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ORIGINAL RESEARCH

Incidence of fatigue associated with immune checkpoint inhibitors in patients with cancer: a meta-analysis

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Background: Fatigue is one of the most common adverse effects associated with cancer immunotherapy using checkpoint inhibitors (CPIs). Because treatment-related fatigue also frequently occurs in patients treated with non-immunological therapies, our study aimed to compare the incidence of fatigue in CPI-treated patients with that associated with non-immune therapies in randomised trials.

Methods: PubMed and ClinicalTrials.gov were searched for phase III studies using a CPI alone or in combination with chemotherapy or non-immunologic targeted therapy in the experimental arm and control arm using inactive therapies such as placebo or observation, chemotherapy, or non-immunologic targeted therapy. Adverse events listed in the full texts as well as those available from clinicaltrials.gov were reviewed for all identified studies.

Results: A total of 60 studies involving 41 435 patients were included in the analysis. All-grade fatigue was reported in 30.4% of patients [95% confidence interval (CI) 29.9% to 31.0%] in the immunotherapy arms of the analysed studies. Using anti-programmed cell death protein 1 agents as reference, the odds ratio (OR) for fatigue was significantly higher both for anti-cytotoxic T lymphocyte-associated antigen 4 agents (OR 1.46, 95% CI 1.04-2.04) and the combination of anti-cytotoxic T lymphocyte-associated antigen 4 and anti-programmed cell death protein agents (OR 1.43, 95% CI 1.12-1.83). Fatigue was significantly less likely to occur in patients treated with CPI compared with patients receiving chemotherapy (OR 0.79, 95% CI 0.73-0.85), but significantly was more common in patients receiving the combination of CPI/chemotherapy compared with patients receiving chemotherapy alone (OR 1.12, 95% CI 1.03-1.22).

Conclusions: Although immunotherapy using CPIs was associated with treatment-related fatigue, the occurrence of all-grade fatigue was significantly higher in patients treated with chemotherapy compared with patients receiving CPIs. The risk of fatigue was higher for CPI/chemotherapy combinations than for chemotherapy alone. These results suggest that although the effects of CPIs and chemotherapy are additive, chemotherapy was the dominant cause of treatment-related fatigue in the analysed trials.

Key words: checkpoint inhibitors, fatigue, meta-analysis, chemotherapy, immunotherapy, targeted therapy

INTRODUCTION

Checkpoint inhibitors (CPIs) targeting the programmed cell death protein 1(PD-1) receptor and its ligand programmed death-ligand 1 (PD-L1) and the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) receptor are used for a variety of cancers in monotherapy or in combinations. These immunotherapies have revolutionised the treatment of many types of solid and haematological malignancies over the past decade.

Fatigue is a syndrome characterised by diminished energy and/or increased need to rest disproportionate to activity level. It can also be accompanied by feelings of generalized weakness, diminished concentration, decreased interest in usual activities, sleep disturbances, emotional instability, and cognitive problems.[1]

Fatigue is the most common adverse event associated with CPI therapy.[2,3] Fatigue is also commonly associated with chemotherapy and persists for many months or years after its completion.[1,4] Targeted therapy, particularly oral tyrosine kinase inhibitors, is also significantly associated with fatigue that leads to treatment reduction in 10%-20% of patients.[5-7]

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The aim of the present meta-analysis was to carry out a systematic analysis of randomised clinical trials to compare the incidence of fatigue between patients with solid cancers treated with CPIs and those receiving other antineoplastic systemic therapies including chemotherapy and non-immunologic targeted therapies.

METHODS

Study selection

PubMed and clinicaltrials.gov were searched using terms 'cancer' and 'ipilimumab or MDX-010', 'nivolumab or MDX-1106', 'avelumab or MSB0010718C', 'durvalumab or MEDI-4736', 'pembrolizumab or MK-3475', 'atezolizumab or MPDL3280A', 'tremelimumab or CP-675,206', 'cemiplimab or REGN2810'. The database searches were run on 1 February 2021. The reference lists of retrieved records were scanned for relevant records. Other recent systematic analytical studies were also screened for possible reports missed by the above search.[8,9] The study selection process is shown in Figure 1. The search was limited to studies in English with tabulated adverse event data and to phase III studies per clinicaltrials.gov. Adverse events listed in the full texts as well as those available from clinicaltrials.gov were reviewed for all identified studies. The study was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[10]

Statistical analysis

For each selected toxicity, the percentages and confidence intervals (CIs) of patients with the relevant type of adverse events are reported within each study, and jointly according to the type of immunotherapy. As part of the study arm comparison, the odds ratio (OR) and CI for each study are reported separately. We considered the following types of treatment in the CPI arms: CPI, CPI with chemotherapy, CPI with non-immunologic targeted therapy. Differences between types of CPI were analysed for the following categories: anti-PD-1 agents, anti-PD-L1 agents, anti-CTLA4 agents, and combinations of anti-CTLA4 agents with anti-PD-1/PD-L1 antibodies (anti-PD-1 and anti-PD-L1 agents were considered jointly in combinations with anti-CTLA4 drugs).

