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REVIEW

Vaccination for seasonal influenza, pneumococcal infection and SARS-CoV-2 in patients with solid tumors: recommendations of the Associazione Italiana di Oncologia Medica (AIOM)

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Patients with cancer have a well-known and higher risk of vaccine-preventable diseases (VPDs). VPDs may cause severe complications in this setting due to immune system impairment, malnutrition and oncological treatments. Despite this evidence, vaccination rates are inadequate. The Italian Association of Medical Oncology [Associazione Italiana di Oncologia Medica (AIOM)] has been involved in vaccination awareness since 2014. Based on a careful review of the available data about the immunogenicity, effectiveness and safety of flu, pneumococcal and anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, we report the recommendations of the AIOM about these vaccinations in adult patients with solid tumors. The AIOM recommends comprehensive education on the issue of VPDs. We believe that a multidisciplinary care model may improve the vaccination coverage in immunocompromised patients. Continued surveillance, implementation of preventive practices and future well-designed immunological prospective studies are essential for better management of our patients with cancer.

Key words: influenza, vaccine-preventable diseases (VPDs), pneumonitis, cancer, vaccine hesitancy, COVID-19

INTRODUCTION

Patients with cancer have a well-known and higher risk of vaccine-preventable diseases (VPDs).[1] VPDs may cause severe complications in this setting due to the immune system impairment, malnutrition and oncological treatments.[2] They represent a serious economic burden with a delay in the treatment of the underlying cancer.[3] Despite this evidence, vaccination rates are inadequate: during the 2021-2022 season, the receipt of seasonal influenza vaccine among subjects over 64 years of age was 57.2%.[4] Vaccine hesitancy is mainly due to the fear about the side effects of vaccines, progressive decrease in the awareness of the dangerousness of VPDs, negative attitudes towards vaccination, limited access to health care services and lack of confidence in prevention measures.[5] Vaccine hesitancy has been identified as one of the top 10 threats to global health by the World Health Organization (WHO) and has become increasingly prominent during the coronavirus disease (COVID-19) pandemic.[6] The Italian Association of Medical Oncology [Associazione Italiana di Oncologia Medica (AIOM)] has been involved in vaccination awareness since 2014. The first recommendations on seasonal influenza vaccination were published in 2014,[7] and they were subsequently updated and implemented with those on pneumococcal vaccination in 2018.[8] More recently, the AIOM has published the recommendations about the vaccination for herpes zoster.[9]

In this position paper, we will report:

- the revision of the available data about the immunogenicity, effectiveness and safety of flu, pneumococcal and anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in patients with solid tumors according to the different types of oncological treatments
- AIOM recommendations

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MATERIALS AND METHODS

A web-based search of MEDLINE/PubMed library data published from 2014 to January 2023 was carried out by associating "seasonal flu vaccine" OR "pneumococcal vaccine" "anti-SARS-CoV-2 vaccine" OR "COVID-19 vaccine" with "cancer" OR "chemotherapy" OR "immunotherapy" OR "radiotherapy" OR "targeted therapy". A manual screening for references from original articles was also done in order to identify additional studies. The authors selected >100 articles. Only articles published in English were reviewed. A panel of virologists and infectious diseases specialists, selected by the board of AIOM, provided additional information to complete the discussion.

INFLUENZA VIRUSES

Influenza viruses are enveloped negative-sense RNA members of the family Orthomyxoviridae.[10,11] Currently, the circulating seasonal influenza viruses consist of A (H1N1), A (H3N2) and the two lineages of influenza B viruses.[12] Influenza viruses are the primary etiology of acute respiratory infections that may be life-threatening in immunocompromised patients.[13] Malignancy is a strong independent predictor of 30-day mortality [odds ratio (OR) 2.26, 95% confidence interval (CI) 1.50-3.40] during viral pneumonia.[14]

Influenza viruses may present respiratory complications such as primary influenza viral pneumonia and influenza viral co-infection with community-acquired bacterial pneumonia and may lead to respiratory failure, acute respiratory distress syndrome (ARDS), septic shock and multiorgan failure.[14] Influenza viruses may exacerbate asthma and chronic obstructive pulmonary disease.[15] Several studies described extrapulmonary complications such as myositis and rhabdomyolysis, elevation of hepatic aminotransferases, cerebrovascular accident and cardiac complications without underlying cardiac disease.[16,17] The acute infections are linked to an increased risk of developing venous thromboembolic events.[18] Jansen and colleagues demonstrated an inverse correlation between patient influenza viral load and platelet count.[19] This evidence might explain the mechanism of influenza virus-induced thrombocytopenia and the increased risk of ARDS and ARDS-related mortality in those patients with influenza virus infection and concomitant thrombocytopenia.[20]

