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# Vaccination for seasonal influenza in patients with cancer: recommendations of the Italian Society of Medical Oncology (AIOM)

P. Pedrazzoli[1*,†], F. Baldanti[2,†], I. Donatelli[3,†], M. R. Castrucci[3], F. Puglisi[4], N. Silvestris[5] & S. Cinieri[6]

[1]*Division of Medical Oncology, Department of Hemato-oncology;* [2]*Molecular Virology Unit, Virology, Department of Microbiology, IRCCS Policlinico 'San Matteo' Foundation, Pavia;* [3]*Department of Infectious, Parasitic and Immune-Mediated Diseases, Istituto Superiore di Sanità, Rome;* [4]*Department of Oncology, University Hospital of Udine, Udine;* [5]*Division of Medical Oncology, 'Giovanni Paolo II' Cancer Institute, Bari;* [6]*Medical Oncology Division and Breast Unit, Sen. Antonio Perrino Hospital, Brindisi, Italy*

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**Background:** Influenza virus causes annual epidemics in the winter–spring season with significant morbidity in the general population and important mortality in high-risk groups, including cancer patients. Opinions on the suitability of patients with malignancies not undergoing active treatment and in different phases of antineoplastic therapy, to receive influenza vaccination, vary considerably among oncologists, sometimes even within one center.

**Methods:** We reviewed available data, including recommendations by national health authorities, on impact of influenza in patients with cancer and their capacity to mount protective immunological responses to vaccination, thus allowing, on behalf of Italian Association of Medical Oncology, to make suitable recommendations for the prevention and treatment of seasonal influenza.

**Results and discussion:** Patients with cancer often have disease- or treatment-related immunosuppression, and as a consequence, they may have a suboptimal serologic response to influenza vaccination. The protective effect of the different preparations of influenza vaccines in patients with cancer has not been widely investigated, especially in adult patients harboring solid tumors. The optimal timing for administration of influenza vaccines in patients receiving chemotherapy is also not clearly defined. However, since vaccination is the most effective method, along with antiviral drugs in selected patients, for preventing influenza infection, it has to be recommended for cancer patients. Implementing vaccination of close contacts of oncology patients would be an additional tool for enhancing protection in fragile patient populations.

**Key words:** vaccination, influenza, cancer

## introduction

Influenza virus is an enveloped virus belonging to the Orthomixoviridae. Peculiar to this virus is the segmented and single-stranded negative-sense RNA genome, which enhances its potential for recombination. Three types of influenza virus (A, B, and C) have been so far recognized, but only influenza virus type A and B have been associated with seasonal epidemics, and only influenza virus type A can occasionally give rise to worldwide pandemics [1].

Three HA antigens (H1, H2, and H3) and two NA antigens (N1 and N2) of influenza A viruses have caused widespread disease and sustained human-to-human transmission while, in birds, 16 different HA antigens (H1–H16) and 9 NA antigens (N1–N9) are currently known. Minor antigenic variants arise yearly within the specific H1N1 and H3N2 subtypes during seasonal epidemics. Influenza B viruses also undergo antigenic drift and a significant part of the annual influenza burden is caused by two co-circulating, antigenically distinct lineages called the Yamagata and Victoria lineages.

Influenza virus type A and B show similar pathogenic potential in humans, and co-circulate during seasonal epidemics. More complex is the mechanism at the basis of pandemic events. In these cases, major antigenic variants of influenza A (antigenic shift) may be generated through genetic reassortment between virus strains of human and avian origin (the largest reservoir of influenza A strains) in host mammals susceptible to both infections, such as swine. Viruses circulating in different animal species may also be introduced directly into the human population [2]. Avian influenza viruses of the H5, H7, and H9 subtypes have also been associated with sporadic infections in

*Correspondence to:* Dr Paolo Pedrazzoli, SC Oncologia, Fondazione IRCCS Policlinico S. Matteo, Viale Golgi 19, 27100 Pavia, Italy. Tel: +39-0382-502164; Fax: +39-0382-501654; E-mail: p.pedrazzoli@smatteo.pv.it

†PP, FB and ID equally contributed to the paper.

humans. The level of herd immunity in humans to new reassortant viruses is usually very low, making it possible their rapid spread worldwide (pandemics) and underlies the increased virulence of pandemic influenza A strains.

