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Symptom Management and Supportive Care

Safety and Tolerability of PD-1/PD-L1 Inhibitors Compared with Chemotherapy in Patients with Advanced Cancer: A Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Chemotherapy • PD-1/PD-L1 inhibitor • Meta-analysis • Systematic review • Toxicity

Abstract

Background. Compared with chemotherapy, significant improvement in survival outcomes with the programmed death receptor-1 (PD-1) inhibitors nivolumab and pembrolizumab and the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab has been shown in several types of advanced solid tumors. We conducted a systematic review and meta-analysis to compare safety and tolerability between PD-1/PD-L1 inhibitors and chemotherapy.

Methods. PubMed and American Society of Clinical Oncology (ASCO) databases were searched 1966 to September 2016. Eligible studies included randomized controlled trials (RCTs) comparing single-agent U.S. Food and Drug Administration–approved PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, or atezolizumab) with chemotherapy in cancer patients reporting any all-grade (1–4) or high-grade (3–4) adverse events (AEs), all- or high-grade treatment-related symptoms, hematologic toxicities and immune-related AEs, treatment discontinuation due to toxicities, or treatment-related deaths. The summary incidence, relative risk, and 95% confidence intervals were calculated.

Results. A total of 3,450 patients from 7 RCTs were included in the meta-analysis: 4 nivolumab, 2 pembrolizumab, and 1 atezolizumab trials. The underlying malignancies included were non-small cell lung cancer (4 trials) and melanoma (3 trials). Compared with chemotherapy, the PD-1/PD-L1 inhibitors had a significantly lower risk of all- and high-grade fatigue, sensory neuropathy, diarrhea and hematologic toxicities, all-grade anorexia, nausea, and constipation, any all- and high-grade AEs, and treatment discontinuation. There was an increased risk of all-grade rash, pruritus, colitis, aminotransferase elevations, hypothyroidism, and hyperthyroidism, and all- and high-grade pneumonitis with PD1/PD-L1 inhibitors.

Conclusion. PD-1/PD-L1 inhibitors are overall better tolerated than chemotherapy. Our results provide further evidence supporting the favorable risk/benefit ratio for PD-1/PD-L1 inhibitors. ***The Oncologist*** 2017;22:470–479

Implications for Practice: We conducted a systematic review and meta-analysis to compare summary toxicity endpoints and clinically relevant adverse events between programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors and chemotherapy. PD1/PD-L1 inhibitors were associated with a lower risk of treatment-related symptoms (fatigue, anorexia, nausea, diarrhea, constipation, and sensory neuropathy) but a higher risk of immune-related adverse events (AEs). Summary toxicity endpoints favor PD1/PD-L1 inhibitors (any all- and high-grade AEs and treatment discontinuation). PD1/PD-L1 inhibitors are overall better tolerated than chemotherapy. In addition to efficacy data from trials, our findings provide useful information for clinicians for well-balanced discussions with their patients on the risks and benefits of treatment options for advanced cancer.

Introduction

The development of immune checkpoint inhibitors (ICIs) represents a major breakthrough in cancer therapy. ICIs enhance antitumor immune responses by releasing the "brakes" on the immune system [1]. They are designed to block immunosuppressive receptors expressed on the surface of T lymphocytes such as cytotoxic T-lymphocyte–associated antigen 4, programmed death receptor-1 (PD-1), and the programmed death-ligand 1 (PD-L1) expressed on tumor cells and tumor-infiltrating immune cells [2]. ICIs targeting the PD-1/PD-L1 pathway have shown especially significant improvement in progression-free survival and overall survival (OS) compared with standard care in different advanced solid tumors [3–9]. Their superior efficacy led to U.S. Food and Drug Administration (FDA) approval of PD-1 inhibitors, nivolumab, and pembrolizumab for the treatment of unresectable or metastatic melanoma and advanced non-small cell lung cancer (NSCLC)

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in the second-line setting [10, 11]. Nivolumab is also approved for patients with metastatic renal cell carcinoma following prior treatment with an anti-angiogenic therapy [10]. Recently, the FDA approved the PD-L1 inhibitor atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma after prior platinum-based chemotherapy [12]. Based on the remarkable durable responses in single-arm trials, the FDA approved nivolumab for relapsed or refractory Hodgkin's lymphoma and pembrolizumab for recurrent or metastatic head and neck squamous cell carcinoma [10, 11]. The indications for these agents are expected to continue expanding as they are studied in different treatment settings, including first-line therapy for advanced disease and a wide variety of other malignancies [13].

Treatment decision-making for patients with advanced cancer is a major challenge for oncologists. The goals of therapy are often palliative: prolongation of survival, control of symptoms, and maintenance or improvement of quality of life. In order to attain these goals, it is essential to have a balanced discussion of treatment options that focuses on the benefits and risks of each treatment, taking into account patient preferences and values. Currently, both novel immunotherapy agents and traditional cytotoxic chemotherapy are approved treatment options for advanced cancer. In addition to efficacy data derived from trials of impact on survival outcomes, a comprehensive understanding of the toxicity profile of immunotherapy compared chemotherapy is needed for informed treatment decisions. Inhibition of the immune checkpoints can lead to immune dysregulation that clinically manifests with symptoms similar to autoimmune disease. These side effects are termed immune-related adverse events (AEs) and include dermatologic, gastrointestinal, hepatic, endocrine, and pulmonary events [14]. In addition to these unique AEs, classical chemotherapy toxicities, such as fatigue, anorexia, nausea, and diarrhea, have also been seen in patients treated with the PD-1/PD-L1 inhibitors [3–9]. These treatment-related symptoms are important, as they affect patients' quality of life [15, 16]. However, to date, there has been no systematic comparison of tolerability between PD-1/PD-L1 inhibitors and chemotherapy. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare summary toxicity endpoints and clinically relevant AEs between PD-1/PD-L1 inhibitors and chemotherapy.

