAEs, endocrine irAEs, pneumonitis and liver irAEs. And the two authors checked the extracted data before data analysis.

2.4. Risk-of-bias assessment

The Cochrane risk bias assessment tool^[30](Fig. 1) were used to evaluate the quality of the literature by two reviewers (Jingjing Gu and Weidong Zhang). The seven major sources of biases (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias) were classified into three grades including 'yellow represents unclear risk', 'green represents low risk' and 'red represents high risk' which were assessed using the Cochrane risk bias assessment tool.

2.5. Outcome measures

The study endpoints were dermatologic irAEs (pruritus and rash), gastrointestinal irAEs(diarrhea and constipation), endocrine irAEs (hypothyroidism and hyperthyroidism), pneumonitis and liver irAEs(increased alanine aminotransferase, increased aspartate aminotransferase level and hepatitis). Review criteria were based on the National Cancer Institute Common Terminology Criteria for Adverse Events^[31]

2.4 Data synthesis and statistical analysis

The loops to illustrate the network geometry were generated using Stata13.0. In this Bayesian framework network meta-analysis, summary RRs and 95% confidence intervals were used as the results of the effect size of PD-1/PD-L1 inhibitor-based drugs on the risk of irAEs in NSCLC patients. RR greater than 1 represented a low probability of irAEs in the control group. Markov chain Monte Carlo (MCMC) methods were used to establish random-effects and consistency models calculating the RR and 95% confidence intervals within the Bayesian framework by using R(version 4.0.1) (CoreTeam 2019, Vienna, Austria) and JAGS (version 4.3.0) with the package“getmcmc”(version 0.8.2) ^[32–33]. Heterogeneity of the included studies was assessed by I^2 statistics. I^2 values below 25%, between 25% and 50%, and above 50% represented low, medium, and high heterogeneity, respectively^[34]. If the heterogeneity is low, the fixed effects model would be selected, otherwise the random effects model would be selected. In order to explore the inter-study heterogeneity of each outcome comparison, the values of different parameters of a log-normal distribution were fitted as a prior distribution^[35]. To obtain the posterior distribution, 10,000 burn-ins and 50,000 iterations of 4 each chain and a thinning interval of 10 were generated for each outcome by using MCMC methods. We judged whether each MCMC chain reached a stable and good iteration during the calculation process through the Brookse-Gelmane-Rubin diagnostic plot with a cut-off value of 1, so as to determine whether the degree of convergence of the model was satisfactory. The surface under the cumulative ranking curve (SUCRA) metric was used to rank the probabilities of irAEs of each treatment and identify the best treatment. In this network meta-ananlysis the SUCRA value ranged from 1 to 0, representing the worst and best treatment regimes^[36]. A funnel plot was used to assess the publication bias and symmetrical distribution in funnel plot suggests no publication bias^[37]. Sensitivity analysis was performed to assess the stability of the results which were considered stable if there was significant consistency between direct and indirect results^[38]. We conducted a inconsistency test(that is, the comparison of the differences between direct and indirect comparisons) using the nodal analysis and $P>0.05$ indicated that there is no inconsistency^[39–40].

3. Results

3.1 Literature search results and study characteristics

Through the literature search, 539 studies were initially retrieved. After removing duplicates, 352 studies were used to filter through screening titles and abstracts, then 39 studies were assessed by screening full text. Finally, 12 RCTs[13–24]including 8,453 patients were considered eligible for inclusion in this network meta-analysis. The literature retrieval strategy is shown in Fig. 2. The included RCTs involved 1 Phase II/III trial and 11 Phase III trials and described eight treatment regimes(pembrolizumab, nivolumab, durvalumab, atezolizumab, pembrolizumab + platinum, atezolizumab + platinum, nivolumab + ipilimumab and platinum-based chemotherapy). The Network diagrams of comparisons on all outcomes in this network meta-analysis are presented in Fig. 3. The dermatologic irAEs(pruritus and rash), gastrointestinal irAEs(diarrhea and constipation) and endocrine irAEs(hypothyroidism and hyperthyroidism) involved seven different treatment regimens(pembrolizumab, nivolumab, durvalumab, pembrolizumab + platinum, atezolizumab + platinum, nivolumab + ipilimumab and platinum-based chemotherapy) in 11 studies^[13–21, 23](Fig. 3A).The pneumonitis involved seven different treatment regimens(pembrolizumab, nivolumab, durvalumab, atezolizumab, pembrolizumab + platinum, atezolizumab + platinum, nivolumab + ipilimumab and platinum-based chemotherapy) in 11 studies^[13–22] (Fig. 3B), and liver irAEs(Increased ALT level,Increased AST level and hepatitis) involved six different treatment regimens(pembrolizumab, nivolumab, durvalumab, atezolizumab, pembrolizumab + platinum, atezolizumab + platinum) in 10 studies^[13–21](Fig. 3C). Key features of all the studies are shown in Tables 1 and 2.