For the purpose of comparing pooled data within the type of immunotherapy, the OR and CI were derived from a random effect model as recommended by Tufanaru et al.[11] For three-arm studies with two immunotherapy arms and a non-immunotherapy control arm, we proceeded according to guidance published by Rücker et al.[12] using the method of splitting the shared group to include results of multi-arm trials in pairwise meta-analysis. Heterogeneity between studies is described using Cochrane Q statistics and I^2 statistics. Comparisons between different types of immunotherapy were carried out using a logistic model with random effect. All statistical analyses were carried out using software R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) using the R package meta.[13]

RESULTS

Selection of studies

We screened a total of 8632 records of phase III studies for cancer, of which 93 studies included treatment with CPIs. A total of 60 studies (including six three-arm studies) involving 41 435 patients with evaluated toxicity were included in the analysis. The characteristics of the included studies and the retrieved data are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100474.[14-74] The cancer types were breast cancer ($n = 3$), colorectal cancer ($n = 1$), gastroesophageal cancer ($n = 4$), hepatocellular cancer ($n = 1$), head and neck carcinoma

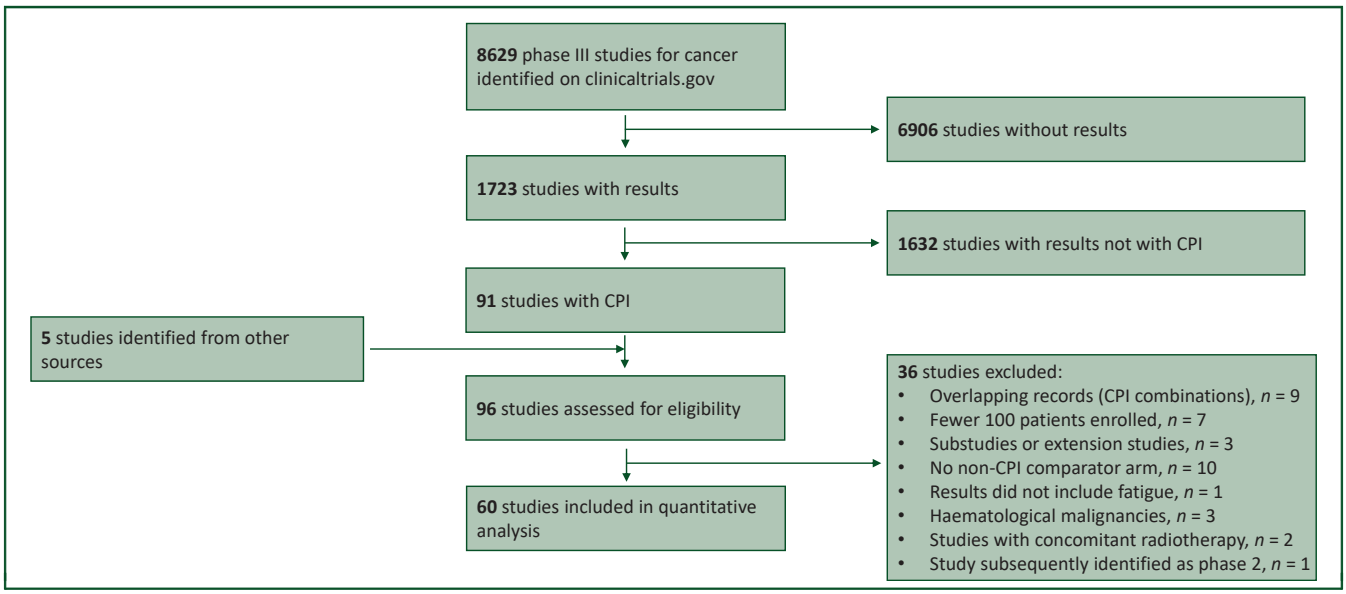


Figure 1. Selection process of the studies used in meta-analysis.
CPI, checkpoint inhibitor.