Materials and Methods

Data Source

This analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses statement [17]. Two authors (TFN and SSS) conducted independent reviews of PubMed from January 1966 to September 30, 2016. Search terms included "nivolumab," "pembrolizumab," and "atezolizumab." The search was limited to clinical trials. We also searched abstracts and virtual meeting presentations utilizing the same search terms from the American Society of Clinical Oncology (ASCO) conferences held through September 2016 to identify relevant studies. Independent searches of the Web of Science, Embase, and Cochrane electronic databases were also performed. In instances of duplicate publications, only the most complete, recent, and up-to-date report of the study was included.

Study Selection

Clinical trials that met the following criteria were included: (a) phase II and III trials in patients with cancer; (b) random assignment of participants to treatment with single-agent PD-1/PD-L1 inhibitor or chemotherapy; and (c) reporting of events or event rate and sample size for any all-grade (1–4) or high-grade (3–4) AEs, individual all- or high-grade AEs, treatment discontinuation for AEs, or treatment-related deaths. For the individual AEs, we included immune-related AEs (rash, pruritus, colitis, hypothyroidism, hyperthyroidism, hypophysitis, hepatitis, and pneumonitis), hematologic toxicities (neutropenia, anemia, and thrombocytopenia), and the core set of 12 clinically relevant symptoms recommended for assessment in clinical trials by the National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee [18]. These 12 symptoms are fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems, anxiety, nausea, depression, sensory neuropathy, constipation, and diarrhea. Reviewers (TFN and SSS) independently screened reports that included the key terms by their titles and abstracts for relevance. Then, full texts of relevant articles were retrieved to assess eligibility. The references of relevant reports were also reviewed manually to identify additional studies.

Data Extraction

Two investigators (TFN and SSS) independently performed data extraction. Any discrepancies between reviewers were resolved by consensus. The following information was recorded for each study: first author's name, year of publication, trial phase, masking, underlying malignancy, treatment arms, number of patients available for analysis, age, follow-up duration, Common Terminology Criteria for AEs (CTCAE), any all- or high-grade AEs, individual all- or high-grade AEs (fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems, anxiety, nausea, depression, sensory neuropathy, constipation, diarrhea, neutropenia, thrombocytopenia, anemia, rash, pruritus, colitis, hypothyroidism, hyperthyroidism, hypophysitis, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations, and pneumonitis), treatment discontinuation for AEs, and treatment-related deaths. AEs were recorded according to the CTCAE. The quality of trials was rated using the five-point Jadad scale, which is based on the reporting of randomization method, blinding method, withdrawals, and dropouts [19].

Statistical Analysis

The primary objective of this study was to compare toxicity between PD-1/PD-L1 inhibitors and chemotherapy. The relative risk (RR), corresponding 95% confidence intervals (CIs), and incidence of toxicity outcomes were calculated. We calculated the RRs and CIs with data extracted from RCTs and assessed the incidence of toxicity events in patients assigned to PD-1/PD-L1 inhibitors compared with chemotherapy in the same trial. To calculate the 95% CIs, the variance of the log-transformed study-specific RR was derived using the delta method. For studies reporting zero AEs in any arm, we applied a classic half-integer continuity correction to calculate the RR and variance. For the calculation of RRs, we used random- or fixed-effects models depending on the heterogeneity of

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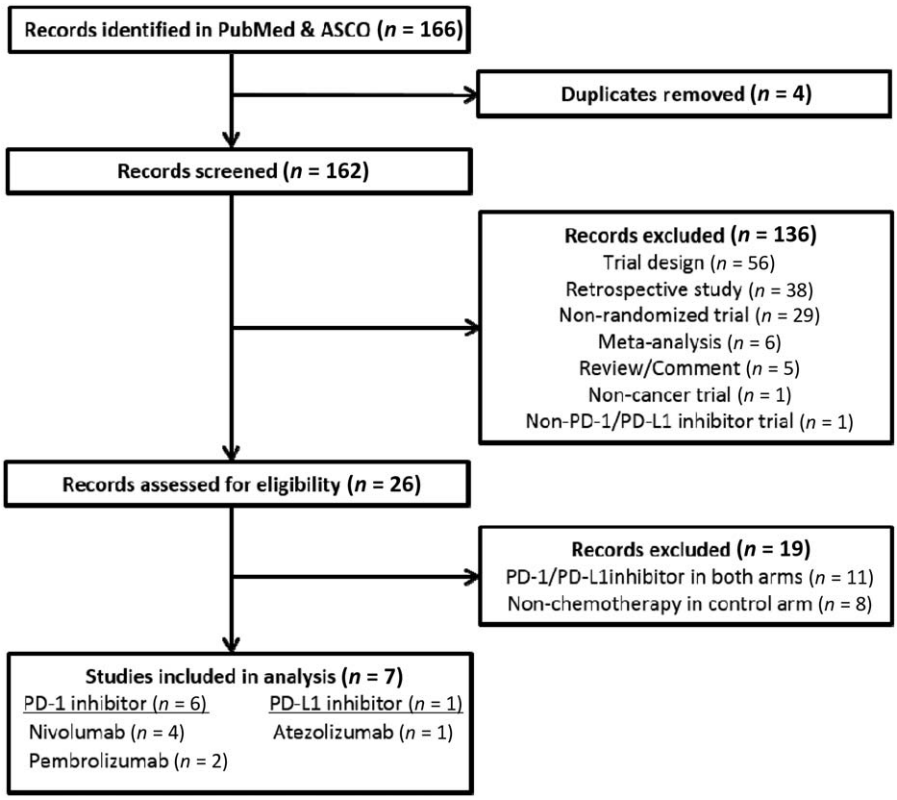

