OPINION ARTICLE

Should safety of the flu vaccine for cancer patients be reexamined? [version 1; referees: awaiting peer review]

Slobodan Paessler¹,², Veljko Veljkovic ³

¹Department of Pathology, Galveston National Laboratory, University of Texas Medical Branch, Galveston, TX, USA
²Galveston National Laboratory, Institute for Human Infectious and Immunity, Galveston, TX, USA
³Biomed Protection, Galveston, TX, USA

Abstract
Seasonal flu vaccine is recommended as the best protection for cancer patients against influenza infection. Recent in silico and experimental data suggest that antibodies elicited with influenza vaccine could activate bradykinin receptor B2-associated signaling pathway, which is also involved in cell proliferation and migration of tumor cells. These results point to an urgent need for the reexamination of safety of influenza vaccine(s) in cancer patients.

Corresponding author: Veljko Veljkovic (veljko@biomedprotection.com)

Author roles: Paessler S: Conceptualization, Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing; Veljkovic V: Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Paessler S and Veljkovic V. Should safety of the flu vaccine for cancer patients be reexamined? [version 1; referees: awaiting peer review] F1000Research 2018, 7:1 (doi: 10.12688/f1000research.13428.1)

Copyright: © 2018 Paessler S and Veljkovic V. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Cancer and cancer treatment can weaken the immune system making cancer patients particularly vulnerable to complications of infections, especially from acute respiratory infections such as influenza. For this reason, seasonal flu vaccine is recommended for most people with cancer and cancer survivors as the best protection against the influenza infection.

Several epidemiological studies have suggested that vaccination against seasonal influenza virus(es) significantly reduces the risk of major cardio-vascular events in patients with acute coronary syndrome or coronary artery disease. The first clinical study on the effect of influenza vaccination after heart attack on future cardiovascular prognosis is underway. The molecular mechanism underlying protection of flu vaccine against cardiovascular diseases is unknown; however, this phenomenon is independent from vaccine efficacy against influenza A infections. Recently, it was suggested that the vaccine against influenza A viruses could elicit agonistic antibodies for bradykinin receptor B2 (BKB2R), which activates a BKB2R-associated signaling pathway that may contribute to the protection against cardiovascular diseases. Moreover, it has been established that antibody activation of BKB2R is possible, with all biological activities associated with it. Recently, a monoclonal antibody with agonistic BKB2R activity as well as anti-influenza A activity has been patented for multiple purposes. Taken together, these data support the hypothesis of “molecular mimicry” between BKB2R and hemagglutinin (HA) of influenza A viruses that may allow for generation of cross reactive antibodies.

In addition, it was found that levels of kinins in biological fluids of cancer patients are increased and that activation of kinin receptors expressed on cancer cells produces an increase in cell proliferation and migration of tumor cells [reviewed in Ref. 7]. Additionally, it has been demonstrated that tumor growth is increased by stimulation of kinin receptors expressed on other cells within the tumor microenvironment, and that bradykinin and its receptors are involved in pathogenesis of numerous common cancers (gastric, hepatocellular, brain, bladder, renal, prostate and breast). These data point out that, because of possible activation of BKB2R with antibodies elicited by influenza vaccine, safety of this vaccine in cancer patients is an important issue.

Screening of the clinical trials database (clinicaltrial.gov) for trials that investigated safety of the influenza vaccine in cancer patients with solid tumors (literature data connect pathogenesis of this type of tumors with BKB2R-pathway) revealed only five completed studies (Table 1). Patients were monitored in the period between 21 days and 6 months following vaccination and results were released only for one study (NCT01666782 in Table 1) for the monitoring time frame of 21 days. These short-term studies suggest that influenza vaccination is effective and safe in cancer patients in general. However, long-term studies might be needed to test the hypothesis that if antibodies elicited by the seasonal flu vaccine may contribute to activation of BKB2R in cancer patients with potentially far-reaching consequences.

In conclusion, previously published results suggest that influenza vaccines could produce antibodies with BKB2R-agonistic activity. On the other hand, experimental and clinical data showed that activation of the bradykinin pathways plays an important role in pathogenesis of several common solid tumors. All these data suggest that until the role of the influenza vaccine in activation of BKB2R is clarified, vaccination of cancer patients against flu should be taken with some caution, and vaccines need to be monitored beyond the flu season. This especially concerns children with cancer, who represent the most vulnerable population of oncology patients. In addition, previous in silico analysis of informational properties of BKB2R and HAs from different

<table>
<thead>
<tr>
<th>Clinical Trial study</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Monitoring time frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial to compare the Immunogenicity, Safety, and Tolerability of an Adjuvanted A(H1N1) Influenza Vaccine Versus Non-Adjuvanted A(H1N1) Influenza Vaccine in Patients With Invasive Solid Tumors</td>
<td>NCT01031719</td>
<td>3 months</td>
</tr>
<tr>
<td>Safety of a Flu Vaccine Spray, Called FluMist, in Children with Cancer</td>
<td>NCT00112112</td>
<td>42–180 days</td>
</tr>
<tr>
<td>A Study of a Live Intranasal Influenza Vaccine in Children With Cancer (FMRESP)</td>
<td>NCT00906750</td>
<td>6 months</td>
</tr>
<tr>
<td>Study Comparing High-Dose Flu Vaccine to Standard Vaccine in Cancer Patients Less Than 65 Receiving Chemotherapy (IMMUNE)</td>
<td>NCT01666782</td>
<td>28 days</td>
</tr>
<tr>
<td>Immunogenicity of Fluzone HD, A High Dose Flu Vaccine, In Children With Cancer or HIV</td>
<td>NCT01205581</td>
<td>21 days</td>
</tr>
</tbody>
</table>
influenza A viruses suggested that flu vaccines are not equally efficient in production of agonistic antibodies for BKB2R. This opens the possibility for selection of antigens with low crossreactivity with BKB2R and design influenza vaccines incapable of inducing production of cross-reactive antibodies for safer use in cancer patients.

**References**


**Competing interests**

No competing interests were disclosed.

**Grant information**

The author(s) declared that no grants were involved in supporting this work.
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com