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REVIEW

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Influenza vaccination in cancer patients receiving immune checkpoint inhibitors: A systematic review

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Abstract

Background: There is a concern that influenza vaccination may increase the incidence of immune-related adverse events in patients receiving immune checkpoint inhibitors (ICIs). The aim of this systematic review was to summarize the available data on the safety and efficacy of influenza vaccination in cancer patients receiving ICIs.

Methods: Studies reporting safety and efficacy outcomes of influenza vaccination in cancer patients receiving ICIs were included. Only descriptive statistics were conducted to obtain a pooled rate of immune-related adverse events in vaccinated patients.

Results: Ten studies assessing the safety and eight assessing the efficacy of influenza vaccination in cancer patients receiving ICIs were identified, for a total of 1124 and 986 vaccinated patients, respectively. Most patients had melanoma or lung cancer and received a single agent anti-PD-1, but also other tumour types and immunotherapy combinations were represented. No severe vaccination-related toxicities were reported. The pooled incidence of any grade immune checkpoint inhibitor–related adverse events was 28.9%. In the 6 studies specifying the incidence of grade 3-4 toxicities, the pooled incidence was 7.5%. No grade 5 toxicities were reported. No pooled descriptive analysis was conducted in studies reporting efficacy outcomes due to the heterogeneity of endpoints and data reporting. Nevertheless, among the eight studies included, seven reported positive efficacy outcomes of influenza vaccination.

Conclusion: The results of this systematic review support the safety and efficacy of influenza vaccination in cancer patients receiving ICIs. These results are particularly relevant in the context of the SARS-CoV-2 pandemic.

KEYWORDS

anti-PD-1, COVID-19, immune checkpoint inhibitors, immunotherapy, influenza vaccination, lung cancer, melanoma, SARS-CoV-2 pandemic

1 | BACKGROUND

Immune checkpoint inhibitors (ICIs) have become a mainstay of cancer immunotherapy in recent years for a number of solid and haematologic malignancies, such as melanoma, lung cancer, renal cell carcinoma and Hodgkin lymphoma.[1] They increase antitumour immunity by blocking intrinsic downregulators of immunity, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1). The interaction between PD-1 and PD-L1 inhibits T cells in peripheral tissue, while CTLA-4 is generally believed to inhibit T-cell activation at a proximal step in the immune response.[2] With the introduction of ICIs in everyday clinical practice, a new category of anticancer therapy–related adverse events has emerged. Unlike traditional chemotherapy, ICIs can induce a spectrum of adverse events of autoimmune pathogenesis (irAEs), due to nonspecific activation of the immune system targeting healthy tissues and organs.[2] Although the exact pathophysiology underlying irAEs remains to be further characterized, it is believed to be closely related to the function that immune checkpoints play in maintaining immunological homeostasis and avoiding autoimmune reactions.[2] The backbone of immune-related toxicity management is corticosteroid therapy. Guidelines for the management of irAEs are provided by the most influent scientific societies such as the European Society for Medical Oncology (ESMO),[3] the American Society of Clinical Oncology (ASCO) [4] and the National Comprehensive Cancer Network (NCCN).[5]

There is a concern that influenza vaccination may increase the incidence of irAEs in patients with cancer receiving ICIs.[6] In an early report on the safety of influenza vaccination, among 23 patients receiving anti-PD-1 monoclonal antibodies, 6 (26.1%) had severe irAEs following the administration of the influenza vaccine, including rare events such as encephalitis (8.7%) and neuropathy (4.3%).[6] The authors of that report speculated that PD-1 blockade together with vaccination could boost the breakage of tolerance by enhancing the mechanisms associated with irAEs.[6] However, cancer patients are at higher risk for developing complications related to influenza infection,[7-9] and vaccination is the most important protective strategy against this infection.[10-13] A Cochrane review of influenza vaccines in patients with cancer receiving chemotherapy revealed lower mortality and infection-related outcomes with influenza vaccination.[14]

The aim of this systematic review was to summarize and discuss the currently available data assessing the safety and efficacy of influenza vaccination in cancer patients receiving ICIs.