Diagnosis

Molecular diagnostics [rapid molecular assays, reverse transcription polymerase chain reaction (RT-PCR) and other nucleic acid amplification tests] are the gold standard for influenza diagnosis.[21] Nasopharyngeal swabs are more sensitive than throat swabs.[22] In the case of negative results but with high suspicion of viral pneumonia, bronchoalveolar lavage might be done to confirm the diagnosis.[21] Molecular assays show a sensitivity higher than 90%-95% and high specificity while rapid influenza antigen detection tests (antigen detection tests) are characterized by a high specificity (90%), speed of response (from 15 to 30 min), but low sensitivity (50%-70%).[23] The Infectious Diseases Society of America (IDSA) recommends the use of RT-PCR or other molecular assays for the diagnosis of influenza viruses in hospitalized patients.[24]

Therapy

Antiviral therapy should be started as soon as possible (within 48 h), because there is no evidence of benefit to start beyond 5 days after the onset of illness.[23,25] Oseltamivir is the initial therapeutic choice; it is administered orally at a dose of 75 mg twice daily for at least 5 days.[23] Longer duration of antiviral treatment is indicated for patients with a documented or suspected immunocompromising condition or patients with ARDS. Oseltamivir should be administered as post-exposure antiviral chemoprophylaxis in severely immunocompromised subjects as soon as possible for at least 7 days.[24]

Influenza vaccine

Currently, there are three main types of influenza licensed for use worldwide: attenuated influenza vaccine, recombinant hemagglutinin vaccine and inactivated vaccine. The live attenuated vaccine is not recommended to subjects with immunodeficiency.[26] The recombinant hemagglutinin vaccine presents low immunogenicity.[27] The recommended inactivated influenza vaccine is the quadrivalent vaccine. According to the Centers for Disease Control and Prevention (CDC), there is a wide year-to-year variability of the seasonal influenza vaccine effectiveness.[28] As recommended by CDC, subjects with a history of egg allergy of any severity should receive 'any licensed, recommended and age-appropriate influenza vaccine'.[29]

The influenza vaccine immunogenicity may be improved by the use of two vaccine doses (booster) in the same influenza season or high-dose vaccines (twofold or fourfold dose). A meta-analysis of randomized controlled trials (RCTs) compared the immunogenicity and safety of alternative higher-dose and standard-dose trivalent influenza vaccines in immunocompromised patients. The paper demonstrated significantly superior immunogenicity in reinforcing seroconversion (SCR) and seroprotection (SPR) for the H1N1 strain in patients with cancer undergoing chemotherapy. Moreover, no significant differences between higher-dose and standard-dose vaccination in terms of safety were highlighted.[30] Adjuvanted vaccines such as MF59-adjuvanted seasonal influenza vaccine have an adjuvant as an ingredient that is added to create a stronger immune response to vaccination and can improve the vaccine efficacy in immunocompromised patients.[31]

Immunogenicity of influenza vaccine in patients with solid tumors

A systematic Cochrane review considered RCTs, prospective and retrospective cohort studies and case-control studies with the comparison between inactivated influenza vaccines and placebo or no vaccination. The collected data evidenced lower mortality and infection-related outcomes after seasonal influenza vaccination.[32] The immunogenicity

of influenza vaccines is measured by the evaluation of the acquired antibody levels after vaccination SPR and the quantitative rise in antibody titers after vaccination SCR. Vollaard and colleagues reviewed the SPR rates in 16 studies in cancer patients with a wide range of increase between studies and virus strains (20%-100%) and during cycles of chemotherapy (32%-100%). The authors concluded that the majority of patients showed an adequate response to vaccination, irrespective of the type of cancer, treatment and age.[33]

In a small cohort of 38 breast cancer patients on chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide, the geometric mean titers (GMTs) before and after vaccination were compared. Twenty patients received the influenza vaccine on day 4 of the chemotherapy cycle (early group), while 18 patients received the influenza vaccine on day 16 (late group). GMTs were not significantly different ($P > 0.05$) when comparing early and late group.[34] In a prospective open-label multicenter study, 20 breast cancer patients during trastuzumab treatment in the adjuvant setting and 37 controls were analyzed. The SPR rate between trastuzumab-treated patients and controls revealed no difference for H1N1 (100% in both groups) and B strain (78.9% versus 89.2%, P value $= 0.423$).[35]