Figure 1. Flow diagram: selection process for the studies.
Abbreviations: ASCO, American Society of Clinical Oncology; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1.

included studies. Statistical heterogeneity in results between studies included in the meta-analysis was examined using Cochrane's Q statistic, and inconsistency was quantified with I^2 statistic (100% × (Q − df)/Q) [20]. The assumption of homogeneity was considered invalid for *p* values less than .10. Summary RRs were calculated using random- or fixed-effects models depending on the heterogeneity of included studies. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported by using the inverse variance method. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported by using the DerSimonian and Laird method, which considers both within-study and between-study variations [21]. For the calculation of incidence, the proportion of patients with adverse outcomes and 95% CIs was derived from each trial. We used a random-effects model to produce a pooled overall estimate for incidence of adverse outcomes. We evaluated publication bias using funnel plots and the Begg and Egger tests [22, 23]. A two-tailed *p* value of less than .05 was considered statistically significant. Statistical analyses were performed using the comprehensive meta-analysis program (Version 2, Biostat, Englewood, NJ, USA).

Results

Search Results and Patient Characteristics

Our search strategy yielded 166 potentially relevant records in the PubMed and ASCO databases, of which 159 publications were excluded. Our selection process and reasons for study exclusion are shown in Figure 1. A total of four phase III, one phase II/III, and two phase II randomized clinical trials were considered eligible for the meta-analysis. A total of 3,450 patients (PD-1/PD-L1 inhibitors: 2,090; chemotherapy: 1,360) were included in the analysis from four nivolumab trials, two pembrolizumab trials, and one atezolizumab trial. The underlying malignancies were NSCLC (4 trials) and melanoma (3 trials). The baseline characteristics in each trial are presented in Table 1.

Comparison of Toxicity Profiles

Summary Toxicity Endpoints

The incidence of any all-grade (67.6% versus 82.9%) or high-grade (11.4% versus 35.7%) AEs was lower in PD-1/PD-L1 inhibitors compared with chemotherapy (Table 2). PD-1/PD-L1 inhibitors also had significantly lower risk of any all-grade (RR 0.82; $p < .001$) and high-grade AEs (RR 0.32; $p < .001$; Fig. 2). Patients treated with PD-1/PD-L1 inhibitors stopped therapy for toxicity less frequently than those treated with chemotherapy (4.5% versus 11.1%); the RR of treatment discontinuation due to AEs was 0.44 ($p < .001$). Deaths attributed to study treatment occurred in 7 patients in the PD-1/PD-L1 inhibitor group and 11 patients in the chemotherapy group. There was no significant difference in the incidence of treatment-related deaths between the two groups. The random-effects model was used for the RR analysis of any all- and high-grade AEs because there was significant heterogeneity among the studies. The test for heterogeneity was not significant for treatment discontinuation and treatment-related deaths. Therefore, the

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Table 1. Characteristics of the studies included in the meta-analysis

Author, year [reference]	Phase	Masking	Histology	Treatment arms	No. of patients foranalysis	Age in years (median)	Follow-up (months)	CTCAE version	Jadad score
Robert, 2014 [3]	III	Double-blind	Melanoma	Nivolumab 3 mg/kg q2 weeks + Placebo	210	64 (18–86)	16.7	4	5
				Dacarbazine 1,000 mg/m^2 q3 weeks + Placebo	208	66 (26–87)			
Weber, 2014 [4]	III	Open-label	Melanoma	Nivolumab 3 mg/kg q2 weeks	268	59 (23–88)	8.4	4	3
				Investigator-choice chemotherapy[a]	102	62 (29–85)			
Brahmer, 2015 [5]	III	Open-Label	Squamous NSCLC	Nivolumab 3 mg/kg q2 weeks	135	62 (39–85)	11	4	3
				Docetaxel 75 mg/m^2 q3 weeks	137	64 (42–84)			
Ribas, 2015 [6]	II	Open-Label	Melanoma	Pembrolizumab 2 mg/kg q3 weeks	180	62 (15–87)	10	4	3
				Pembrolizumab 10 mg/kg q3 weeks	181	60 (27–89)			
				Investigator-choice chemotherapy[b]	179	63 (27–87)			
Borghaei, 2015 [7]	III	Open-Label	Nonsquamous NSCLC	Nivolumab 3 mg/kg q2 weeks	292	61 (37–84)	17.2	4	3
				Docetaxel 75 mg/m^2 q3 weeks	290	64 (21–85)			
Herbst, 2016 [8]	II/III	Open-Label	NSCLC	Pembrolizumab 2 mg/kg q3 weeks	339	63 (56–69)	13.1	4	3
				Pembrolizumab 10 mg/kg q3 weeks	343	63 (56–69)			
				Docetaxel 75 mg/m^2 q3 weeks	309	62 (56–69)			
Fehrenbacher, 2016 [9]	II	Open-Label	NSCLC	Atezolizumab 1,200 mg q3 weeks	142	62 (42–82)	14.8	4	3
				Docetaxel 75 mg/m^2 q3 weeks	135	62 (36–84)			