Table 1
General characteristics of the included randomised control trials for this network meta-analyses.

First author,year	Study ID	Region	Trial phase	Trail number	Experimental group	Control group
Carbone 2017	Checkmate 026	MN	II	423	Nivolumab 3mg/kg	Platinum-based chemotherapy
Naiyer 2020	Mystic	MN	II	721	Durvalumab 20 mg/kg	Platinum-based chemotherapy
Paz-Ares 2018	Keynote-407	USA	II	559	Pembrolizumab 200mg + platinum-based chemotherapy	Platinum-based chemotherapy
Gandhi 2018	Keynote-189	MN	II	616	Pembrolizumab 200mg + platinum-based chemotherapy	Platinum-based chemotherapy
Mok 2019	Keynote-042	MN	II	1274	Pembrolizumab 200mg	Platinum-based chemotherapy
Reck 2019	Keynote-024	MN	II	305	Pembrolizumab 200mg	Platinum-based chemotherapy
Borghaei 2016	Keynote-021	USA, Taiwan	III/II	123	Pembrolizumab 200mg + platinum-based Chemotherapy	Platinum-based chemotherapy
Rivero 2018	Impower 132	MN	II	578	Atezolizumab 1200mg + platinum-based Chemotherapy	Platinum-based chemotherapy
Robert 2018	Impower 131	MN	II	1021	Atezolizumab 1200mg + platinum-based Chemotherapy	Platinum-based chemotherapy
West 2019	Impower 130	MN	II	724	Atezolizumab 1200mg + platinum-based Chemotherapy	Platinum-based chemotherapy
Spigel 2019	Impower 110	MN	II	572	Atezolizumab 1200mg	Platinum-based chemotherapy
Hellmann 2018	Checkmate 227	MN	II	1537	Nivolumab 3mg/kg Nivolumab 3 mg/kg + Ipilimumab 1mg/kg	Platinum-based chemotherapy
(Abbreviations: MN,multinational;NA, not applicable.)						

Table 2
Patient characteristics and extracted data for study end-points in the included randomised controlled trials.

Study ID	Treatment	Trail number	Dermatologic irAEs(pruritus and rash)	Gastrointestinal irAEs(diarrhea and constipation)	Endocrine irAEs (hypothyroidism and hyperthyroidism)	Pneumonitis	Liver irAEs(Increased ALT level,Increased AST level and hepatitis)
Checkmate 026	Nivolumab 3mg/kg	267	92	105	20	23	60
	Platinum-based chemotherapy	263	48	133	7	17	36
Mystic	Durvalumab 20 mg/kg	369	107	72	40	32	33
	Platinum-based chemotherapy	352	88	58	4	23	37
Keynote-407	Pembrolizumab 200mg + platinum-based Chemotherapy	278	92	147	82	25	58
	Platinum-based chemotherapy	280	58	126	14	8	23
Keynote-189	Pembrolizumab 200mg + platinum-based chemotherapy	405	145	266	43	18	116
	Platinum-based chemotherapy	202	50	107	11	5	35
Keynote-042	Pembrolizumab 200mg	636	107	130	116	104	170
	Platinum-based chemotherapy	615	44	212	13	41	181
Keynote-024	Pembrolizumab 200mg	154	42	31	27	19	33
	Platinum-based chemotherapy	150	6	38	5	2	34
Keynote-021	Pembrolizumab 200mg + platinum-based Chemotherapy	59	22	23	14	2	19
	Platinum-based chemotherapy	62	11	12	4	0	12
Impower 132	Atezolizumab 1200mg + platinum-based Chemotherapy	291	75	10	23	16	13
	Platinum-based chemotherapy	274	60	4	6	6	2
(Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; MN,multinational;NA, not applicable.)							

