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State of the art about influenza vaccination for advanced cancer patients receiving immune checkpoint inhibitors: When common sense is not enough

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ABSTRACT

Influenza vaccination is recommended for advanced cancer patients, since impaired immunity is presumed to be due not only to the tumor itself but also to immunosuppressive treatments, such as chemotherapy and radiotherapy. The recent advances in the systemic management of metastatic solid tumors, with the introduction of immune checkpoint inhibitors for several indications in clinical practice, has re-actualized simple clinical issues, such as the vaccinal recommendations and counseling, for which common sense is not enough to support pragmatic choices. In the present review, we summarized the evidence about influenza vaccine administration during immune checkpoint blockade, emphasizing the need of prospective data to definitely guide our advices to a growing group of cancer patients.

1. Introduction

Influenza is an acute respiratory syndrome caused by infection by seasonal influenza viruses (type A, B and C), affecting the respiratory tract and including both respiratory and systemic symptoms, such as fever, myalgia, headache, cough, chills, nasal congestion and sore throat. Influenza A and B viruses cause seasonal epidemics on winter, while type C infection is milder and occurs less frequently (Brankston et al., 2007). Complications of influenza, mostly due to bacterial superinfection, include pneumonia (which is the major and often the most severe), but also otitis media and exacerbation of chronic respiratory disease. The major morbidity associated with influenza includes the worsening of chronic health conditions, especially in frail patients who are classified at high-risk due to their underlying situations: elderly age, pregnancy, chronic diseases, cancer (Bitterman et al., 2018). People with solid cancers undergoing chemotherapy are at increased risk of influenza-related complications, due to their impaired cell-mediated and antibody-mediated immunity and, particularly in the case of lung cancer, to the frailty of the respiratory system commonly existing in these patients (Kohno et al., 1994). Indeed, a low absolute lymphocyte count has been reported as an independent predictor of influenza-related pneumonia (Chemaly et al., 2006). On the other side, neutropenia, that is the main immune impairment in cancer patients treated with chemotherapy, is associated with a higher risk of bacterial infections rather than viral infections. Therefore, despite a likely similar probability to develop influenza, patients with neutropenia are more prone to higher rates of influenza-related bacterial complications compared to the general population and to higher influenza-related hospitalization rates and higher mortality, as well, associated with a reported lethality rate of 9% (Cooksley et al., 2005). Worthwhile, influenza and its complications may also reduce the compliance to treatment, requiring discontinuations, thus compromising dose intensity and potentially reducing treatment efficacy (Taha et al., 2015).

The major measure that can be adopted to prevent the influenza infection is currently represented by vaccination. A recently updated Cochrane review stated that observational data suggest lower mortality and infection-related outcomes by the use of influenza vaccination in immunocompromised cancer patients. Although limited by the small number of studies, this review showed that the benefits overweigh the potential risks when adults with cancer are vaccinated against influenza

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(Bitterman et al., 2018). Furthermore, so far, international and national guidelines recommend influenza vaccination in cancer patients (Rubin et al., 2014; Pedrazzoli et al., 2014; Grohskopf et al., 2018). The Centers for Disease Control and Prevention (CDC) in 2018 updated the recommendation for administrating the vaccine to individuals at higher risk for medical complications attributable to severe influenza, in particular patients who are immunocompromised due to any cause, including immunosuppression caused by medications, as well as persons who live with or care for such patients. The Infectious Diseases Society of America (IDSA), in the 2013 Clinical Practice Guideline, stated that patients with solid tumor malignancies should receive inactivated influenza vaccine annually.

The current advent of the new immunotherapy with immune checkpoint inhibitors (CKI), recently approved with multiple indications for advanced cancer patients (Bersanelli and Buti, 2017; Banna et al., 2018), overturned all our certainties about traditionally "simple" issues, such as the concomitant administration of common medications: antibiotics, corticosteroids, and even vaccines (Derosa et al., 2018; Garant et al., 2017; Chung, 2018). On the other hand, the influenza-related morbidity and mortality of cancer patients treated with anti-PD-1/PD-L1 CKIs have not been explored yet. Currently, no solid data support the efficacy of influenza vaccination administration in this subgroup of patients since prospective evidence about its safety, its clinical efficacy and its possible interactions with CKIs are still unavailable.

The present systematic review aims at summarizing the evidence emerged about this issue, mostly coming from retrospective experiences and needing of confirmation by prospective data.