2 | METHODS

Reporting of this study conforms to broad EQUATOR guidelines[15]; specifically, Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) guidelines were used for the conduct and reporting of this systematic review (Figure 1).[16-18]

Studies reporting data on the safety and efficacy of influenza vaccination in cancer patients receiving ICIs were included in this systematic review. The following data were extracted from each report: study design, type of vaccine, number of vaccinated patients, incidence and severity of ICI-related AEs (ie irAEs) in vaccinated patients, incidence of severe vaccination-related AEs, number of nonvaccinated patients and differences in outcomes between nonvaccinated and vaccinated patients (in studies comparing the two populations).

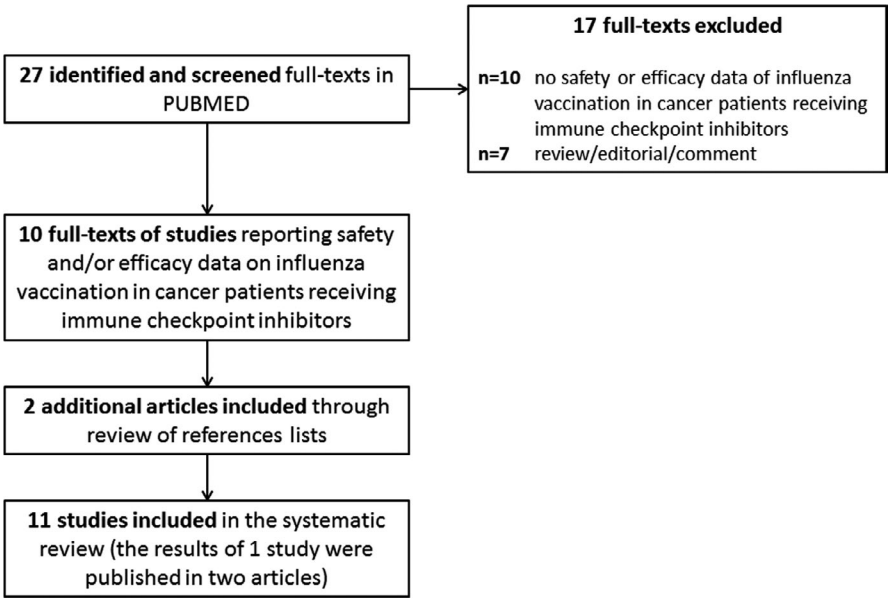

FIGURE 1 The PRISMA flow chart summarizing the process for the identification of the eligible studies

Studies were identified by a computerized search on the PubMed search engine with the string ("pembrolizumab"[Supplementary Concept] OR "pembrolizumab"[All Fields] OR ("nivolumab"[MeSH Terms] OR "nivolumab"[All Fields] OR "nivolumab s"[All Fields]) OR "anti-PD-1"[All Fields] OR ("ipilimumab"[MeSH Terms] OR "ipilimumab"[All Fields]) OR (("cell cycle checkpoints"[MeSH Terms] OR ("cell"[All Fields] AND "cycle"[All Fields] AND "checkpoints"[All Fields]) OR "cell cycle checkpoints"[All Fields] OR "checkpoint"[All Fields] OR "checkpoints"[All Fields]) AND ("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields] OR "inhibitor s"[All Fields]))) AND (("influenza s"[All Fields] OR "influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields] OR "influenzae"[All Fields] OR "influenzas"[All Fields]) AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields])). The search was performed on the 16 December 2020 with no date restriction and no filters. Conference abstracts were included in our analysis, and additional studies were identified following review of references lists. Only English-language publications were considered for inclusion.

Data were independently extracted by two investigators (FS and AB) to ensure homogeneity of collection and to rule out the effect of subjectivity in data gathering and entry. Disagreements were resolved by iteration, discussion and consensus.

Only descriptive statistics were conducted to obtain a pooled response rate of irAEs by severity in vaccinated patients.

3 | RESULTS

The agreement rate between the two investigators who independently extracted data was 100% after iteration and consensus. Twelve records reporting data from 11 studies were identified: safety outcomes were assessed in 10 studies, while efficacy endpoints were reported in 8 studies (Figure 1).