Another prospective single-arm study recruited 53 patients with solid tumors during the 2011 and 2012 influenza seasons. The patients received a single dose of 2011/2012 trivalent vaccine before or in-between treatment cycles and haemagglutination inhibition antibody titers were measured at baseline, 3, 6 and 24 weeks after the vaccination. The multivariate analysis showed a rise in haemagglutination inhibition antibody-protective titers from baseline similar to the general population, but 24 weeks after vaccination, which corresponds to the end of the influenza season, the titers were non-sustained.[36]

A pilot prospective cohort study evaluated the immunogenicity of the trivalent inactivated influenza vaccine in patients with central nervous system (CNS) malignancies. Thirty-eight patients were enrolled. Twenty-eight days after the influenza vaccine, humoral responses were significantly lower than those published in healthy adults ($P < 0.001$). The authors demonstrated a significant reduction in influenza vaccine immunogenicity among patients with CNS malignancies and suggested alternative vaccination strategies, such as high-dose or two-dose regimens.[37]

Nakashima and colleagues prospectively collected serum samples from 25 patients with lung cancer on chemotherapy before vaccination and 4-6 weeks after vaccination. They noted that the patients with lung cancer receiving the platinum doublet treatment exhibited a lower SPR rate than those receiving a single agent.[38]

The timing of vaccine administration during chemotherapy remains one of the main issues. The IDSA suggests the vaccination at the furthest time from the next chemotherapy cycle.[39] Keam et al. demonstrated that the antibody responses to influenza vaccine, administered concurrently with chemotherapy (day 1) or during the cytopenic period (day 11) of a 3-week cytotoxic chemotherapy cycle, were comparable.[40]

Effectiveness of influenza vaccine in patients with solid tumors

The clinical benefits of influenza vaccination for patients with cancer are typically reduction in hospitalization rates, delays in chemotherapy administration and mortality.[32,41] One of the largest observational retrospective test-negative study evaluating the influenza vaccine effectiveness (VE) among patients with cancer was conducted in Canada. The authors identified 26 463 patients with cancer who underwent influenza testing. In particular, 18 205 patients (69%) had solid tumors and 23% were on active chemotherapy. VE was 25% (95% CI 18% to 31%). No significant difference in VE was evaluated between patients on active chemotherapy (VE 14%, 95% CI −1% to 26%) and patients not on active chemotherapy (VE 22%, 95% CI 15% to 28%; P for interaction $= 0.38$).[42] These data strongly support influenza vaccination among patients with solid tumor regardless of active chemotherapy.

Discordant results were obtained from a population-based retrospective cohort study in Taiwan. Wu and colleagues compared VE (all-cause mortality, emergency admission, hospitalization and hospital costs for influenza-related complications during the influenza season) in elderly women and elderly patients with newly diagnosed breast cancer with the evidence of no statistically significant differences between influenza-vaccinated and unvaccinated patients with breast cancer, irrespective of adjuvant treatments. The authors concluded that the causes of these results are multifactorial, including chemotherapy, radiotherapy and mental stress.[43,44]

An intriguing study reported that influenza vaccination among patients with chronic obstructive pulmonary disease (COPD) seems to reduce the risk of lung cancer [adjusted hazard ratio (HR) $= 0.40$, 95% CI 0.35-0.45, $P < 0.001$]. The authors found a dose-dependent protective effect after stratifying patients according to the total number of vaccinations during the follow-up period.[45] The influenza vaccine might play a key role in reducing the exacerbations in patients with COPD caused by influenza virus infection with the consequent reduction of chronic inflammation. In lung cancer, a lower viral clearance is reported; the prolonged infection and chronic inflammation may lead to the alteration of the tumor microenvironment (TME) and consequently the progression of disease. Indeed, vaccination prevents influenza from a direct modulation of TME.[46]

A recent study has reported that influenza vaccination in patients undergoing curative surgery for solid tumors is associated with a decrease in overall mortality (HR $= 0.89$, 95% CI 0.81-0.99, $P = 0.03$) and cancer-related mortality (HR $= 0.82$, 95% CI 0.71-0.93, $P = 0.003$) compared to the patients never receiving influenza vaccine.[47]

The same authors found a reduced risk of recurrence in patients with colorectal cancer receiving an influenza vaccine from 6 to 12 months before curative surgery compared to non-vaccinated patients. These results might be due to the modulation of local TME in favor of cytotoxic immunity done by influenza vaccine.[48]