2. Materials and methods

PRISMA guidelines were followed for the present systematic review (Anon, 2018). A systematic assessment of literature and peer-reviewed presentations was performed by searching PubMed (MEDLINE) and major oncology meeting (American Society of Clinical Oncology, www.ASCO.org and European Society for Medical Oncology, www.ESMO.org) resources, from the database inception until December 5, 2018. The references of the included article were also reviewed for any further potential publication. Two authors independently performed the search, to increase accuracy.

The following keywords were used: ("influenza vaccination" or "flu vaccination" or "influenza vaccine") and ("immune checkpoint inhibitors" or "immunotherapy") and "cancer patients". Publications not primarily published in English were excluded. All types of original clinical studies were included. Automatic filters were avoided: a manual selection of publications was performed after reading all titles and abstracts. The full text of the selected publications was obtained, and the content was then tabulated and summarized by one author for the final selection. Any study reporting or considering the use of influenza vaccination during therapy with CKI was included. All types of endpoint about efficacy and safety of the vaccine, or about its interactions with CKI, were considered.

3. Results

Despite the wide and well-documented literature about the use of vaccines for immunocompromised patients, enriched by at least three randomized controlled trials, the new oncological population treated with CKI is not yet considered in the currently available studies (Bitterman et al., 2018). Table 1 summarizes the literature search results. Currently, there are no reliable data to support the use of split vaccines during cancer immunotherapy; the safety and the efficacy of the vaccine during CKI therapy are not specifically proven. Patient counseling in this setting is therefore not based on reliable scientific evidence, but until now only on clinical common sense. Only based on the pharmacological characteristics of CKI antibodies, influenza vaccination has been considered as potentially safe in patients treated with cancer immunotherapy.

3.1. Retrospective studies

Only few retrospective studies are currently available in the literature on this topic.

Looking for explorative data, our group conducted the first retrospective study (the INVIDIa study), collecting preliminary evidence about efficacy and compatibility of flu vaccination with CKI therapy in cancer patients. The INVIDIa study was the only exploring the clinical efficacy of influenza vaccination (Bersanelli et al., 2018). It was a multicenter study, conducted with the aim of exploratively addressing the unmet issue of the counseling about influenza vaccination for cancer patients treated with immunotherapy, by enrolling consecutive advanced cancer outpatients receiving CKI during the 2016–2017 influenza season. Of the 300 patients included in the analysis, 79 received influenza vaccination. The incidence of ILI was 24.1% among vaccinated patients *vs* 11.8% among controls; OR = 2.4 (95% CI = 1.23–4.59; p = 0.009). The clinical ineffectiveness of vaccine was more pronounced among elderly: 37.8% of ILI among vaccinated patients *vs* 6.1% among unvaccinated, OR = 9.28 (95% CI = 2.77–31.14), p < 0.0001. However, the severity of influenza syndrome was mild irrespective of the vaccination, with no lethal cases in the overall population. No statistically significant differences were seen in terms of objective response rate, disease control rate and time to treatment failure with CKI therapy between vaccinated and control patients, respectively, or between patients developing ILI or not in the overall study population. Interestingly, subgroup data suggested that the inefficacy of influenza vaccination was less pronounced for lung cancer patients. Moreover, despite data for overall survival (OS) were immature, a statistically significant positive correlation with the vaccine administration and/or ILI development was demonstrated in this subgroup: 1-year OS was 86.7% (95% CI = 75.7–97.7) for the vaccine/ILI group versus 66.7% (95%CI = 53.6–79.8), p = 0.02; this finding was confirmed at the multivariate analysis. Thus, the increased morbidity of influenza in vaccinated patients did not negatively impact the clinical outcome. We hypothesized that CKI treatment may have been responsible for greater immunocompetence against the infection and its bacterial complications since the severity and lethality of ILI were prevented in patients treated with CKI irrespective of the vaccine administration (Schenk, 2017). On the other hand, a possible enhanced aberrant T cell response could paradoxically contribute to the ILI immunopathology and the observed increased incidence of infection in vaccinated CKI-treated patients (Srikiatkhachorn et al., 2010). As far as the impact on the anticancer treatment outcome is concerned, we hypothesized that vaccine-induced or influenza-induced antigen stimulation may have a similar positive effect on the cell-mediated immune response to CKI treatment, acting as a synergic immunogenic stimulus. In the INVIDIa study population, the immune activation given by the viral particles of the split vaccine, and possibly by the natural infection itself, may have been contributed to the antitumor effect of immunotherapy (Hobohm, 2001).