Table 1. Risk of all-grade fatigue—summary of results

Type of analysed studies	Arms	Number of participants	Number of study arm pairs	Rate of events (95% CI)	Odds ratio (95% CI)	Heterogeneity		Certainty of evidence[a]
						Q (*P* value)	I^2 (95% CI) (%)	
All	CPI Control	23 235 18 200	66	30.4 (29.9-31.0) 30.8 (30.2-31.5)	0.99 (0.91-1.07)	202.6 (<0.001)	67.9 (58.6-75.1)	Moderate
CPI versus inactive control	CPI Control	4330 3383	12	30.1 (28.8-31.5) 23.8 (22.4-25.3)	**1.46 (1.13-1.89)**	61.0 (<0.001)	82.0 (69.7-89.3)	Low
CPI versus CT	CPI Control	9105 7011	28	24.8 (23.9-25.7) 29.1 (28.0-30.2)	**0.79 (0.73-0.85)**	28.1 (0.405)	4.0 (0.0-33.2)	High
CPI + CT versus CT	CPI Control	5851 4704	16	34.1 (32.9-35.4) 31.8 (30.4-33.1)	**1.12 (1.03-1.22)**	7.3 (0.949)	0.0 (0.0-1.8)	High
CPI + TT versus TT	CPI Control	2082 2059	5	39.1 (37.0-41.3) 41.4 (39.2-43.5)	0.92 (0.76-1.12)	9.0 (0.061)	55.5 (0.0-83.6)	Moderate

Statistically significant differences between arms per odds ratio are in bold.
CI, confidence interval; CPI, checkpoint inhibitor; CT, chemotherapy; TT, targeted therapy.
[a]Assessed per Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines.[75]

($n = 4$), lung cancer ($n = 24$), melanoma ($n = 7$), mesothelioma ($n = 2$), prostate cancer ($n = 2$), renal cancer ($n = 7$), and urothelial cancer ($n = 6$). There were 67 study arm pairs included in the pairwise analysis. All-grade toxicities were analysed due to low occurrence of high-grade fatigue in the included studies.

Overall incidence of fatigue in patients treated with CPIs. All-grade fatigue was reported in 30.4% of patients (95% CI 29.9%-31.0%) in the immunotherapy arms of the analysed studies (Table 1 and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100474). Using anti-PD-1 agents as reference, OR for fatigue was significantly higher both for anti-CTLA4 agents (OR 1.46, 95% CI 1.04-2.04) and the combination of anti-CTLA4 and anti-PD-1/PD-L1 agents (OR 1.43, 95% CI 1.12-1.83) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100474). There was no significant difference in the incidence of fatigue between patients treated with anti-PD-1 agents and those receiving anti-PD-L1 agents (OR 1.12, 95% CI 0.89-1.42). The heterogeneity was intermediate (Supplementary Table S4 and Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100474)

CPI versus inactive control arm (placebo, observation, or best supportive care). This category included 12 study arm pairs. Not surprisingly, fatigue was significantly more likely in patients receiving the active treatment with CPI (OR 1.46, 95% CI 1.13-1.89). There was, however, a high degree of heterogeneity among the studies (Table 2).

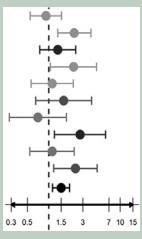
CPI versus chemotherapy. Twenty-six studies were retrieved for the analysis. Fatigue was significantly less likely to occur in patients treated with CPI compared with patients receiving chemotherapy (OR 0.79, 95% CI 0.73-0.85) (Table 3). There was an intermediate heterogeneity among the studies (Table 1).

CPI with chemotherapy versus chemotherapy alone. Fifteen studies (16 study arm pairs) were included in the analysis with the majority of the trials ($n = 10$; 66%) carried out in patients with lung cancer. Fatigue was slightly, but significantly more common in patients treated with the combination of CPIs with chemotherapy compared with patients receiving chemotherapy alone (OR 1.12, 95% CI 1.03-1.22) (Table 4). There was low heterogeneity (Table 1).

CPI with non-immunologic targeted therapy versus non-immunologic targeted therapy alone. All studies in this category were randomised trials for metastatic renal cell carcinoma. No significant difference was found in the occurrence of fatigue (OR 0.92, 95% CI 0.76-1.12) (Table 5). There was an intermediate heterogeneity among the studies (Table 1).