Influenza virus A and B are eliminated at high titer in respiratory secretions and are spread through droplets, but also through contact with contaminated hands or objects.

It is generally assumed that both innate and adaptive immunity play a role in controlling influenza virus infection at the individual level. In particular, the presence of cross-reactive memory B and T cells is responsible for the differing susceptibility to influenza virus infection and disease severity, observed between young people and adults. In Italy, data collected from the nationwide active sentinel surveillance network (INFLUNET) show that among clinical swabs collected during 2010–2011 season, 31% were tested positive for influenza (http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=0&codLeg=39451&parte=1%20&serie=). The incidence of seasonal influenza decreases with age and reaches a minimum value in healthy adults, which correlates with the pre-existing influenza immunity.

Influenza infection can be limited at the upper respiratory tract, but can also spread to the lower respiratory tract and cause respiratory failure. In addition, lung failure can be exacerbated by bacterial and fungal superinfections in debilitated individuals. When evaluating the effectiveness of influenza vaccine, it is important to point out that, during the winter–spring season, a number of respiratory viruses co-circulate together with influenza A and B (rhinovirus, metapneumovirus, respiratory-syncitial virus, enterovirus, coronavirus, adenovirus). In Italy, seasonal influenza epidemics are associated with an annual average of about 8000 excess deaths. In the 2010–2011 season, 6700 deaths (84%) were among elderly people aged ≥65 with underlying cardiopulmonary conditions or other chronic diseases.

Influenza infection is a potential cause of additional morbidity and mortality in subjects who are immunocompromised because of underlying disease or its therapy [3]. In fact, people with cancer are more likely to get influenza complications such as upper and lower respiratory tract infections. Hospitalization because of influenza infections is three to five times higher in cancer patients than in the general population, and the mortality rate is 9% in oncology patients (relative risk of 4 compared with the general population) [4]. As a consequence, the health authorities recommend vaccination against influenza in the immunocompromised host and in close contacts [3]. Vaccination is also important to prevent intercurrent infections that may require dose reduction and delays in the treatment of the underlying malignancy.

The purpose of this article is to highlight the impact of influenza in patients with cancer and their capacity to mount protective immunological responses to vaccination, thus allowing the Italian Association of Medical Oncology (AIOM) to make suitable recommendations for the prevention and treatment of seasonal influenza.

## methods

We reviewed available data present in the literature, including recommendations by national health authorities, on impact of influenza in patients with cancer and their capacity to mount protective immunological responses to vaccination. Data on available vaccines, strategies to improve the efficacy of influenza vaccination, and treatment of established infection were also reviewed.

In addition, experts from the Italian society of Virology and the Italian Health Authority, who are listed among authors, provided additional biological, clinical, and epidemiologic information which greatly helped in clarifying some issues in the absence of clear-cut information from the literature.

## results

### available vaccines and their potential side-effects

Two types of influenza vaccines are available: (i) the inactivated, injectable vaccine approved for use in subjects older than 6 months, including healthy people, pregnant women, and people with chronic medical conditions; (ii) the live attenuated influenza vaccine (LAIV) administered as a nasal spray. LAIV is approved for use in healthy people from 2 to 49 years of age who are not pregnant. Trivalent inactivated Influenza vaccines may include adjuvants to enhance immunogenicity, and are usually administered as a single shot in immunocompetent individuals, while immunosuppressed subjects may need booster administration.

Seasonal influenza vaccines contain antigens that match the three different influenza strains co-circulating during the seasonal epidemics (A H1N1, A H3N2, and influenza B). Due to the constant emergence of antigenic drift variants under herd immunity pressure, the Influenza vaccine needs yearly update to include the escape variants detected during each seasonal epidemic which are predicted to circulate during the next winter–spring season. This update is organized by the WHO through the network of sentinel practitioners and reference laboratories (INFLUNET). If the viruses in the vaccine are closely matched to those circulating in the community, vaccine effectiveness is greater. However, even when the viruses are not closely related, the vaccine can still be expected to provide some cross-protection against different, but related, strains of influenza viruses. Based on the limited cross-protection between the two influenza B lineages and the inability to accurately predict which influenza B lineage will circulate, a quadrivalent influenza vaccine including both influenza B strains [5] has recently been approved by the FDA and the European Medicines Agency. Pharmaceutical companies will likely transition to predominantly producing the quadrivalent vaccine.