Among the 10 studies assessing the safety of influenza vaccination in patients with cancer receiving ICIs, for a total of 1124 vaccinated subjects (Table 1),[6,19-27] the majority of patients had melanoma or lung cancer, but also several other types of cancers were represented (data not shown). Most patients received an anti-PD-1 as single agent, but also patients receiving combined anti-PD-1 and anti-CTLA-4 treatment were included.[23,24] Common Terminology Criteria for Adverse Events (CTCAE) versions 4.0 or 5.0 were used in all but one study,[27] where safety was assessed using the FDA toxicity grading scale for clinical trials; notably, this information was missing in 3 studies.[19,24,25] No severe vaccination-related adverse events were reported. The pooled incidence of any grade ICI-related irAEs was 28.9%. In the 6 studies reporting the incidence of grade 3-4 toxicities, the pooled incidence was 7.5%.[6,20-23,27] No grade 5 toxicities were reported. Among 5 studies assessing the incidence of irAEs in vaccinated and nonvaccinated patients, two studies reported a statistically significant lower incidence in the vaccinated group[20,24] and one study a statistically significant higher frequency of irAEs in vaccinated patients, albeit with a very sample size of only 23 vaccinated patients.[6] One study comparing the safety of ICIs in 385 vaccinated and 149 nonvaccinated patients showed a trend towards lower incidence of irAEs in vaccinated patients[25]; finally, one small study reported a trend towards lower incidence of irAEs in nonvaccinated patients.[26]

The results of the eight studies assessing the efficacy of influenza vaccination in 986 patients with cancer receiving ICIs are summarized in Table 2.[6,19,21-23,25,27-29] No pooled descriptive analysis was conducted due to the heterogeneity of efficacy endpoints and reporting of data. Nevertheless, among the eight studies included in this systematic review, seven reported positive efficacy outcomes of influenza vaccination in cancer patients receiving ICIs.[6,19,21-23,25,27,28]

4 | DISCUSSION

Influenza vaccination is the best strategy to protect cancer patients against this infection and showed to reduce mortality and flu-related complications in those receiving chemotherapy.[14] However, in one of the first reports on the safety of influenza vaccination in cancer patients receiving ICIs, major concerns about an increased risk of severe immunological complications were raised. Despite these data being based on only 23 subjects, many clinicians started advising their patients under ICIs against vaccination.[6,23] As highlighted in our systematic review, most subsequent and larger studies showed that the overall safety and efficacy of influenza vaccination in cancer patients receiving ICIs is not substantially different from that observed in the general population.

The SARS-CoV-2 pandemic had a major impact on health system reorganization and on the management of patients with cancer, who are at increased risk of infection-related

TABLE 1 Summary of safety endpoints' results in patients who received anti-PD-1/PD-L1 immunotherapy and influenza vaccine

First author and date of publication	Study design	Safety endpoints	Type of vaccine	Number of vaccinated patients
Bayle et al 2020[19]	Prospective case series	Incidence of irAEs in vaccinated patients	NR	30
Failing et al 2020[20]	Retrospective case-control study	Incidence of irAEs in the vaccinated group compared with the nonvaccinated group	High or standard dose, inactivated, nonadjuvanted trivalent or quadrivalent	70
Gwynn et al 2020[21]	Prospective case series	Incidence of irAEs in vaccinated patients	Standard dose, inactivated, quadrivalent	24
Keam et al 2020[22]	Prospective case series	Incidence of irAEs in vaccinated patients treated with ICI compared with CT	Standard dose, quadrivalent	47
Chong et al 2019[23]	Retrospective case series	Incidence and severity of new onset irAEs in vaccinated patients	High or standard dose, inactivated, nonadjuvanted trivalent or quadrivalent	370[b]
Awadalla et al 2019[24]	Retrospective case-control study	Vaccination rate in patients who had ICI-related myocarditis compared with those who had not Incidence of irAEs in vaccinated and nonvaccinated cases	NR	105[c]
Gopalakrishnan et al[25]	Retrospective case series	Incidence of irAEs in vaccinated and nonvaccinated patients	NR	385
Läubli et al 2018[6]	Prospective case series with retrospective control cohort	Incidence of irAEs in vaccinated patients	Standard dose, inactivated, nonadjuvanted trivalent	23
Wijn et al 2018[26]	Retrospective case-control study	Incidence of irAEs in the vaccinated group compared with the nonvaccinated group	Standard dose, inactivated, nonadjuvanted trivalent	42
Kanaloupitis et al 2017[27]	Prospective case series	Incidence of irAEs in vaccinated patients	NR	28