[a]Dacarbazine, or paclitaxel plus carboplatin.
[b]Paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; q, every.

fixed-effects model was used for these RR analyses. The RR and incidence for each AE are summarized in Table 2.

Clinically Relevant Treatment-Related Symptoms

Of the core set of 12 clinically relevant symptoms, fatigue, anorexia, nausea, constipation, diarrhea, and pain were reported in all 7 trials. The overall incidence of all-grade or high-grade pain in the trials could not be obtained because only incidences of pain in specific sites were reported. Data for sensory neuropathy were available from six trials, and data for insomnia and dyspnea were available from three trials. Only one trial reported anxiety, and no trial reported cognitive problems or depression. Based on the availability of data, summary incidence and RR were calculated for the following eight symptoms: fatigue, anorexia, nausea, constipation, diarrhea, sensory neuropathy, insomnia, and dyspnea. PD-1/PD-L1 inhibitors were associated with a significantly lower risk for six of the eight evaluated all-grade AEs when compared with chemotherapy (Table 3): fatigue (19.1% versus 27.7%; RR 0.69), anorexia (10.2% versus 15.8%; RR 0.65), nausea (11.5% versus 28.4%; RR 0.41), constipation (5.2% versus 9.9%; RR 0.57), diarrhea (10.2% versus 17.3%; RR 0.61), and sensory neuropathy (1.2% versus 8.6%; RR 0.16). The risk of three high-grade AEs was significantly lower in the PD-1/PD-L1 inhibitor group compared with the chemotherapy group: fatigue (0.7% versus 4.0%; RR 0.19), sensory neuropathy (0.3% versus 1.1%; RR 0.20), and diarrhea (0.6% versus 1.9%; RR 0.30). We found no statistically significant differences between the groups for all-grade insomnia, dyspnea, high-grade anorexia, nausea, constipation, insomnia, or dyspnea.

Hematologic Toxicities

Patients treated with PD-1/PD-L1 inhibitors had a significantly lower risk of all-grade neutropenia (0.5% versus 16.1%; RR 0.04), anemia (3.4% versus 16.2%; RR 0.22), and thrombocytopenia (0.6% versus 7.0%; RR 0.11). A risk of high-grade neutropenia, anemia, and thrombocytopenia was also statistically significant lower in the PD-1/PD-L1 inhibitor group compared with the chemotherapy group (Table 3).

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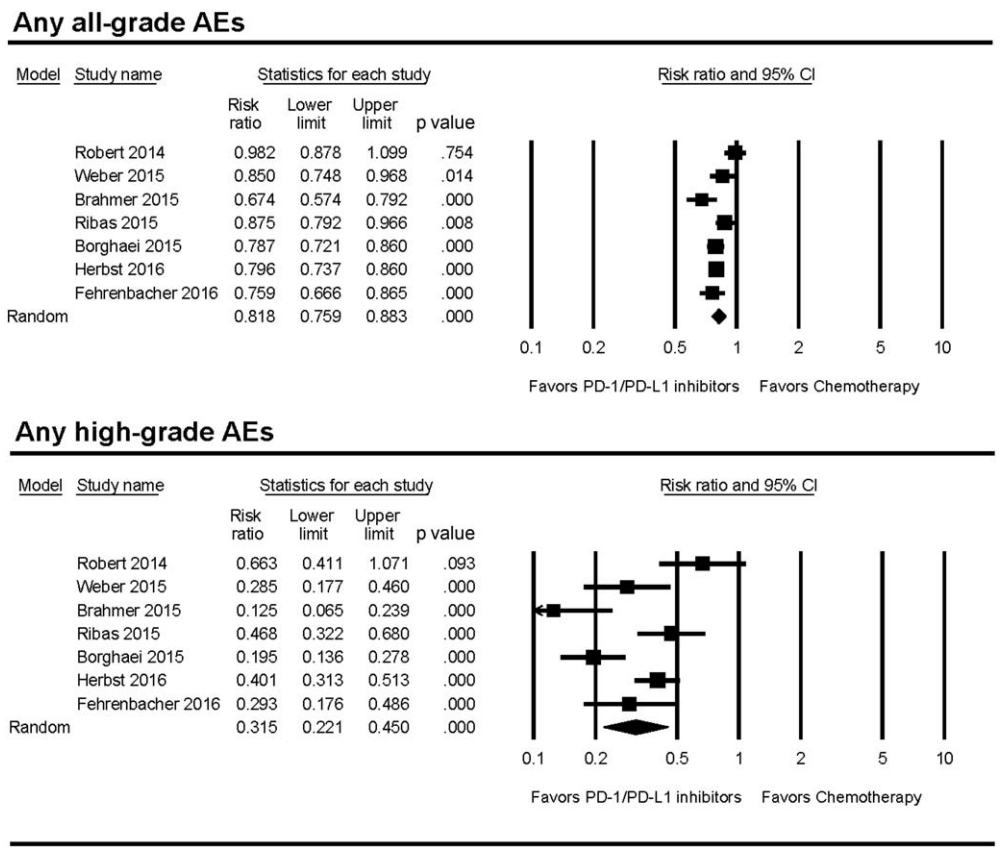

Figure 2. Forest plots of relative risk of any all- and high-grade AEs associated with PD-1/PD-L1 inhibitors versus chemotherapy.
Abbreviations: AE, adverse event; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1.