Immunogenicity of influenza vaccine in patients with solid tumors during immune checkpoint inhibitors

From September to November 2018, a prospective study enrolled patients with cancer who received either immune checkpoint inhibitors (ICIs) or cytotoxic chemotherapy. All patients received a single dose of seasonal quadrivalent influenza vaccine on day 1 of the cycle. The humoral immunogenicity of influenza vaccination was significantly higher in the ICI group than in the cytotoxic chemotherapy group.[49] The cell-mediated immune (CMI) responses following influenza vaccination were measured in some patients enrolled from the aforementioned study.[50] The authors arbitrarily defined the adequate CMI response as an increase in polyfunctional cells after vaccination in both the H1N1 and H3N2 strains. The vaccine-elicited cytokine or granule production and the increase in polyfunctional T cells were found to be higher in the ICI group than in the chemotherapy group.[50]

Recently, Herati and colleagues have evaluated the impact of anti-programmed cell death protein 1 (PD-1) immunotherapy on the follicular helper CD4 T cells (Tfh)-B cell axis. Patients received influenza vaccine on the same day of ICI therapy. Across all three strains of influenza included in the vaccine, neutralizing antibody titers increased by a median of fourfold in the ICI group compared with twofold without ICI therapy. This study demonstrated that the anti-PD-1 treatment is associated with enhancement of cTfh, B cell and gastrointestinal cancer (GC) responses following influenza vaccination.[51]

Effectiveness of influenza vaccine in patients with solid tumors during immune checkpoint inhibitors

An Italian multicenter prospective observational study (INVIDIa-2) evaluated the effectiveness of influenza vaccine in terms of incidence and severity of influenza-like illness (ILI) in patients with cancer on ICIs. Influenza vaccination did not modify ILI incidence: the time to ILI was similar in the vaccinated and unvaccinated groups ($P = 0.62$). However, influenza vaccination diminished the incidence of complications (11.8% versus 38.3% in the unvaccinated group, $P = 0.002$). ILI lethality was absent in vaccinated patients and reached 4.3% in unvaccinated ones.[52] A systematic review summarized the available data on the efficacy of influenza vaccination in patients with cancer undergoing ICIs. The authors included eight studies with positive results in terms of reduction in influenza infection and/or complications. The heterogeneity of efficacy endpoints and data (type of vaccine, population enrolled) did not allow a pooled descriptive analysis.[53]

Influenza vaccines and adverse events during oncological treatment

A systematic review evaluated the rates of immune-related adverse events (irAEs) in the vaccinated group compared to the unvaccinated group. This rate was slightly lower (32%) than that reported in the unvaccinated group (41%) with a difference not significant (response rate 0.90, 95% CI 0.72-1.1, $n = 2485$, $I2 = 64.8\%$).[54] In a retrospective cohort of patients with cancer undergoing ICIs, the rate of influenza vaccine cases was lower among ICI-related myocarditis than controls on ICIs without myocarditis. However, there was less myocardial injury and a lower risk of major adverse cardiac events among those who had received the influenza vaccine.[55] Another retrospective analysis retrieved the Vaccine Adverse Event Reporting System (VAERS) and VigiBase to find cases of myocarditis in which the influenza vaccine and ICI were registered as suspected and reported concomitantly. Three cases of myocarditis were recovered in VigiBase. No cases were classifiable for a causality assessment due to a lack of latency data.[56] In a single-center, prospective case series, 24 patients with cancer on ICIs were enrolled and received 0.5mL intramuscular of inactivated quadrivalent influenza vaccine. After a follow-up period of 2 months, seven patients (29%) experienced new irAEs and two of them reported grade 3 nephritis and grade 4 diabetes. The majority of irAEs were grades 1-2, and ICI therapy did not change.[57] The most frequently reported events were endocrine events, pneumonitis, rash, colitis and arthritis, essentially the same as for non-vaccinated subjects.[58]