Study ID	Treatment	Trail number	Dermatologic irAEs(pruritus and rash)	Gastrointestinal irAEs(diarrhea and constipation)	Endocrine irAEs (hypothyroidism and hyperthyroidism)	Pneumonitis	Liver irAEs(Increased ALT level,Increased AST level and hepatitis)
Impower 131	Atezolizumab 1200mg + platinum-based Chemotherapy	334	74	104	34	23	58
	Platinum-based chemotherapy	334	39	94	4	5	29
Impower 130	Atezolizumab 1200mg + platinum-based Chemotherapy	473	119	199	53	62	30
	Platinum-based chemotherapy	232	28	77	1	22	14
Impower 110	Atezolizumab 1200mg	286	NA	NA	NA	14	NA
	Platinum-based chemotherapy	263	NA	NA	NA	17	NA
Checkmate 227	Nivolumab 3mg/kg	576	73	50	25	NA	NA
	Nivolumab 3mg/kg + Ipilimumab 1mg/kg	391	117	117	67	NA	NA
	Platinum-based chemotherapy	570	34	141	0	NA	NA
(Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; MN,multinational;NA, not applicable.)							

3.2. Head-to-head comparisons for the endpoints

In addition to platinum-based chemotherapy, in terms of dermatologic irAEs, durvalumab had the lowest rate compared to pembrolizumab + platinum (RR, 0.62, 95% CI, 0.17 to 2.26), nivolumab (RR, 0.42, 95%CI, 0.11 to 1.66), atezolizumab + platinum (RR, 0.65, 95% CI, 0.18 to 2.43), nivolumab (RR, 0.37, 95% CI, 0.06 to 2.61), pembrolizumab (RR, 0.30, 95% CI, 0.06 to 1.12), nivolumab + ipilimumab (RR, 0.19 95% CI, 0.04 to 0.92) (Fig. 4A). In terms of gastrointestinal irAEs, pembrolizumab had the lowest rate compared to nivolumab (RR, 0.92, 95% CI, 0.42 to 2.20), nivolumab + ipilimumab (RR, 0.64, 95% CI, 0.25 to 1.68), durvalumab (RR, 0.45, 95% CI, 0.17 to 1.30), atezolizumab + platinum (RR, 0.40, 95% CI, 0.18 to 0.88), and pembrolizumab + platinum (RR, 0.33, 95% CI, 0.15 to 0.72) (Fig. 4B). For endocrine irAEs, pembrolizumab + platinum had the lowest rate compared to pembrolizumab (RR, 0.52, 95% CI, 0.02 to 12.18), atezolizumab + platinum (RR, 0.43, 95% CI, 0.02 to 7.44), durvalumab (RR, 0.55, 95% CI, 0.03 to 9.22), nivolumab (RR, 0.31, 95% CI, 0.01 to 6.44), and nivolumab + ipilimumab (RR, 0.08, 95% CI, 0.001 to 2.58) (Fig. 4C). For pneumonitis, atezolizumab had the lowest rate compared to durvalumab (RR, 0.82, 95% CI, 0.05 to 10.42), nivolumab(RR, 0.53, 95% CI, 0.03 to 9.30), atezolizumab + platinum (RR, 0.29, 95% CI, 0.03 to 2.94), pembrolizumab + platinum (RR, 0.23, 95% CI, 0.02 to 2.33), and pembrolizumab (RR, 0.17, 95% CI, 0.01 to 1.77)(Fig. 4D). For liver irAEs, durvalumab had the lowest rate compared to pembrolizumab (RR, 0.92, 95% CI, 0.23 to 3.42), nivolumab (RR, 0.44, 95% CI, 0.10 to 2.13), atezolizumab + platinum (RR, 0.41, 95% CI, 0.10 to 1.40), pembrolizumab + platinum (RR, 0.37, 95% CI, 0.10 to 1.31) (Fig. 4E).