Table 2. Incidence and RR of summary toxicity endpoints, including 95% CI and number of trials in each analysis

Summary AE endpoints	No. of trials	PD-1/PD-L1 inhibitor incidence % (95% CI)	Chemotherapy incidence % (95% CI)	RR (95% CI)	*p* value
Any all-grade AEs	7	67.6 (64.2–70.8)	82.9 (78.9–86.2)	0.82 (0.76–0.88)	<.001
Any high-grade AEs	7	11.4 (9.9–13.1)	35.7 (26.0–46.8)	0.32 (0.22–0.45)	<.001
Treatment discontinuation	7	4.5 (3.5–5.7)	11.1 (8.5–14.3)	0.44 (0.33–0.57)	<.001
Treatment-related deaths	3	0.6 (0.3–1.1)	1.4 (0.7–2.5)	0.42 (0.16–1.13)	.09

Abbreviations: AE, adverse event; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; RR, relative risk.

Immune-Related AEs

PD-1/PD-L1 inhibitors were associated with a significantly higher risk for all-grade immune-related AEs, including dermatologic (rash and pruritus), gastrointestinal (colitis), hepatic (AST/ALT elevations), endocrine (hypothyroidism and hyperthyroidism), and pulmonary (pneumonitis) events. There was also a small but statistically significant increase in the risk of high-grade pneumonitis with PD-1/PD-L1 inhibitors compared with chemotherapy (1.3% versus 0.6%; RR 3.21).

Exploratory Subgroup Analysis

To investigate possible reasons for heterogeneity, we did subgroup analyses with regard to the RRs by type of chemotherapy regimen (docetaxel versus others) and type of tumor (NSCLC versus melanoma). As all NSCLC trials used docetaxel and all melanoma trials used non-docetaxel regimens in the chemotherapy arms, the same results were obtained from the subgroup analyses according to chemotherapy type and tumor type. Using Q statistics, there were significant differences in the risk of all-grade fatigue, anorexia, and diarrhea, all- and high-grade nausea, and any all-grade AEs between these subgroups. Otherwise, a similar toxicity profile in comparison with PD-1/PD-L1 inhibitors was observed in both chemotherapy subgroups. The exploratory subgroup analyses are summarized in Table 4.

Study Quality and Publication Bias

Six trials were open label, whereas one trial was double blind placebo controlled. The Jadad score ranged from 3 to 5 with a mean was 3.3, indicating that overall study quality was fair

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Table 3. Incidence and RR of individual AEs, including 95% CI and number of trials in each analysis