Influenza vaccines and cancer-related outcomes during ICIs

Two recent studies[59,60] have demonstrated longer progression-free survival (PFS) for vaccinated patients with cancer during ICIs compared with unvaccinated patients and discordant results about the overall survival (OS). Erickson and colleagues reported that the vaccinated group had longer PFS than the unvaccinated group (HR = 0.67, 95% CI 0.47-0.97), but not OS (HR = 0.95, 95% CI 0.62-1.46).[58] Indeed, Valachis and colleagues reported a statistically significant longer PFS and OS in multivariate analyses in the vaccinated group compared to the unvaccinated one after adjustment for age, sex, comorbidity, performance status, brain metastases and line of treatment ($P = 0.041$ and 0.028, respectively).[59] Bersanelli et al., in the INVIDIa study, showed that in the lung cancer and elderly subgroups, influenza vaccine was related to OS advantage ($P = 0.04$ and $P = 0.05$, respectively).[60]

Cocoon vaccination

'Cocooning' vaccination is a public health policy targeting the protection of a vulnerable individual through the immunization of close contacts.[61] Household contacts and caregivers of patients with cancer should receive the influenza vaccine, but there is a low acceptance rate probably due to few educational interventions by general

practitioners and oncologists. In a retrospective Dutch study, the influenza vaccination rates of patients with cancer and their caregivers were 43.9% and 44.9%, respectively. The main reasons for not being vaccinated were the absence of an invitation from the physicians and the belief that it was unnecessary.[62]

Influenza vaccination in health care workers

The oncologist has a central role in the dissemination of correct and unambiguous information about vaccination. Unfortunately, even today not all health care workers (HCWs) receive the influenza vaccination. Many approaches, such as offering vaccination at the workplace and during working hours, educational forms and mandating influenza vaccination for all HCWs without contraindications, have been shown to increase HCW vaccination rates.[63]

An 8-year study conducted in Texas evaluated the relationship between HCW vaccination rates and nosocomial influenza infections in patients with cancer. The proportion of nosocomial influenza infections was significantly associated with increased HCW vaccination rates in nursing staff ($P = 0.043$) and in personnel working in high-risk areas ($P = 0.0497$).[64]

STREPTOCOCCUS PNEUMONIAE

Streptococcus pneumoniae (*S. pneumoniae*, pneumococcus) is a Gram-positive bacterium and colonizes the nasopharynx. It is primarily an asymptomatic commensal in the upper respiratory tract of healthy adults but among the immunocompromised, or in the elderly, can cause a variety of diseases such as otitis media, pneumonia, bacteremia and meningitis.[65] After fluctuating between 9.1 and 9.9 from 2012 to 2018, the overall invasive annual incidence dropped from 9.2 cases per 100 000 population in 2019 to 5.4 in 2020 due to the COVID-19 pandemic lockdown and preventive measures.[66] Pneumococcal pneumonia is the main type of pneumococcal disease worldwide and viral infections, such as influenza, can enhance the susceptibility of the lower airway for bacterial establishment and accelerate progression to invasive disease.[67]

Diagnosis

Bacterial cultures and Gram-staining tests using body fluids are currently used to determine the strain of bacteria. It usually takes $\geq$48 h before the identification of a specific bacterium, and unfortunately the rate of positive blood cultures is very low (from 4.7% to 16%). One useful tool in the case of suspected pneumonitis is the urinary antigen test (UAT) which monitors the levels of the C-polysaccharide antigen of pneumococcus in the urine. UAT is a non-invasive, easy-to-perform test, which can produce results within 15 min of urine sample collection and is not influenced by the previous administration of antibiotics.[68]

Therapy

The WHO declared that the pneumococcus is one of the top priority pathogens that urgently requires novel antimicrobial strategies due to the spread of pneumococcal clones resistant to beta-lactams, macrolides, fluoroquinolone and sulfamethoxazole-trimethoprim worldwide.[69,70]

Indeed, the therapy of resistant *S. pneumoniae* is a growing issue. An antimicrobial stewardship can lead to the choice of the correct drugs for the correct timing and usage, but enhanced preventive measures seem to be the best choice.

Pneumococcal vaccine

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has proven protection against 80%-90% of the pneumococcal capsular serotypes causing disease. It is supplied as either a single dose of 0.5 ml or a multidose 5.0-ml vial to be administered either intramuscularly or subcutaneously into the deltoid muscle or lateral midthigh. Common side effects include mild site injection reactions, headache, fatigue and myalgia. It is recommended that all adults 65 years of age and older receive one dose of PPSV23. Before 65 years of age, a single vaccination with PPSV23 is recommended for at-risk adults such as patients with cancer. The first 7-valent pneumococcal polysaccharide conjugate vaccine (PCV7) was developed in 2002. The 13-valent pneumococcal conjugate vaccine (PCV13) contains the seven serotypes of PCV7, five serotypes found in PPSV23 and one unique serotype found in neither PPSV23 nor PCV7, serotype 6A.[71] On 20 October 2021, the Advisory Committee on Immunization Practices licensed the use of either the 20-valent pneumococcal conjugate vaccine (PCV20) alone or 15-valent pneumococcal conjugate vaccine (PCV15) in adults either as sequential vaccination followed by PPV23 or as single vaccine PCV20 (+/− PPV23).[72]