3.3. Determining the ranking

We ranked the probabilities of immune-related adverse events for all treatments by estimating the SUCRA value. A higher SUCRA value indicated a higher probability of irAEs and a poorer treatment regimen. For dermatologic irAEs, the corresponding ranking of incidences of the seven groups from low to high was: platinum-based chemotherapy(4.7%), durvalumab(17.5%), atezolizumab + platinum(39.9%), pembrolizumab + platinum(43.3%), nivolumab(67.1%), pembrolizumab(80.1%), nivolumab + ipilimumab(97.4%)(Fig. 5A, supplementary figure S1A). For gastrointestinal irAEs, the corresponding ranking of incidences of the seven groups from low to high was: pembrolizumab(11.5%), platinum-based chemotherapy(32.6%), nivolumab(33.5%), nivolumab + ipilimumab(40.3%), atezolizumab + platinum(43.7%), pembrolizumab + platinum(81.2%), durvalumab(97.2%)(Fig. 5B, supplementary figure S1B). For endocrine irAEs, the corresponding ranking of incidences of the seven groups from low to high was: platinum-based chemotherapy(0.3%), pembrolizumab + platinum(33.5%), nivolumab(45.7%), atezolizumab + platinum(60.4%), pembrolizumab(61.9%), durvalumab(69.1%), nivolumab + ipilimumab(79.1%)(Fig. 5C, supplementary figure S1C). For pneumonitis, the corresponding ranking of incidences of the seven groups from low to high was: atezolizumab(14.6%), platinum-based chemotherapy(21.6%), nivolumab(40.3%), durvalumab(40.8%), atezolizumab + platinum(68.8%), pembrolizumab + platinum(75.4%), pembrolizumab(88.6%)(Fig. 5D, supplementary figure S1D). For liver irAEs, the corresponding ranking of incidences of the six groups from low to high was: durvalumab(14.5%), pembrolizumab(15.7%), platinum-based chemotherapy(30.9%), nivolumab(73.7%), atezolizumab + platinum(74.8%), pembrolizumab + platinum(90.4%)(Fig. 5E, supplementary figure S1E).

3.4. Model convergence, heterogeneity and publication bias

As shown in supplementary figure S2, all comparisons of different irAEs all suggested that the contraction factor in Brookse-Gelmane-Rubin diagnostic plots were equal to the predefined cut-off value 1, suggesting that the study model had good convergence. In this network meta-analysis the comparisons showed low, medium or high heterogeneity(supplementary figure S3), then the random effects model was selected. The funnel plots were all symmetrically distributed, suggesting no publication bias(Fig. 6).

3.5. Risk-of-bias assessment and sensitivity analysis

As shown in Fig. 1, 9 included RCTs^[13–14,18–24] were regarded as high risk on blinding of participants and personnel and 5 included RCTs^[14–17,21] were considered high risk on incomplete outcome data. Other domains indicated unclear risk or low risk. The inconsistency test conducted that P values ≥ 0.5 indicated there was significant consistency between direct and indirect results of all comparisons, and then the sensitivity analysis indicated stable results.

Discussion

Programmed cell death receptor-1 (PD-1) is a type I transmembrane glycoprotein^[41], which is an inhibitory receptor of T cells. It can bind and interact with the specific ligands PD-L1 (B7-H1) and PD-L2 (B7-H2). Tumor cells can activate PD-1, thereby promoting it to bind to PD-L1 and PD-L2 on the surface of antigen presenting cells, inhibiting the proliferation of effector T cells and preventing T cells from recognizing dangerous molecules in a timely and effective manner, thus enabling tumor cells to evade the pursuit of immune cells. PD-1/PD-L1 inhibitors promote the activation and proliferation of T cells by inhibiting the expression of PD-1/PD-L1, thus stimulating the killing of tumor cells^[42]. In recent years, since the PD-1/PD-L1 inhibitors nivolumab^[43], pembrolizumab^[44], atezolizumab^[45] and durvalumab^[46] were approved for NSCLC owing to their good clinical efficacy, a number of RCTs have successively evaluated PD-1/PD-L1 inhibitor + chemotherapy, PD-1/PD-L1 inhibitor alone, dual PD-1/PD-L1 inhibitors combination versus chemotherapy in terms of efficacy and safety in the first-line treatment of advanced NSCLC. These RCTs suggested that the efficacy and treatment-related side effects of PD-1/PD-L1 inhibitor + chemotherapy, PD-1/PD-L1 inhibitor alone, dual PD-1/PD-L1 inhibitors combination combined with chemotherapy were better than chemotherapy alone, however the irAEs showed a tendency to be more prevalent in PD-1/PD-L1 inhibitors than in chemotherapy. Which immune-based treatment regimen is more likely to induce irAEs is controversial. The purpose of this study was to indirectly compare the probabilities of irAEs with different PD-1/PD-L1 inhibitor treatment regimens through an NMA.