	No. of trials	PD-1/PD-L1 inhibitor incidence % (95%CI)	Chemotherapy incidence % (95%CI)	RR	*p* value		No. of trials	PD-1/PD-L1 inhibitor incidence % (95%CI)	Chemotherapy incidence % (95% CI)	RR (95% CI)	*p* value
All-grade treatment-related symptoms						High-grade treatment-related symptoms					
Fatigue	7	19.1 (15.6–23.2)	27.7 (22.9–33.1)	0.69 (0.55–0.86)	.001	Fatigue	6	0.7 (0.4–1.3)	4.0 (2.5–6.5)	0.19 (0.10–0.37)	<.001
Anorexia	7	10.2 (5.9–16.8)	15.8 (13.3–18.6)	0.65 (0.43–0.96)	.032	Anorexia	5	0.6 (0.3–1.1)	0.8 (0.4–1.5)	0.81 (0.28–2.30)	.692
Nausea	7	11.5 (8.5–15.3)	28.4 (21.6–36.3)	0.41 (0.30–0.57)	<.001	Nausea	6	0.4 (0.2–0.9)	1.2 (0.7–2.2)	0.46 (0.17–1.27)	.134
Diarrhea	7	10.2 (7.6–13.5)	17.3 (13.1–22.6)	0.61 (0.40–0.91)	.016	Diarrhea	7	0.6 (0.3–1.0)	1.9 (1.3–2.9)	0.30 (0.14–0.65)	.002
Constipation	7	5.2 (2.2–11.6)	9.9 (6.9–14.0)	0.57 (0.33–0.97)	.040	Constipation	2	0.3 (0.1–0.8)	0.5 (0.2–1.2)	0.54 (0.10–2.87)	.473
Sensory neuropathy	6	1.2 (0.6–2.3)	8.6 (6.5–11.3)	0.16 (0.10–0.26)	<.001	Sensory neuropathy	5	0.3 (0.1–0.7)	1.1 (0.6–2.0)	0.20 (0.05–0.77)	.019
Insomnia	3	4.7 (1.2–15.9)	5.4 (2.4–11.6)	0.98 (0.65–1.49)	.928	Insomnia	2	0.4 (0.1–1.3)	0.5 (0.1–2.6)	0.94 (0.11–8.01)	.955
Dyspnea	3	13.1 (3.8–36.6)	13.3 (5.2–30.0)	1.02 (0.80–1.29)	.888	Dyspnea	3	2.9 (0.9–9.5)	2.2 (1.0–4.6)	1.36 (0.45–4.13)	.588
All-grade hematologic AEs						High-grade hematologic AEs					
Neutropenia	7	0.5 (0.3–1.0)	16.1 (10.2–24.6)	0.04 (0.02–0.08)	<.001	Neutropenia	7	0.2 (0.1–0.6)	12.3 (7.1–20.5)	0.02 (0.01–0.05)	<.001
Anemia	6	3.4 (2.7–4.4)	16.2 (11.5–22.2)	0.22 (0.12–0.43)	<.001	Anemia	5	0.5 (0.3–1.0)	3.0 (1.8–5.0)	0.18 (0.08–0.38)	<.001
Thrombocytopenia	4	0.6 (0.3–1.2)	7.0 (3.9–12.3)	0.11 (0.05–0.24)	<.001	Thrombocytopenia	4	0.2 (0.1–0.7)	3.4 (1.7–6.7)	0.10 (0.03–0.33)	<.001
All-grade immune-related Aes						High-grade immune-related AEs					
Rash	6	10.3 (8.4–12.7)	4.3 (3.2–5.6)	2.32 (1.47–3.66)	<.001	Rash	5	0.4 (0.2–0.8)	0.6 (0.2–1.6)	1.30 (0.32–5.25)	.71
Pruritus	6	11.6 (7.3–17.7)	2.3 (1.2–4.4)	4.76 (3.20–7.10)	<.001	Pruritus	2	0.2 (0.1–0.6)	0.3 (0.1–0.9)	0.67 (0.07–6.45)	.73
Colitis	6	1.0 (0.6–1.6)	0.3 (0.1–0.9)	3.51 (1.12–10.98)	.03	Colitis	6	0.6 (0.3–1.1)	0.3 (0.1–0.9)	2.18 (0.66–7.25)	.2
Hypothyroidism	7	6.5 (5.4–7.9)	0.4 (0.2–1.0)	15.05 (6.14–36.90)	<.001	Hypothyroidism	1	—	—	—	—
Hyperthyroidism	5	2.8 (1.8–4.4)	0.7 (0.3–1.5)	5.13 (2.14–12.30)	<.001	Hyperthyroidism	1	—	—	—	—
Hypophysitis	3	0.4 (0.2–1.0)	0.2 (0.0–1.1)	2.52 (0.42–14.95)	.31	Hypophysitis	3	0.2 (0.1–0.7)	0.3 (0.1–0.8)	2.14 (0.35–13.11)	.41
AST elevation	5	2.7 (1.9–3.9)	1.3 (0.7–2.3)	2.02 (1.01–4.03)	.047	AST elevation	5	0.4 (0.2–0.8)	0.4 (0.1–1.2)	1.18 (0.32–4.33)	.80
ALT elevation	5	3.0 (2.2–4.0)	1.3 (0.8–2.2)	2.08 (1.10–3.95)	.02	ALT elevation	5	0.6 (0.3–1.1)	0.4 (0.2–1.2)	1.19 (0.30–4.68)	.80
Pneumonitis	7	3.4 (2.0–5.5)	1.1 (0.5–2.4)	3.41 (1.89–6.13)	<.001	Pneumonitis	5	1.3 (0.6–2.8)	0.6 (0.3–1.3)	3.21 (1.33–7.75)	.01

Abbreviations: —, no data; AE, adverse event; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; RR, relative risk.