Abbreviations: and RR, rate ratio; CT, chemotherapy; ICI, immune checkpoint inhibitors; irAE, immune-related adverse event; NA, not applicable; NR, not reported.

[a]Not equal to the sum of grade 1-4 AEs because a single patients may have more than one AE.

[b]Including 82 patients treated with anti-CTLA-4 + anti-PD-1, 42 patients with anti-PD-1 + experimental drugs and 15 with anti-CTLA-4 followed by anti-PD-1.

[c]Including also patients treated with anti-CTLA-4 + anti-PD-1.

[d]Excluding myocarditis.

complications.[30-32] Protection of cancer patients from influenza infection is extremely important: influenza vaccination has clearly shown to lower mortality and infection-related outcomes in this setting.[14] In the context of the current SARS-CoV-2 pandemic, protecting patients from influenza infection has additional relevance also considering that influenza symptoms overlap with those of COVID-19 and may interfere with the proper prosecution of cancer treatments, ultimately decreasing their chances of survival.

Our systematic review has some limitations, mostly related to the heterogeneity of study designs and endpoints among the studies included in our analysis. One of the main limitations of our safety analysis is the variability of recording toxicities outside clinical trials, especially for low-grade AEs. In fact, we found an incidence of low-grade events which suggests a probable underreporting of such events. However, clinically significant AEs, such as those requiring intervention or hospitalizations, are usually reported properly also in observational and/or retrospective studies, and the rate of severe irAEs that we observed in our analysis was in line with that reported in clinical trials, with no deaths due to treatment-related toxicity. Other potential biases include

Immune-related adverse events in the vaccinated population						Severe vaccination-related AEs	Number of nonvaccinated patients	Differences with nonvaccinated group
Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	Any Grade (%)			
15 (50%)			0	0	15 (50%)	NR	NA	NA
NR	NR	4 (5.7%)		0 (0%)	18 (25.7%)	NR	92	OR: 0.4 (95% CI, 0.2-0.9)
2 (8.3%)	4 (16.6%)	1 (4.2%)	1 (4.2%)	0 (0%)	7[a] (29.2%)	NR	NA	NA
4 (8.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (8.5%)	0 (0%)	NA	NA
5 (1.4%)	40 (10.8%)	27 (7.3%)	3 (0.8%)	0 (0%)	75 (20.3%)	0 (0%)	NA	NA
NR	NR	NR	NR	NR	38 (36%)[d]	NR	197	Vaccination rate: 25% in myocarditis group vs 40% in control ($P = .01$ for rate comparison) Rate of any grade irAEs other than myocarditis: 36% in vaccinated vs 55% unvaccinated cases ($P = .10$)
NR	NR	NR	NR	NR	144 (37.4%)	NR	149	Rate of irAEs: 37.4% in vaccinated vs 42.6% in nonvaccinated patients ($P = .067$)
6 (26.1%)		6 (26.1%)		0 (0%)	12 (52.2%)	0 (0%)	40	Frequency of irAEs was significantly higher in vaccinated patients
NR	NR	NR	NR	NR	11 (26.2%)	NR	85	RR: 1.20 (95% CI, 0.51-2.65)
0	1 (3.6%)	0	0	0	1 (3.6%)	0 (0%)	NA	NA

the lack of data about reasons for receiving or not influenza vaccination (possibility of self-selection bias) and, for retrospective studies, the selection bias intrinsic to such study design. For the efficacy analysis, we could not conduct a pooled descriptive analysis due to the vast heterogeneity of efficacy endpoints and reporting of data.