In previous studies, Cheng Xu et al^[26] compared the occurrences of irAEs with different immunotherapy regimens for all cancers in 2018. They found that atezolizumab had the best overall safety, while nivolumab had the best overall safety in the treatment of lung cancer with a combined approach. Xinru Chen et al^[47] investigated different immunotherapy regimens for immune-related pneumonia (IRP), and they concluded that PD-1/PD-L1 inhibitors increased the risk of IRP compared to chemotherapy and that PD-1/PD-L1 inhibitors + chemotherapy was associated with a lower risk of IRP than dual PD-1/PD-L1 inhibitors combination and PD-1/PD-L1 inhibitor monotherapy. Here, we indirectly compared the probability of irAEs caused by different specific PD-1/PD-L1 inhibitors-based treatment regimes for advanced NSCLC. And we conducted that, for dermatologic irAEs, the corresponding ranking of incidences from low to high was: platinum-based chemotherapy, durvalumab, atezolizumab + platinum, pembrolizumab + platinum, nivolumab, pembrolizumab,

nivolumab + ipilimumab. For gastrointestinal irAEs, the corresponding ranking of incidences from low to high was: pembrolizumab, platinum-based chemotherapy, nivolumab, nivolumab + ipilimumab, atezolizumab + platinum, pembrolizumab + platinum, durvalumab. For endocrine irAEs, the corresponding ranking of incidences from low to high was: platinum-based chemotherapy, pembrolizumab + platinum, nivolumab, atezolizumab + platinum, pembrolizumab, durvalumab, nivolumab + ipilimumab. For pneumonitis, the corresponding ranking of incidences from low to high was: atezolizumab, platinum-based chemotherapy, nivolumab, durvalumab, atezolizumab + platinum, pembrolizumab + platinum, pembrolizumab. For liver irAEs, the corresponding ranking of incidences from low to high was: durvalumab, pembrolizumab, platinum-based chemotherapy, nivolumab, atezolizumab + platinum, pembrolizumab + platinum. These conduction will help clinicians manage life-threatening treatment-related adverse events, optimize future trial designs, and modify the prescription of ICI drugs.

All of the articles included in this NMA were RCTs showing good consistency. The Cochrane risk bias assessment tool were used to examine the quality of included studies and to ensure their inherent authenticity by assessing the potential risk of bias in various aspects of RCT design, implementation, and outcome evaluation. Compared to previous studies, first, more patients with advanced NSCLC were included in this study, and all data were up to date. Second, this study only looked at NSCLC, and immune-related treatment regimens were more specific to each treatment regimen, which will help clinicians make better treatment choices based on patients' specific conditions. Third, all of the control experiments in our study were platinum-based chemotherapy, excluding docetaxel-based chemotherapy and others, which would reduce bias and increase credibility. Fourth, some conclusions this study drew were innovative compared to previous studies, which will have some significance for guiding clinical treatment and subsequent studies.