Table 4. RR of toxicities according to chemotherapy type in control arm

	Docetaxel control arm		Non-docetaxel control arm				Docetaxel control arm		Non-docetaxel control arm		
	No. of trials	RR	No. of trials	RR	*p* value[a]		No. of trials	RR	No. of trials	RR	*p* value[a]
Summary AE endpoints						Summary AE endpoints					
Any all-grade AEs	4	0.77 (0.73–0.82)	3	0.90 (0.83–0.98)	.003	Any high-grade AEs	4	0.24 (0.15–0.40)	3	0.45 (0.29–0.70)	.070
Treatment discontinuation	4	0.32 (0.19–0.54)	3	0.60 (0.39–0.93)	.07	Treatment-related deaths	3	0.42 (0.16–1.13)	0	—	—
All-grade treatment-related symptoms						High-grade treatment-related symptoms					
Fatigue	4	0.55 (0.47–0.66)	3	0.92 (0.67–1.27)	.006	Fatigue	3	0.17 (0.08–0.37)	3	0.25 (0.08–0.77)	.57
Anorexia	4	0.83 (0.52–1.34)	3	0.43 (0.30–0.61)	.03	Anorexia	4	0.70 (0.23–2.13)	1	2.40 (0.12–49.77)	.45
Nausea	4	0.56 (0.44–0.72)	3	0.29 (0.20–0.42)	.005	Nausea	4	0.95 (0.28–3.25)	2	0.10 (0.02–0.60)	.04
Diarrhea	4	0.41 (0.31–0.53)	3	1.05 (0.76–1.44)	<.001	Diarrhea	4	0.24 (0.09–0.63)	3	0.45 (0.13–1.61)	.43
Constipation	4	0.69 (0.34–1.39)	3	0.45 (0.19–1.07)	.45	Constipation	1	0.93 (0.13–6.58)	1	0.13 (0.01–3.11)	.30
Sensory neuropathy	4	0.14 (0.06–0.34)	2	0.15 (0.04–0.51)	.95	Sensory neuropathy	4	0.24 (0.06–1.07)	1	0.10 (0.01–1.99)	.59
Insomnia	3	0.98 (0.65–1.49)	0	—	—	Insomnia	3	0.94 (0.11–8.01)	0	—	—
Dyspnea	3	1.02 (0.80–1.29)	0	—	—	Dyspnea	3	1.36 (0.45–4.13)	0	—	—
All-grade hematologic Aes						High-grade hematologic AEs					
Neutropenia	4	0.03 (0.01–0.09)	3	0.04 (0.01–0.21)	.73	Neutropenia	4	0.01 (0.003–0.04)	3	0.03 (0.01–0.15)	.37
Anemia	3	0.15 (0.06–0.34)	3	0.45 (0.12–1.72)	.16	Anemia	3	0.24 (0.09–0.69)	2	0.13 (0.04–0.38)	.39
Thrombocytopenia	1	0.26 (0.08–0.88)	3	0.06 (0.02–0.17)	.08	Thrombocytopenia	1	0.45 (0.03–7.22)	2	0.07 (0.02–0.26)	.23
All-grade immune-related AEs						High-grade immune-related AEs					
Rash	3	1.85 (0.84–4.06)	3	2.84 (1.60–5.05)	.38	Rash	3	1.04 (0.18–6.17)	2	1.85 (0.19–17.71)	.69
Pruritus	3	5.42 (2.78–10.55)	3	5.06 (2.26–11.32)	.90	Pruritus	1	0.15 (0.01–3.70)	1	2.99 (0.12–72.86)	.20
Colitis	3	4.44 (0.77–25.44)	3	2.95 (0.66–13.29)	.73	Colitis	3	3.28 (0.55–19.57)	3	1.56 (0.31–7.89)	.55
Hypothyroidism	4	20.72 (5.86–73.25)	3	10.87 (3.04–38.85)	.48	Hypothyroidism	1	—	0	—	—
Hyperthyroidism	2	5.22 (1.75–15.54)	3	4.97 (1.15–21.49)	.96	Hyperthyroidism	1	—	0	—	—
Hypophysitis	1	2.27 (0.11–47.13)	2	2.66 (0.30–24.00)	.93	Hypophysitis	1	2.27 (0.11–47.13)	2	2.07 (0.22–19.87)	.96
AST elevation	3	2.92 (1.21–7.08)	2	1.08 (0.27–4.40)	.24	AST elevation	3	1.30 (0.21–7.97)	2	1.06 (0.13–8.56)	.88
ALT elevation	3	2.37 (1.13–4.98)	2	1.43 (0.40–5.06)	.50	ALT elevation	3	0.74 (0.12–4.48)	2	1.96 (0.30–12.82)	.46
Pneumonitis	4	3.18 (1.70–5.94)	3	5.66 (1.06–30.28)	.53	Pneumonitis	4	3.30 (1.31–8.28)	1	2.40 (0.12–49.77)	.84

[a]*p* value for difference in RR.

Abbreviations: —, no data; AE, adverse event; CI, confidence interval; RR, relative risk.

(Table 1). For RR of all-grade constipation and pneumonitis and high-grade colitis, the Egger test suggested some evidence of publication bias. However, the Begg tests showed no evidence of bias ($p > .05$). This difference in the results obtained from the two methods may be due to a greater statistical power of the Egger test [24].

Discussion

We compared the tolerability of ICIs targeting PD1/PD-L1 pathway and standard-of-care chemotherapy in patients with advanced cancer by performing a meta-analysis of RCTs. PD1/PD-L1 inhibitors were associated with a lower risk of treatment-related symptoms (fatigue, anorexia, nausea, diarrhea, constipation, and sensory neuropathy) and hematologic toxicities. However, there was an increased risk of immune-related AEs, including dermatologic, gastrointestinal, hepatic, endocrine, and pulmonary events in patients treated with PD1/PD-L1 inhibitors. Most of these events were low-grade, but high-grade events were described, especially pneumonitis [25]. Clinicians need to be aware of the risk of these unique toxicities and manage them appropriately according to the algorithm for diagnosis and treatment adapted from guidelines used across anti-PD-1/PD-L1 trials [26].

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Our analysis of summary toxicity endpoints revealed a lower risk of any all- and high-grade AEs and treatment discontinuation in the PD1/PD-L1 inhibitor group. Importantly, absolute difference in risk and RR was more substantial for any high-grade AEs (11.4% versus 35.7%, RR 0.32) than for any all-grade AEs (67.6% versus 82.9%, RR 0.82), and this is related to the lower incidence of treatment discontinuation due to toxicities (4.5% versus 11.1%, RR 0.44) in the PD1/PD-L1 inhibitor group compared with the chemotherapy group. Overall, PD1/PD-L1 inhibitors in these clinical trials were better tolerated than chemotherapy.