Table 2. Meta-analysis of studies comparing checkpoint inhibitor versus inactive control

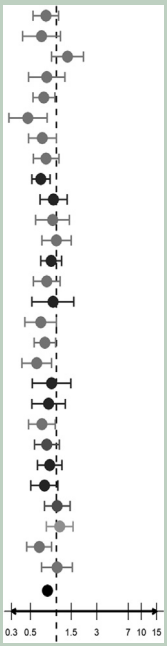
Study	Diagnosis	Inhibitor	*N* (control/CPI)	OR (95% CI)[a]		*P* value
Kwon et al., 2014[16]	Prostate	CTLA4	396/393	0.91 (0.55-1.52)		0.722
Eggermont et al., 2016[21]	Melanoma	CTLA4	474/471	2.28 (1.34-3.89)		0.003
Antonia et al., 2017[26]	Lung	PD-L1	234/475	1.34 (0.75-2.39)		0.329
Beer et al., 2017[27]	Prostate	CTLA4	199/399	2.22 (1.05-4.69)		0.036
Maio et al., 2017[31]	Mesothelioma	CTLA4	189/380	1.12 (0.57-2.21)		0.746
Ferris et al., 2020[52]	Head and neck	CTLA4 + PD-1	240/246	1.62 (0.66-3.98)		0.294
Finn et al., 2020[72]	HCC	PD-1	134/279	0.71 (0.28-1.78)		0.461
Powles et al., 2020[59]	Urothelial	PD-L1	345/344	2.74 (1.20-6.27)		0.017
Owonikoko et al., 2021[66]	Lung	PD-1	273/279	1.12 (0.55-2.28)		0.764
Owonikoko et al., 2021[66]	Lung	CTLA4 + PD-1	273/165	2.37 (1.18-4.78)		0.016
Total			2484/3431	1.49 (1.13-1.96)		0.005



CI, confidence interval; CPI, checkpoint inhibitors; CTLA4, cytotoxic T lymphocyte-associated antigen 4; HCC, hepatocellular carcinoma; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
[a]Control arm as a reference group.

Table 3. Meta-analysis of studies comparing checkpoint inhibitor versus chemotherapy

Study	Diagnosis	Receptor	*N* (control/CPI)	OR (95% CI)[a]	*P* value
Borghaei et al., 2015[17]	Lung	PD-1	268/287	0.76 (0.53-1.07)	0.116
Brahmer et al., 2015[18]	Lung	PD-1	129/131	0.67 (0.40-1.12)	0.129
Robert et al., 2015[20]	Melanoma	PD-1	205/206	1.36 (0.88-2.09)	0.165
Ferris et al., 2016[22]	Head and neck	PD-1	111/236	0.78 (0.47-1.27)	0.309
Herbst et al., 2016[23]	Lung	PD-1	309/682	0.72 (0.53-0.96)	0.026
Reck et al., 2016[24]	Lung	PD-1	150/154	0.47 (0.28-0.78)	0.004
Bellmunt et al., 2017[28]	Urothelial	PD-1	255/266	0.69 (0.47-1.00)	0.053
Carbone et al., 2017[29]	Lung	PD-1	263/267	0.76 (0.54-1.07)	0.120
Rittmeyer et al., 2017[32]	Lung	PD-L1	578/609	0.66 (0.52-0.85)	0.001
Barlesi et al., 2018[73]	Lung	PD-L1	365/393	0.93 (0.64-1.34)	0.698
Larkin et al., 2018[37]	Melanoma	PD-1	102/268	0.91 (0.57-1.43)	0.671
Paz-Ares et al., 2018[39]	Lung	PD-1	280/278	1.01 (0.68-1.50)	0.963
Powles et al., 2018[40]	Urothelial	PD-L1	443/459	0.87 (0.66-1.16)	0.352
Shitara et al., 2018[41]	Gastric	PD-1	276/294	0.77 (0.54-1.11)	0.160
Bang et al., 2018[43]	Gastric	PD-L1	177/184	0.92 (0.52-1.61)	0.761
Cohen et al., 2019[44]	Head and neck	PD-1	234/246	0.66 (0.43-1.01)	0.055
Mok et al., 2019[46]	Lung	PD-1	615/635	0.73 (0.55-0.98)	0.036
Wu et al., 2019[70]	Lung	PD-1	156/337	0.59 (0.40-0.89)	0.011
Ferris et al., 2020[52]	Head and neck	PD-L1	240/237	0.88 (0.52-1.48)	0.635
Herbst et al., 2020[54]	Lung	PD-L1	263/286	0.81 (0.52-1.28)	0.370
Kojima et al., 2020[56]	Esophagus	PD-1	296/314	0.68 (0.47-0.98)	0.037
Powles et al., 2020[58]	Urothelial	CTLA4 + PD-1	315/340	0.77 (0.55-1.08)	0.136
Powles et al., 2020[58]	Urothelial	PD-L1	315/345	0.84 (0.60-1.17)	0.304
Rizvi et al., 2020[60]	Lung	PD-L1	352/369	0.73 (0.50-1.05)	0.088
Rizvi et al., 2020[60]	Lung	CTLA4 + PD-1	352/371	1.03 (0.73-1.45)	0.885
Baas et al., 2021[62]	Mesothelioma	CTLA4	284/300	1.10 (0.76-1.58)	0.612
Powles et al., 2021[67]	Urothelial	PD-1	342/302	0.63 (0.45-0.88)	0.008
Winer et al., 2021[68]	Breast	PD-1	292/309	1.02 (0.67-1.54)	0.925
Total			6718/9105	0.79 (0.73-0.85)	<0.001