In all of the studies of irAEs included, almost all comparisons showed low heterogeneity except for some comparisons, from which we can see this study has several limitations. First, different terms were used to describe irAEs in the RCTs. Although we found that the rating systems and terminology used in the reports were consistent and compatible, the diagnosis of each irAE was based solely on the experience of each clinician, rather than on a centralized review, which can lead to bias in irAE evaluation. Second, some irAEs were delayed diseases, and clinicians could not have observed the symptoms of patients within the clinical timeframe, leading to the loss of clinical data, which would bring some potential heterogeneity to this study. Third, the median follow-up time for each RCT was different, which would increase the frequency of irAEs associated with immunotherapy and increase the confounding factors for these events. Fourth, the integration of different drugs with similar mechanisms into the same arm may lead to heterogeneity and bias. Fifth, although we included the latest RCT data that could be retrieved, some studies had a small sample size, so that further updates and experiments are still needed.

Conclusions

Although several limitations applied, this systematic review and NMA suggested that, for patients with advanced NSCLC at high risk of irAEs, durvalumab for patients with dermatologic and liver irAEs, pembrolizumab for patients with gastrointestinal irAEs, pembrolizumab+platinum for patients with endocrine irAEs, and atezolizumab for patients with pneumonitis may be the preferred treatment regimens rather than other immune-based therapies.

Abbreviations

PD-1: programmed cell death receptor 1

PD-L1: programmed cell death ligand-1

irAEs: immune-related adverse events

NSCLC: non-small cell lung cancer

RCTs: randomized clinical trials

RRs: risk ratios

NMA: network meta-analysis

PRISMA: preferred reporting items for systematic reviews and meta-analysis

MCMC: Markov chain Monte Carlo

SUCRA: surface under the cumulative ranking curve

Declarations

Ethics approval and consent to participate

This network meta-analysis is a data reintegration based on the original data, which does not involve ethics.

Consent for publication

Not applicable.

Availability of data and material

Some or all data, models, or code generated or used during the study are available from the first author by request.

Competing interests

Not applicable.

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Authors' contributions:

Author GHH(Doctor) and CMB have given substantial contributions to the conception or the design of the manuscript, author JJG and author WZD to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, author GHH revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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47. A.

Figures

A

B

Figure 1

The Cochrane risk bias assessment tool was used to evaluate bias from seven key sources: 1. Random sequence generation; 2. Allocation concealment; 3. Blindness of subjects and researchers; 4. Blindness of outcome evaluation; 5. Incomplete data; 6. Selective reporting of results; 7. Other biases. Green represents low risk, yellow represents unclear risk, and red represents high risk. (A) Risk of bias graph; (B) Risk of bias summary.

Figure 2

Flowchart of the systematic search PRISMA flow diagram

Figure 3

Network diagrams of comparisons on all outcomes in this network meta-analysis. (A) Comparisons on dermatologic,gastrointestinal and endocrine irAEs in patients with advanced NSCLC. (B) Comparisons on pneumonitis in patients with advanced NSCLC. (C) Comparisons on liver irAEs in patients with advanced NSCLC.(The circles represent treatment regimens and the size of each circle represents the number of participants, while the yellow line represents double-blind RCTs and the green is not blind.)

A

Atezolizumab+Platinum	0.65 (0.18, 2.43)	1.56 (0.56, 4.40)	3.35 (0.99, 11.96)	2.13 (0.82, 7.12)	1.05 (0.42, 2.74)	0.54 (0.28, 1.03)
1.54 (0.41, 5.60)	Durvalumab	2.39 (0.60, 9.50)	5.14 (1.09, 23.77)	3.29 (0.90, 15.40)	1.61 (0.44, 6.02)	0.82 (0.27, 2.53)
0.64 (0.23, 1.79)	0.42 (0.11, 1.66)	Nivolumab	2.15 (0.76, 6.19)	1.37 (0.48, 4.98)	0.67 (0.24, 1.95)	0.34 (0.15, 0.78)
0.30 (0.08, 1.01)	0.19 (0.04, 0.92)	0.47 (0.16, 1.31)	Nivolumab + Ipilimumab	0.64 (0.19, 2.80)	0.31 (0.09, 1.11)	0.16 (0.06, 0.46)
0.47 (0.14, 1.23)	0.30 (0.06, 1.12)	0.73 (0.20, 2.09)	1.57 (0.36, 5.40)	Pembrolizumab	0.49 (0.15, 1.35)	0.25 (0.09, 0.53)
0.95 (0.37, 2.39)	0.62 (0.17, 2.26)	1.48 (0.51, 4.20)	3.20 (0.90, 11.05)	2.04 (0.74, 6.88)	Pembrolizumab+Platinum	0.51 (0.25, 0.99)
1.86 (0.97, 3.62)	1.21 (0.40, 3.72)	2.91 (1.29, 6.55)	6.27 (2.20, 18.15)	4.00 (1.90, 10.78)	1.97 (1.01, 3.96)	Platinum