CTCAE has been the standard method to evaluate toxicities and has been widely used in cancer clinical trials for more than 2 decades. AEs are graded based on the clinician's assessment of toxicity [27]. However, studies have shown that clinician-measured CTCAEs underestimated the incidence and/or severity of symptoms actually experienced by cancer patients [28]. Basch et al. longitudinally collected clinician, as compared with patient, adverse symptom reports from 163 patients with lung cancer receiving chemotherapy [29]. This study found that clinician CTCAE assessments are better in predicting unfavorable clinical events, such as death and emergency room admissions, but that patients generally reported symptoms earlier and more frequently that better reflected their daily health status. The authors concluded that clinician and patient-reported measures are complementary, each providing clinically meaningful information. Based on these findings, patient-reported outcomes (PRO) have been added to recent cancer clinical trials. The recent clinical trials of PD1/PD-L1 inhibitors have incorporated the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and other PRO measures [3–9]. Of the clinical trials included in our meta-analysis, two trials reported the results of PROs. In the clinical trial of pembrolizumab versus chemotherapy in advanced melanoma, EORTC QLQ-C30 data were collected at baseline and at week 12 [6]. A significant deterioration in the global health status quality-of-life score (10 points or more) was experienced by 7% to 12% fewer patients in the pembrolizumab group compared with the chemotherapy group. Patients treated with pembrolizumab had consistently smaller decrements in the symptoms scales for fatigue, nausea, anorexia, diarrhea, and constipation. Recently, Long et al. reported PRO outcomes in the trial of nivolumab versus dacarbazine in patients with advanced melanoma [30]. The EORTC QLQ-C30 was evaluated at baseline and every 6 weeks while on treatment. Compared with dacarbazine, patients treated with nivolumab maintained better global health longer (hazard ratio [HR] 0.65; 95% CI 0.46–0.92) and better physical function (HR 0.60; 95% CI 0.42–0.87). These results suggested that PD1 inhibitors were better tolerated than chemotherapy based on the patients' perspective and were consistent with the findings in our meta-analysis.

Based on the efficacy and favorable toxicity profile of ICIs, their utility in the treatment of older patients and patients with impaired functional status is of great interest. Our group performed a meta-analysis of nine RCTs comprising 5,265 patients to compare the efficacy of ICIs between younger and older patients. We showed that ICIs significantly improved OS compared with controls in both younger (HR 0.75; 95% CI 0.68–0.82) and older (HR 0.73; 95% CI 0.62–0.87) patients, using an older age cut-point of 65–70 years [31].

Recently, the FDA performed a pooled analysis of 1,030 patients from four registration trials of nivolumab for advanced cancer [32]. Toxicity was reported separately for three age groups ($<$65 years, 616 patients; 65 to $<$70 years, 414 patients; and $\geq$70 years, 212 patients). The incidence of any grade 1–2 and grade 3–4 toxicities were, respectively, $<$65 years: 39% and 44%; 65 to $<$70 years: 35% and 45%; $\geq$70 years: 37% and 46%. The frequency and severity of AEs were similar across the age groups in this retrospective analysis. To assess the efficacy and safety in more general patient population, a phase IV study of nivolumab was conducted in patients with advanced NSCLC [33]. This trial included 65 patients with performance status (PS) 2. Notably, there was no obvious difference in efficacy and toxicity outcomes between PS 2 patients and PS 0–1 patients. As PS is a crude measure of patients' functional status, further studies of PD1/PD-L1 inhibitors in older and/or frail patients using geriatric assessments are warranted to evaluate efficacy and safety as well as health-related quality-of-life outcomes.

Our study has some limitations. First, the results described here are affected by the limitations of individual clinical trials that were selected for this meta-analysis. As five of six included trials used an open-label design, these trials were liable to ascertainment bias. Second, this is a meta-analysis at the study level; therefore, variables at the patient level were not included

in the analysis. Thus, we could not establish risk factors associated with the development of toxicities. Third, the patients in studies selected for our meta-analysis were a select group of patients with good PS who were recruited into clinical trials conducted at academic centers. The actual incidence of toxicities in patients with organ dysfunction and/or an impaired functional status is likely to be higher in clinical practice. However, the patient selection into the trails in our study is unlikely to introduce bias into the RR analysis of the toxicities. Finally, significant heterogeneity was observed in the included studies for some of the planned RR analyses. We minimized heterogeneity influence by using the random-effects model and also performed exploratory subgroup analyses based on type of chemotherapy regimen (docetaxel versus others) and type of tumor (NSCLC versus melanoma). As there were differences in the risk of some individual AEs between the subgroups, the observed heterogeneity may be partially explained by the differences in these factors.

Conclusion

Our analysis suggests that PD1/PD-L1 inhibitors are better tolerated than standard-of-care chemotherapy in patients with advanced cancer. In addition to the efficacy results from trials, our findings provide useful information for clinicians for well-balanced discussions with their patients on the risks and benefits of treatment options for advanced cancer. Further research on this promising immunotherapeutic approach is needed to assess efficacy, toxicity, and PROs in older patients and patients with poorer health status who are generally not included in the clinical trials.

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Disclosures

The authors indicated no financial relationships.

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Implications for Practice:

The potential adverse events of immune checkpoint inhibitors differ from conventional chemotherapy and can require a multidisciplinary approach. Continued education is important for all physicians to ensure optimal care for patients.