Despite these limitations, and in line with previous reports,[33,34] the results of our systematic review support influenza vaccination in patients with cancer receiving immune checkpoint inhibitor therapy. These results are particularly relevant in the context of the SARS-CoV-2 pandemic.

CONFLICT OF INTEREST

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Matteo Lambertini acted as consultant for Roche, AstraZeneca, Lilly and Novartis, and received speaker honoraria from Sandoz, Roche, Takeda, Pfizer, Lilly and Novartis outside the submitted work. Francesco Spagnolo acted as consultant for Novartis, MSD, Sun Pharma and Pierre Fabre, and received speaker honoraria from Roche, Novartis, BMS, MSD, Merck, Sun Pharma,

TABLE 2 Summary of efficacy endpoints' results in patients who received anti-PD-1/PD-L1 immunotherapy and influenza vaccine

First author and date of publication	Study design	Efficacy endpoints	Type of vaccine	Number of vaccinated patients	Results
Bayle et al 2020[19]	Prospective case series	Antibody titres (seroprotective rate)	NR	30	Seroprotective rates: 67% against H1N1, and 63% against H3N2
Gwynn et al 2020[21]	Prospective case series	Incidence of influenza or flu-like symptoms	Standard dose, inactivated, quadrivalent	24	No patients reported influenza infection or flu-like symptoms during the study period
Keam et al 2020[22] Kang et al 2020[28]	Prospective case series	Antibody titres (seroprotective and seroconversion rates) Incidence of influenza	Standard dose, quadrivalent	47	Seroprotection rates ranged from 76% to 89% in ICI-treated patients Seroconversion rates ranged from 52% to 65% in ICI-treated patients Seroprotection and seroconversion rates were significantly higher in the ICI group than in the cytotoxic chemotherapy group for all strains, except for the H1N1 strain No patient had laboratory-confirmed symptomatic influenza during the study period Cell-mediated immune responses following influenza vaccination were stronger in patients receiving immunotherapy than in those receiving cytotoxic chemotherapy
Chong et al 2019[23]	Retrospective case series	Laboratory-confirmed cases of influenza	High or standard dose, inactivated, nonadjuvanted trivalent or quadrivalent	370[a]	The overall combined incidence of laboratory-confirmed influenza among individuals tested across 3 seasons was 3.5% compared with an institution-wide incidence during the same time of 10.7%
Gopalakrishnan et al[25]	Retrospective case series	Rate of flu prodromal Rate of admissions for flu-related complications	NR	385	Unvaccinated patients were less likely to experience flu prodrome (32.2% vs 43.7%, $P = .067$), but were more likely to be admitted for influenza-related complications (62.4% 23.2%, $P = .032$)
Läubli et al 2018[6]	Prospective case series with retrospective control cohort	Antibody titres (seroprotective rate) Incidence of influenza	Standard dose, inactivated, nonadjuvanted trivalent	23	No differences in terms of antibody titres compared with healthy age-matched controls No influenza infection was diagnosed in any of the vaccinated patients
Bersanelli et al 2017[29]	Retrospective case series	Incidence of influenza syndrome	Inactivated, trivalent or quadrivalent	79	The incidence of influenza syndrome was 24.1% among patients receiving the vaccine compared with 11.8% in the unvaccinated control group (26/221), for an odds ratio = 2.4 (95% CI = 1.23-4.59)
Kanaloupitis et al 2017[27]	Prospective case series	Antibody titres Influenza infection rate, confirmed by rapid antigen testing, and influenza-related hospitalizations	NR	28	IgM responses at 45 d to both influenza A and B common antigens were statistically significant ($P < .05$) IgG response to common influenza B antigens was increased at day 45 ($P = .001$) One of 28 patients contracted influenza B infection, confirmed by rapid antigen testing There were no influenza-related hospitalizations

Abbreviations: ICI, immune checkpoint inhibitors; NR, not reported.

[a]Including 82 patients treated with anti-CTLA-4 + anti-PD-1, 42 patients with anti-PD-1 + experimental drugs and 15 with anti-CTLA-4 followed by anti-PD-1.

Sanofi and Pierre Fabre outside the submitted work. All the other authors declare no conflicts of interest.

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