B

Atezolizumab+Platinum	0.89 (0.31, 2.26)	0.44 (0.19, 0.93)	0.63 (0.25, 1.55)	0.40 (0.18, 0.88)	1.22 (0.58, 2.49)	0.71 (0.40, 1.15)
1.12 (0.44, 3.21)	Durvalumab	0.49 (0.18, 1.37)	0.70 (0.25, 2.21)	0.45 (0.17, 1.30)	1.36 (0.54, 3.80)	0.80 (0.36, 1.87)
2.29 (1.07, 5.25)	2.04 (0.73, 5.46)	Nivolumab	1.42 (0.68, 3.21)	0.92 (0.42, 2.20)	2.75 (1.32, 6.17)	1.63 (0.91, 2.93)
1.60 (0.65, 3.95)	1.42 (0.45, 4.02)	0.71 (0.31, 1.46)	Nivolumab + Ipilimumab	0.64 (0.25, 1.68)	1.91 (0.80, 4.68)	1.14 (0.53, 2.30)
2.53 (1.14, 5.47)	2.25 (0.77, 5.77)	1.09 (0.45, 2.40)	1.56 (0.60, 3.96)	Pembrolizumab	3.02 (1.38, 6.57)	1.77 (0.95, 3.09)
0.82 (0.40, 1.71)	0.73 (0.26, 1.84)	0.36 (0.16, 0.76)	0.52 (0.21, 1.26)	0.33 (0.15, 0.72)	Pembrolizumab+Platinum	0.59 (0.34, 0.95)
1.41 (0.87, 2.47)	1.25 (0.53, 2.77)	0.61 (0.34, 1.10)	0.88 (0.43, 1.90)	0.57 (0.32, 1.05)	1.69 (1.05, 2.90)	Platinum

C

Atezolizumab+Platinum	1.12 (0.02, 67.61)	1.41 (0.06, 70.63)	5.39 (0.14, 796.37)	0.85 (0.03, 19.70)	0.43 (0.02, 7.44)	0.10 (0.01, 0.71)
0.89 (0.01, 65.68)	Durvalumab	1.26 (0.02, 208.47)	4.78 (0.06, 2043.79)	0.74 (0.01, 61.35)	0.38 (0.01, 23.13)	0.09 (0.00, 3.11)
0.71 (0.01, 16.28)	0.79 (0.00, 47.20)	Nivolumab	3.84 (0.19, 141.79)	0.60 (0.01, 15.93)	0.31 (0.01, 6.44)	0.07 (0.00, 0.69)
0.19 (0.00, 6.96)	0.21 (0.00, 17.99)	0.26 (0.01, 5.17)	Nivolumab + Ipilimumab	0.16 (0.00, 6.58)	0.08 (0.001, 2.58)	0.02 (0.00, 0.33)
1.18 (0.05, 37.96)	1.35 (0.02, 105.26)	1.65 (0.06, 127.70)	6.32 (0.15, 1467.35)	Pembrolizumab	0.52 (0.02, 12.18)	0.12 (0.01, 1.41)
2.30 (0.13, 51.29)	2.62 (0.04, 152.90)	3.24 (0.16, 176.01)	12.45 (0.39, 2137.95)	1.92 (0.08, 48.12)	Pembrolizumab+Platinum	0.22 (0.03, 1.75)
10.23 (1.40, 106.41)	11.57 (0.32, 477.50)	14.50 (1.45, 436.81)	55.39 (2.99, 6153.36)	8.68 (0.71, 107.58)	4.47 (0.57, 33.34)	Platinum