CI, confidence interval; CPI, checkpoint inhibitors; CTLA4, cytotoxic T lymphocyte-associated antigen 4; HCC, hepatocellular carcinoma; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
[a]Control arm as a reference group.

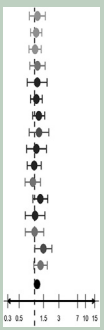
DISCUSSION

The aetiology of fatigue in cancer patients is multifactorial, and the symptom may be associated with cancer itself as well as with cancer therapies and other medications, psychological consequences of cancer and its treatment, nutritional problems, and concomitant diseases. Fatigue ranks among the most common symptoms of cancer and antineoplastic therapies. As fatigue is also common with non-immunological therapies, our study aimed to compare its incidence in CPI-treated patients with that associated with non-immune therapies in randomised trials, to ascertain whether the risk of fatigue should be a factor in guiding treatment decisions.

In the present study, we analysed the incidence of fatigue, a common and important toxicity of therapy with CPIs despite a less striking clinical manifestation. Fatigue has been reported to affect 12%-37% of patients treated with CPI for cancers.[2] In a recent comprehensive meta-analysis of adverse events associated with CPI given in combinations, Zhou et al.[3] found that fatigue occurred in 31% of patients receiving CPI with chemotherapy, 34% of

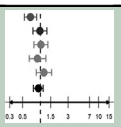
Table 4. Meta-analysis of studies comparing CPI in combination with chemotherapy versus chemotherapy alone

Study	Diagnosis	Inhibitor	N (control/CPI)	OR (95% CI)[a]	*P* value
Robert et al., 2011[15]	Melanoma	CTLA4	251/247	1.14 (0.79-1.62)	0.486
Reck et al., 2016[25]	Lung	CTLA4	561/562	1.07 (0.83-1.38)	0.576
Govindan et al., 2017[30]	Lung	CTLA4	473/475	1.02 (0.78-1.35)	0.868
Gandhi et al., 2018[35]	Lung	PD-1	202/405	1.14 (0.81-1.61)	0.461
Horn et al., 2018[36]	Lung	PD-L1	196/198	1.13 (0.72-1.76)	0.608
Schmid et al., 2018[42]	Breast	PD-L1	430/460	1.09 (0.83-1.41)	0.538
Socinski et al., 2018[33]	Lung	PD-L1	394/793	1.21 (0.92-1.58)	0.171
Paz-Ares et al., 2019[74]	Lung	CTLA4 + PD-1	266/266	1.22 (0.79-1.90)	0.371
Paz-Ares et al., 2019[74]	Lung	PD-L1	266/265	1.09 (0.69-1.70)	0.717
West et al., 2019[51]	Lung	PD-L1	232/473	0.98 (0.72-1.34)	0.903
Burtness et al., 2019[71]	Head and neck	PD-1	287/276	0.92 (0.65-1.31)	0.652
Jotte et al., 2020[55]	Lung	PD-L1	334/334	1.30 (0.93-1.82)	0.125
Mittendorf et al., 2020[57]	Breast	PD-L1	164/167	1.02 (0.66-1.59)	0.923
Rudin et al., 2020[61]	Lung	PD-1	223/223	1.00 (0.66-1.52)	>0.999
Paz-Ares et al., 2021[48]	Lung	CTLA4 + PD-1	349/358	1.49 (1.02-2.18)	0.041
Powles et al., 2021[67]	Urothelial	PD-1	342/349	1.31 (0.97-1.78)	0.083
Total			4704/5851	1.12 (1.03-1.22)	0.008



CI, confidence interval; CPI, checkpoint inhibitors; CTLA4, cytotoxic T lymphocyte-associated antigen 4; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
[a]Control arm as a reference group.