The results of three subsequent retrospective analyses about the impact of the vaccine on the outcome of cancer patient treated with immunotherapy, were reported at the 2017 and 2018 annual meeting of the American Society of Clinical Oncology (ASCO). Some of their results confirmed, as it was in the INVIDIa study, an improvement in OS in vaccinated patients, regardless of the clinical efficacy of the vaccine, which was not specifically tested (Schenk, 2017; Gopalakrishnan et al., 2018; Chong et al., 2018).

A further retrospective study, recently conducted on a prospective population of 127 patients with lung cancer treated with nivolumab in an expanded access program in the Netherlands, did not found significant differences in terms of immune-related adverse events (irAEs) between the vaccinated cohort compared with that of non-vaccinated

Table 1
Available data from studies describing the impact of influenza vaccination in advanced cancer patients undergoing immunotherapy with immune checkpoint inhibitors.

Author and year	Study type	Number of patients	Clinical efficacy of the vaccine	Humoral efficacy of the vaccine	Immunotherapy efficacy	Overall survival	Safety
Chong CR 2019 (Chong et al., 2019)	Retrospective	370	+	NA	NA	NA	+ +
Awadalla M 2019 (Awadalla et al., 2019)	Retrospective	302	NA	NA	NA	NA	+ +
Bersanelli M 2018 (Bersanelli et al., 2018)	Retrospective	300	- - -	NA	+ +	+	NA
Schenk EL 2017 *(abstract)* (Schenk, 2017)	Retrospective	108	NA	NA	+ +	+ +	-
Gopalakrishnan R 2018 *(abstract)* (Gopalakrishnan et al., 2018)	Retrospective	534	+	NA	+	+ +	+
Chong CR 2018 *(abstract)* (Chong et al., 2018)	Retrospective	147	NA	NA	NA	NA	+
Wijn DH 2018 (Wijn et al., 2018)	Retrospective	127	NA	NA	+	NA	+
Weber JS 2012 (Weber et al., 2012)	Prospective	82	NA	+ +	NA	NA	NA
Laubli H 2018 (Topalian et al., 2012)	Prospective	23	NA	+ + +	NA	NA	-

NA = not assessed; + / + + / + + + and - / – / — values were assigned basing on the consensual opinion of the authors about the strength of the data reported in the studies, with the clear limitations of their heterogeneity and of indirect comparisons.

patients (Wijn et al., 2018). The authors reported an incidence of irAEs of 26% and 22%, respectively in the vaccinated and unvaccinated patients (OR = 1.20, 95% confidence interval [CI] 0.51–2.65), and a respective rate of severe irAEs of 7% and 4% (OR = 2.07, 95% CI 0.28–15.43). In this series, vaccination showed no correlation with the rate of therapy discontinuation, nor with the objective response to cancer treatment (Wijn et al., 2018).

More recently, two further publications added retrospective data regarding the safety of influenza vaccination during CKI therapy in cancer patients. Chong et al reported the findings from a large patient population receiving the flu vaccine during immunotherapy, reporting irAEs rates comparable to published clinical trials (20% any grade, 8% severe irAEs) and without variations with order of administration between vaccine and CKI (Chong et al., 2019). In the same study, the rate of occurrence of confirmed influenza was quite low when compared to the overall cancer patients from the same institution (3.5% vs 10.7%), suggesting a possible clinical efficacy of the vaccine, despite the statistical significance was not explored (Chong et al., 2019).

Finally, Awadalla et al reported a lower incidence rate of influenza vaccination among cancer patients developing CKI-related myocarditis, compared to a large cohort of cases receiving CKI without myocarditis (Awadalla et al., 2019). Moreover, the authors reported that myocarditis cases receiving the vaccine had a lower rate of immune-related pneumonitis when compared to unvaccinated cases (12% vs 36%, p = 0.03). Also, myocarditis cases who received vaccination were at a lower risk of cumulative major adverse cardiac events when compared to unvaccinated cases (24% vs 59%, p = 0.002) (Awadalla et al., 2019). No data were reported about the occurrence of influenza among vaccinated or non-vaccinated patients, neither about the outcome of patients to CKI cancer therapy.