Over the years, hundreds of millions of people worldwide have received seasonal influenza vaccines, essentially without serious consequences. The most common side-effects reported are soreness, redness, tenderness, or swelling of the injection site. Less common are mild arthromyalgia, low-grade fever, and nausea. When such problems occur, they start soon after vaccination and persist for1–2 days. On rare occasions, Influenza vaccination has been associated with more serious complications, such as severe allergic reactions. Before inactivation, influenza viruses are cultured in chicken eggs, so administration of influenza vaccines in subjects with allergy to chicken egg proteins should be avoided.

Influenza vaccination has been reported to increase the risk of Guillain–Barré syndrome (GBS) up to 8.8-fold over background rates, mainly based on the experience in 1976 when mass immunization was conducted to prevent an A H1N1 influenza epidemic

[6]. Enhanced surveillance for GBS, conducted in 2009–2010, suggested that influenza vaccines were of public health benefit, albeit being associated with a small increased risk of GBS [6].

## response and timing of vaccination in cancer patients

Successful immunization depends on an intact immune system that can produce antibodies and T-cell response upon antigen exposure. Patients with cancer are considered functionally immunosuppressed, due to their underlying disease and/or cancer therapy. As a consequence, they may have a suboptimal serologic response to influenza vaccination. Although antiviral prophylaxis has been recently used for prevention of influenza virus infection in specific clinical settings such as perivaccine prophylaxis, postexposure prophylaxis, family cluster prophylaxis, as well as seasonal prophylaxis [5], vaccination is the most effective method for widespread prevention of influenza infection. Indeed, the CDC's Advisory Committee on Immunization Practice (ACIP) in the United States recommends seasonal influenza vaccination for adults without contraindications, who have disease- or medication-related immunosuppression (http://www.cdc.gov/flu/about/disease/high_risk.htm). However, knowledge of serologic response to seasonal influenza vaccine remains scanty in patients with cancer and is particularly sparse in those with solid tumors [7]. Tumor heterogeneity, timing of influenza vaccination relative to different chemotherapy treatments, and a general lack of data concerning the vaccine efficacy against influenza infection, or its complications, make it difficult to compare the clinical studies so far reported in the literature. The results of eight controlled clinical trials looking at the efficacy of influenza vaccination in pediatric cancer patients were reviewed [8]. Children receiving chemotherapy were able to generate immune responses to the vaccine, albeit more weakly than healthy children, children with asthma or children with cancer who had completed chemotherapy more than 1 month before vaccination. Influenza vaccine was safely administered, and there were no reports of persistent adverse reactions in any of the studies, although patients receiving chemotherapy had a higher incidence of general malaise following vaccination. None of these studies reported on clinical outcome. Seroprotection (antibody titer >40) and seroconversion (at least a fourfold rise in HI titers) were achieved in patients with an established diagnosis of lymphoproliferative disorders [9, 10], irrespective of the previous chemotherapy administration.

Another recent review and meta-analysis conducted to assess influenza vaccination in immunocompromised patients showed a significantly lower incidence of influenza-like illness after vaccination in HIV patients, cancer patients, and transplant recipients compared with placebo or no vaccination [11].

An early study investigated the serologic response to bivalent inactivated influenza vaccination in 17 patients with malignancies [12]. Protective immunity against each of the two influenza A strains in the vaccine was achieved by 41% and 47% of patients, respectively. A study conducted on 41 patients with lung cancer showed a rate of response to the inactivated trivalent seasonal influenza vaccination of 78% [13] similar to that seen in healthy subjects [14]. Chemotherapy within the previous 4 weeks, or systemic corticosteroid medication had no significant effect on protective HI response. However, no large trials exist to replicate this information.