D

Atezolizumab	3.42 (0.34, 39.76)	1.83 (0.11, 33.46)	1.88 (0.11, 36.09)	5.80 (0.56, 92.10)	4.37 (0.43, 64.22)	1.37 (0.18, 10.80)
0.29 (0.03, 2.94)	Atezolizumab+Platinum	0.54 (0.05, 5.56)	0.55 (0.05, 5.76)	1.68 (0.29, 12.74)	1.27 (0.22, 9.67)	0.40 (0.11, 1.24)
0.55 (0.03, 9.22)	1.84 (0.18, 20.45)	Durvalumab	1.02 (0.06, 17.66)	3.06 (0.31, 47.88)	2.35 (0.23, 34.86)	0.74 (0.10, 5.67)
0.53 (0.03, 9.30)	1.82 (0.17, 20.05)	0.98 (0.06, 17.40)	Nivolumab	3.07 (0.29, 43.74)	2.30 (0.23, 32.99)	0.73 (0.09, 5.65)
0.17 (0.01, 1.77)	0.60 (0.08, 3.49)	0.33 (0.02, 3.19)	0.33 (0.02, 3.46)	Pembrolizumab	0.75 (0.09, 5.97)	0.24 (0.05, 0.86)
0.23 (0.02, 2.33)	0.79 (0.10, 4.59)	0.43 (0.03, 4.35)	0.43 (0.03, 4.33)	1.33 (0.17, 10.53)	Pembrolizumab+Platinum	0.32 (0.06, 1.07)
0.73 (0.09, 5.57)	2.49 (0.80, 8.78)	1.35 (0.18, 10.17)	1.37 (0.18, 10.78)	4.20 (1.16, 22.04)	3.16 (0.93, 15.93)	Platinum

E

Atezolizumab+Platinum	0.41 (0.10, 1.40)	0.91 (0.23, 3.11)	0.44 (0.15, 1.16)	1.11 (0.40, 2.78)	0.50 (0.23, 0.93)
2.45 (0.72, 9.55)	Durvalumab	2.26 (0.47, 10.18)	1.09 (0.29, 4.35)	2.70 (0.76, 9.96)	1.22 (0.41, 3.66)
1.09 (0.32, 4.36)	0.44 (0.10, 2.13)	Nivolumab	0.49 (0.13, 1.85)	1.22 (0.35, 4.42)	0.55 (0.18, 1.64)
2.25 (0.86, 6.61)	0.92 (0.23, 3.42)	2.03 (0.54, 7.58)	Pembrolizumab	2.51 (0.91, 7.01)	1.11 (0.51, 2.38)
0.90 (0.36, 2.52)	0.37 (0.10, 1.31)	0.82 (0.23, 2.84)	0.40 (0.14, 1.10)	Pembrolizumab+Platinum	0.45 (0.23, 0.85)
2.02 (1.07, 4.43)	0.82 (0.27, 2.46)	1.82 (0.61, 5.42)	0.90 (0.42, 1.95)	2.24 (1.18, 4.38)	Platinum

Figure 4

Pooled estimates of the network meta-analysis. (A) Multiple treatment comparison for dermatologic irAEs based on network consistency. (B) Multiple treatment comparison for gastrointestinal irAEs based on network consistency model. (C) Multiple treatment comparison for endocrine irAEs based on network consistency model. (D) Multiple treatment comparison for pneumonitis based on network consistency model. (E) Multiple treatment comparison for liver irAEs based on network consistency model. (OR=1 means the treatment in top left is worse; Platinum=Platinum based chemotherapy).

Figure 5

Sequence diagram of the network meta-analysis. (A) Multiple treatment comparison for dermatologic irAEs based on Rank Probability.(B) Multiple treatment comparison for gastrointestinal irAEs based on Rank Probability.(C) Multiple treatment comparison for endocrine irAEs based on Rank Probability. (D) Multiple treatment comparison for pneumonitis based on Rank Probability. (E) Multiple treatment comparison for liver irAEs based on Rank Probability.(Platinum=Platinum based chemotherapy).

Figure 6

Funnel plot of (A)dermatologic irAEs, (B)gastrointestinal irAEs, (C)endocrine irAEs, (D)pneumonitis and (E)liver irAEs in the network meta-analysis.(Platinum=Platinum based chemotherapy).

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