3.2. Prospective studies

No prospective studies assessing the clinical efficacy of influenza vaccination during immunotherapy with CKI in cancer patients were found.

The phase II study CA184-004, providing the only formal demonstration of the serological efficacy of vaccines during immunotherapy with CKI, demonstrated humoral responses to influenza vaccine in patients with melanoma treated with ipilimumab (anti-CTLA-4 monoclonal antibody) (Weber et al., 2012). However, no data were provided on the clinical efficacy of the influenza vaccine, in terms of incidence of influenza-like syndrome (ILI) and efficacy of the anticancer therapy in vaccinated subjects. In detail, the study evaluated the administration of the tetanus vaccine ten days before and of influenza and anti-pneumococcal vaccines a week after the start of systemic therapy with ipilimumab in patients with advanced melanoma. Humoral responses were tested at baseline and on the seventh week of therapy. The majority of patients had an increase in levels of specific antibodies (i.e., humoral response) against influenza A and B virus antigens, which were absent in unvaccinated patients. No difference was observed in terms of humoral response in the group of patients receiving 3 mg/kg of ipilimumab compared to those receiving 10 mg/kg (Bersanelli et al., 2018).

On the contrary, very few data are currently available about the same issue in patients receiving nivolumab or other anti-PD-1 / anti-PD-L1 monoclonal antibodies. Influenza vaccination was allowed at any time within the phase I study CA209-003 with nivolumab, but the outcomes about vaccination have not been reported (Topalian et al., 2012).

Recently, a small Swiss prospective study suggested that seasonal influenza vaccination could increase the rate of serious irAEs in patients treated with anti-PD-1 / PD-L1 antibodies. This evidence, of limited strength due to the small sample size (23 patients) and the lack of a control group for the toxicity data, instilled the first doubt of a possible contraindication of influenza vaccination in patients treated with CKIs. The administration of the vaccine was associated with a rather high rate of irAEs: over half of patients had adverse events of any grade and 26% of patients reported severe irAEs. The researchers suggested, as a possible explanation, that patients receiving CKI have a hyperactivated state of the immune system and this could induce excessive responses by the vaccine, thus triggering irAEs with greater frequency and intensity than expected (Läubli et al., 2018). Interestingly, the authors compared the antibody titers against three viral antigens of cancer patients undergoing PD-1 blockade with healthy age-matched controls, finding a higher and faster humoral response in cancer patients. These data may support the hypothesis that patients treated with CKI are more immunocompetent since immunotherapy normalizes cellular and humoral immunity (Läubli et al., 2018).

4. Conclusions

The scarce and controversial evidence about influenza vaccination during anticancer therapy with CKI confirms the need of more robust data on the safety of vaccine during immunotherapy and, consequently, on its advisability in a population where its usefulness has not yet specifically been proven. Although the safety of the vaccine in immune-treated patients has not yet been demonstrated by prospective data, it is known that major complications can ensue from infections in cancer patients, especially in case of lung cancer or respiratory impairment. Currently, a reliable literature in support of this issue is still lacking.

On the basis of this unmet clinical need, prospective *ad hoc* studies are eagerly awaited. Our group is currently conducting a large, multicenter prospective trial, the INVIDIa-2 study, which will collect data during the flu season 2019–2020, aiming at providing reliable results to provide recommendations about influenza vaccination in cancer patients treated with immunotherapy.

4.1. Current recommendation

Considering the currently reported findings, CKI-treated cancer patients should be advised about the risk of possible clinical ineffectiveness of the influenza vaccine. On the other hand, patients could be reassured that the vaccine would not have a negative impact on their anticancer immunotherapy, although no safety prospective data are currently available to rule out possible complications.

Although the uncertainty about the safety of the vaccine in these patients, the evidence for a longer survival observed in vaccinated patients across the available studies irrespective of the clinical efficacy of the vaccine, could not support an abstentionist attitude. Indeed, a synergy in the efficiency of the immune system against the “non-self” whether of viral or tumor origin, could play a role during CKI and following vaccination.

Pending prospective data, the only proper recommendation is currently in favor of a prudential and personalized approach, entailing the consideration of individual patient risk factors, such as age, comorbidities, metastatic sites and organs involved, functional respiratory impairment. In those patients for whom the risk of serious complications from influenza infection is expected to be high, vaccination should be considered in the assumption of a favorable risk/benefit ratio.

Conflict of interest

No conflict of interest for all authors.

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