Data regarding timing of influenza vaccination with regard to chemotherapy administration in adults with solid tumors and hematological malignancies are limited to three studies: one published in 1977 [15], two in recent years [4, 16]. Overall, 126 patients have been investigated in such studies. Despite the paucity of data in a heterogeneous patient population, it can be suggested that tor patients with solid tumors, if possible, vaccination should be given mid-cycle, preferably 2 weeks after chemotherapy and/or before administration of the subsequent cycle. For patients with hematologic malignancies, the highest serologic response appears to occur following vaccination administered when the leukocyte count is normal and just before initiation of a cycle. In a recently published review article, Polleya et al. recommend vaccination at the furthest possible time point away from treatment during a given cycle [17].

Studies, mostly conducted in children, comparing patients who have completed treatment with those who are still receiving treatment, show superior responses in those who have finished treatment [18–20].

All these studies indicate that, in general, both chemotherapy-naïve and -treated cancer patients show reduced responses to influenza vaccination compared with healthy subjects, but that a considerable number of cancer patients do actually reach the cutoff level for seroprotection. Unfortunately, this is not the case in patients treated with Rituximab in which an impaired immune response to influenza vaccine is reported to be associated with persistent memory B-cell depletion [21–25]. Thus, in the context of rituximab-including therapies, alternative or better-defined prophylactic/therapeutic approaches are needed.

## influenza vaccination in patients with solid tumors receiving targeted therapies

Limited data are available on the efficacy of influenza vaccination in patients receiving immunotherapies or biologic agents alone or in combination with chemotherapy.

The VACANCE study [26] showed that biologic agents given in combination with cytotoxic drugs did not seem to negatively affect seroprotection. In the same study, patients on targeted therapy alone, especially multikinase inhibitors, had better immune responses than other treatment groups.

The latter results are in keeping with a recently published report [27] showing that a single shot of influenza vaccination is safe and effective in mounting an antibody immune response in patients treated with sunitinibor sorafenib, and this immune response is comparable with healthy controls. Standard influenza vaccination can be therefore recommended for these patients.

## strategies to improve the efficacy of influenza vaccination

Cancer patients are fragile subjects and influenza vaccine may be less effective due to the impaired immune system. For this reason, they should not be exposed to the LAIV, and the trivalent inactivated vaccine is recommended for annual influenza prophylaxis. Vaccination against influenza can reduce severe illness and complications in immunocompetent individuals, but data demonstrating vaccine effectiveness in immunocompromised

individuals are limited [9]. Among HIV-positive people with low CD4+ T-cell counts, the administration of inactivated trivalent vaccine does not induce protective antibody titers and a second dose of vaccine does not improve their immune responses [28]. The lack of benefit of one versus two doses of inactivated influenza trivalent vaccine has also been documented in 70 patients with hematological tumors [29].

A recent study [22] demonstrated that two doses of adjuvanted vaccine A/H1N1 was required in 197 cancer patients undergoing chemotherapy, to achieve a similar seroprotection rate (82.3% versus 87%) to that achieved in 138 controls given one dose.

Aging decreases the immune response after influenza vaccination, and adjuvants or higher doses of antigen are supposed to improve the immune response with better protection against influenza. In the VACANCE study, including 65 cancer patients receiving cytotoxic and/or targeted therapies [4], one or two doses of AS03A-adjuvanted H1N1v vaccine resulted in seroprotection rates of 48% and 73%, respectively, and seroconversion rates of 44% and 73%, respectively. Thus, two doses of adjuvanted vaccine improved immunoprotection in this population. There was no suggestion of a potential detrimental effect on tumor therapy by the nonspecific inflammatory stimulus due to adjuvants.

The unique immunological characteristics of the skin with its dense network of immune-stimulatory antigen-presenting cells, together with progress in immunization techniques, offer possible ways of improving immunogenicity in low responders, as well as reducing dosage in healthy adults [30]. A study by Jo et al. [31] showed that intradermal injection of one-half the dose of a trivalent inactivated split vaccine, elicited immune responses comparable with those elicited by a full dose of intramuscular vaccine among cancer patients. An open-label study of Fluzone® high-dose vaccine versus the Fluzone® standard dose is currently ongoing in children with cancer or HIV receiving two injections of either dose (www.clinicaltrial.gov: NCT01205581).

