



SEASONAL INFLUENZA VACCINATION IN PATIENTS UNDER IMMUNE CHECKPOINT INHIBITION November 2018

The number of cancer patients treated with immune checkpoint inhibitors (ICI) continues to grow. Now that the flu vaccination campaign is starting, questions are increasingly asked whether influenza vaccination in combination with ICI is (1) effective, (2) safe, and (3) can influence the effectiveness of the cancer immunotherapy.

From the limited published data we can summarize the following observations:

1. Effectiveness of influenza vaccination in cancer patients under immune checkpoint blockade

In a small Swiss observational study, seroconversion after vaccination was found to be more robust in cancer patients under ICI compared to healthy controls administered the same vaccine¹. All patients in this study were vaccinated with a trivalent, inactivated, non-adjuvanted formulation. However, the actual incidence of flu *infection* was not reported. In another retrospective study (INVIDIa, 203 patients with renal cell carcinoma, lung cancer, melanoma) an increased incidence of "flu syndrome" was noted in vaccinated vs non-vaccinated cancer patients under ICI². Still, it is unclear to what extent this reflected true influenza virus infections or merely a manifestation of systemic immune activation. In a larger prospective study³ (Vanderbilt University, 534 patients with various solid tumors), the incidence of flu syndrome was higher in patients under ICI, however the number of hospital admissions due to influenza infection was clearly lower in vaccinated cancer patients.

2. Incidence of immune-related side effects

Data on the incidence of immune-related toxicity after vaccination are limited and contradictory. In the aforementioned non-randomized observational study, a sharp increase in incidence of ICI-related immune toxicity on ICI was reported¹. However, this was a strongly selected study population that may not reflect daily practice. A relevant control arm was not included prospectively as the study used a retrospective cohort of non-vaccinated lung cancer patients under ICI as a comparison. In another retrospective study (Mayo Clinic, 108 patients, mainly melanoma and lung cancer), no increase in ICI-related adverse events was observed in vaccinated patients⁴. In the largest reported series to date (Vanderbilt University), the incidence of immune-related side effects also not increased in vaccinated

vs non-vaccinated cancer patients under ICI³. Strangely enough, the risk of immune-related pneumonitis in that particular study was even *higher* in the *non-vaccinated* group.

3. Effectiveness of the cancer immunotherapy

The Mayo Clinic retrospective study showed that the median survival of vaccinated, ICI-treated cancer patients was significantly longer compared to non-vaccinated controls⁴. In the Italian retrospective INVIDIa study, there seemed to be a trend towards better survival in patients who developed a flu-like syndrome after vaccination (again, unclear if this was true influenza infection -see higher)². In the abovementioned Swiss observational study, there was also a possible survival benefit in the subgroup of lung cancer patients that received the flu vaccine¹. In the large prospective series from Vanderbilt University, influenza vaccination in the setting of cancer immunotherapy did not have a significant impact on progression-free survival, but did have a positive influence on overall survival (+10 months)³.

Conclusions:

- From the limited published data we **cannot conclude that influenza vaccination is less effective in cancer patients treated with immune checkpoint inhibitors**. On the contrary, humoral responses seem to be invigorated, and in one study the number of hospitalizations due to influenza is clearly decreased (in line with expectations in a general population).
- **Nor can it be concluded that influenza vaccination systematically increases the risk to develop ICI-related immune adverse events.**
- **Finally, there is no evidence that influenza vaccination undermines the effectiveness of ICI in cancer patients.** The contrary might even be the case, but this should be confirmed in larger controlled studies.

In contrast to this limited data, there still a high level of evidence supporting the use of influenza vaccination. Especially in older cancer patients (55+) and cancer patients with important comorbidity (eg lung cancer, who often have underlying COPD, or status after resection or radiotherapy) we believe that the benefits of vaccination against seasonal influenza clearly outweigh the risks. The findings published thus far here must of course be confirmed in larger, prospective and preferably randomized studies. In addition, there are still outstanding questions for which no data is available as of this writing:

- To what extent does vaccine formulation matter with respect to the above (ie. adjuvanted vs non-adjuvanted, live vs inactivated viruses) ? Note: in Belgium for the season 2018-2019 only inactivated, non-adjuvanted tetravalent vaccine formulations are available
- Are outcomes different when vaccinating on a background of ICI in monotherapy vs newer combination regimens (ICI + ICI or ICI + chemotherapy)?
- What is the optimal timing of vaccination during the course of ICI therapy? As some patients can develop a self-limiting flu-like syndrome in the first days after vaccination, it would make sense to vaccinate at least 1 week before the next administration of ICI.

Recommendations:

Influenza vaccination remains indicated in cancer patients, even under therapy with immune checkpoint inhibitors. Close monitoring for immune-related toxicity must of course be further maintained.

We recommend vaccination at least one week before administration of ICI therapy to allow for resolution of possible vaccine-induced flu-like syndrome.

Out of precaution, we would however advise against vaccination during an episode of immune-related toxicity under immune checkpoint inhibition, or in patients in the recovery phase of such episode (i.e. as long as there is a need for systemic steroids or other immunosuppressive medication to control the immune-related toxicity).

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