Table 5. Meta-analysis of studies comparing CPI in combination with non-immunologic targeted therapy versus non-immunologic targeted therapy

Study	Diagnosis	Receptor	N (control/CPI)	OR (95% CI)[a]		*P* value
Motzer et al., 2018[38]	Renal	CTLA4 + PD-1	535/547	0.68 (0.53-0.86)		0.002
Motzer et al., 2019[47]	Renal	PD-L1	439/434	0.99 (0.75-1.30)		0.933
Rini and Plimack, 2019[49]	Renal	PD-1	425/429	1.02 (0.78-1.35)		0.862
Choueiri et al., 2021[64]	Renal	PD-1	320/320	0.89 (0.64-1.24)		0.503
Motzer et al., 2021[65]	Renal	PD-1	340/352	1.15 (0.85-1.56)		0.374
Total			2059/2082	0.92 (0.76-1.12)		0.410

CI, confidence interval; CPI, checkpoint inhibitors; CTLA4, cytotoxic T lymphocyte-associated antigen 4; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
[a]Control arm as a reference group.

patients treated with a CPI/targeted therapy combination, 24% of patients with concurrent immunotherapy and radiotherapy, and 26% of patients treated with immunotherapy combinations. Cortellini et al.[76] investigated the association between fatigue and prognosis in patients treated with single-agent CPI for a variety of solid malignancies. They found that fatigue occurring before the 12-week landmark was associated with poor prognosis, whereas late fatigue was not. Early progression, however, is a recognised problem in patients treated with immunotherapy and one of the main reasons for combining CPI with chemotherapy or non-immunologic targeted therapy. Thus, early fatigue could have been associated with early cancer progression in non-responders rather than with autoimmune effects of treatment.

Fatigue in patients treated with CPIs has been associated with cytokine abnormalities, particularly those of interleukin 6 (IL-6). IL-6 is a proinflammatory cytokine with elevated levels in advanced cancer as well as autoimmune adverse events in patients treated with CPIs, as evidenced by the success of the anti-IL-6 agent tocilizumab in treating corticosteroid-refractory autoimmune toxicities.[77-79] Similarly, IL-17 is also associated with fatigue in the context of autoimmune disease, as well as with CPI toxicity.[80,81] A polymorphism described in the cytokine *IL-17F* gene is associated with lower risk of chronic fatigue syndrome, although its role in CPI toxicity remains unexplored.[82] The management of cancer- and cancer treatment-related fatigue is mainly based on non-pharmacological interventions and lifestyle changes. Short-term corticosteroid therapy may be helpful and would probably also suppress the cytokine-mediated mechanisms of CPI-related fatigue.[4]

A limitation of the present analysis includes the possibility of the underreporting of very common symptoms of fatigue, and the fact that the severity of the symptoms changes over the course of cancer and therapy. Longitudinal evolution of fatigue in clinical trials can be assessed using formal quality of life analysis using standard questionnaires which are used in many phase III trials. It is currently unclear how the results of quality of life tools compare with the adverse events collected during randomised trials, however, at least baseline symptoms may be reported more commonly by patients than by physicians.[83] Important changes in self-reported parameters such as fatigue, however, are required to be reported as adverse events per Good Clinical Practice principles.

Conclusions

We found that although immunotherapy is clearly associated with fatigue, the occurrence of all-grade fatigue was significantly higher in patients treated with chemotherapy compared with patients receiving CPIs, with OR of 0.79 (95% CI 0.73-0.85). The risk of fatigue was slightly higher for CPI/chemotherapy combinations than for chemotherapy alone (OR 1.12; 95% CI 1.03-1.22). These results suggest that although the effects of CPI and chemotherapy on fatigue are additive, chemotherapy was the dominant cause of treatment-related fatigue in the analysed trials.

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DISCLOSURE

IK has received research support and honoraria from Roche, Bristol Myers Squibb, Merck Sharp Dohme, Merck, and Servier, all unrelated to the present paper. TB has received research support and honoraria from Roche, Bristol Myers Squibb, Merck Sharp Dohme, Merck, and AstraZeneca, all unrelated to the present paper. All other authors have declared no conflicts of interest.

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