Vaccination apart, protection of cancer patients could be increased by reducing the likelihood of infection. While patients' isolation is not practically feasible, and would not be ethical, vaccination of household contacts and health care personnel is of pivotal importance for increasing the level of herd immunity in the local environment with consequent reduction of influenza virus circulation and likelihood of infection. Moreover, strict preventive measures should be adopted in oncology wards when hospitalized patients develop influenza-like illness, even before the results of viral testing are known. All hygiene precautions (hand washing, surgical masks, etc.) should be enforced together with restrictions on visitors suspected of having respiratory illness. Leukemic children receiving maintenance chemotherapy (lasting 2–3 years) have been reported to be more susceptible to viral infections, probably due to their higher exposure to infected people during school or daycare contacts. Thus, appropriate therapies, together with continued surveillance and implementation of preventive practices, are essential for their care.

### antivirals for documented or suspected infection

Antiviral treatment started as soon as there is suspicion of influenza may make influenza infection milder, shorten the duration of illness, and decrease complications in all populations. Oseltamivir and zanamivir target the neuraminidase enzyme and are effective treatments for influenza infection. Both drugs are typically given for 5 days, but longer duration of therapy have been advocated in patients undergoing chemotherapy or with reduced lymphocyte counts as prolonged viral shedding may occur in these subjects, and when severe influenza (i.e. influenza pneumonia or illness requiring ICU-level care) is documented (http://www.cdc.gov/h1n1flu/recommendations.htm).

Antiviral resistance to oseltamivir and zanamivir among circulating influenza viruses is currently low, but this can emerge during treatment especially when protracted for long periods [32, 33]. In patients with cancer who develop fever or influenza-like illness, early antiviral therapy should be given empirically without awaiting laboratory confirmation. On the other hand, the administration of antiviral drugs may represent the only feasible strategy for the prevention and treatment of influenza in cancer patients who may not benefit from prophylactic vaccination (e.g. patients receiving rituximab-including therapies).

## discussion

It should be emphasized that influenza vaccination in patients with cancer is safe, minimally invasive, and inexpensive. The AIOM recommends vaccination against seasonal influenza for cancer patients without contraindications. Both untreated

**Table 1.** Recommendations and statements on the use of vaccination for seasonal influenza in patients with cancer

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| Influenza vaccination in patients with cancer is safe, minimally invasive, and inexpensive. |
| It should be widely utilized in patients with cancer both untreated and receiving active therapy, including biologic agents for solid tumors. The ideal time to administer the vaccination during a treatment cycle is unclear. |
| Vaccination of household contacts and health care personnel is highly recommended as it bears significant implications in increasing the level of herd immunity in the microenvironment with consequent reduction of influenza virus circulation and likelihood of infection. |
| Strict preventive measures should be adopted in oncology wards in the presence of hospitalized patients who develop influenza-like illness. |
| Trivalent inactivated vaccine should be given. Data suggest an increased seroprotection rate by means of vaccines with adjuvants, an higher doses of antigen, or a second dose of vaccine. A quadrivalent vaccine has been recently approved by the United States and European health authorities. |
| Cancer patients treated with rituximab-containing regimens have persisting perturbations of B-cell compartments and an impaired immune response to influenza vaccine, but also to other common vaccines. Thus, special efforts are needed to improve preventive/therapeutic strategies for these refractory patients, including prophylactic antivirals. |
| Prospective randomized, controlled trials to better define the serological response and the clinical benefits of influenza vaccination are needed in this patient population. |

patients and patients undergoing active treatment in any phase of antineoplastic therapy should be vaccinated. Vaccination of all household contacts and health care personnel is also recommended. Well-designed prospective studies are needed to identify optimal immunogenic strategies for seasonal influenza vaccination in different clinical conditions, together with optimal timing of vaccination relative to chemotherapy administration. A summary of the AIOM recommendations is reported in Table 1.

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## disclosure

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