The CDC recommends pneumococcal vaccination for adults from 19 to 64 years old who have risk factors such as generalized malignancy and iatrogenic immunosuppression, including long-term systemic corticosteroids and radiation therapy.[73]

Pneumococcal vaccination in patients with solid tumors

The latest guideline from the IDSA states that immunocompromised patients should receive PCV13 and PPSV23 program. The guideline states that the timing of vaccination should be at least 2 weeks before the start of chemotherapy, and that the vaccine administered during chemotherapy should not be considered valid.[39] Despite the strong level of recommendation, the quality of evidence is low because there have been insufficient clinical studies about the immunogenicity and optimal timing of PCV13 administration in cancer patients receiving systemic chemotherapy. Moreover, the treatment regimens have changed over time, with the introduction of targeted

therapies and ICIs. Therefore, these guidelines should be modified.

A prospective RCT in patients with gastric or colorectal cancer undergoing adjuvant chemotherapy demonstrated that the serotype-specific SPR of PCV13 did not differ significantly when compared to the timing of vaccination (the first day of therapy versus 2 weeks before the chemotherapy initiation).[74]

Effectiveness of pneumococcal vaccination in patients with solid tumors

The effectiveness of pneumococcal vaccination has been evaluated in the setting of elderly cancer patients. A study considered a cohort of lung cancer patients ≥75 years of age with a primary endpoint as the frequency of all-cause inpatient community-acquired pneumonia according to the administration of PPSV23. The adjusted inpatient community-acquired pneumonia incidence rate in PPSV23 vaccination cohort was 0.74 times lower than the control cohort [incidence rate ratio (IRR) = 0.740, $P = 0.0339$]. The OS rate was 46.6% versus 26.2%, respectively, for lung cancer patients with and without PPSV23 ($P < 0.001$).[75] These results have been confirmed by another study including a large cohort of elderly patients (≥75 years of age) with colorectal cancer. PPSV23 vaccination significantly reduced the risk of pneumonia hospitalization, with an IRR of 0.880 ($P = 0.04$) and demonstrated a significantly better OS in the vaccinated cohort than in the unvaccinated cohort ($P = 0.001$).[76] Finally, Li et al. confirmed that the risk of pneumonia-related hospitalization in patients with prostate cancer aged ≥75 years was 0.48 times lower in the PPSV23 vaccination group than that in the unvaccinated one (adjusted IRR 0.48, $P = 0.046$).[77]

Low adherence of pneumococcal vaccination in patients with solid tumors

The coverage of pneumococcal vaccination is very low and ranges from 4.2%[78] to 16%.[79] In a retrospective study, Ostropolets and colleagues reported vaccination rate in adults aged 19-64 with a new diagnosis of chronic or immunocompromising conditions. They reported that, despite a high risk of invasive pneumococcal disease, adults with cancer were less likely to be vaccinated than adults with diabetes mellitus or HIV. The authors proposed as a possible explanation of these results the multidisciplinary approach adopted in care for HIV/AIDS or diabetes mellitus and suggested that a comprehensive and multidisciplinary care model might improve the pneumococcal vaccination coverage in vulnerable subjects.[80] Mohr and colleagues analyzed the vaccination status of lung cancer patients treated at the University Hospital Regensburg, Germany, in a prospective, single-center study with the evidence of a very low rate (9.4%) of vaccinated patients.[81]

The implementation of initiatives to increase in pneumococcal vaccination may be associated with a significant improvement of the acceptation rate. The paper by McGinnis et al. supports this statement. They conducted a quality improvement study in their gynecological cancer population. They introduced three interventions: an in-house vaccination program, a staff education campaign and a patient care bundle (pre-printed prescription, information brochure). They observed an increase in the vaccination rate (from 5% at study onset to a monthly mean of 61%).[82]

Sitte and colleagues evaluated the role of an infectious disease consultant on vaccination coverage rates in patients with GC or inflammatory bowel disease. In GC patients, the anti-pneumococcal vaccination rate was 87.5% after the specialized consultation compared with 10.1% before. An infectious disease specialist improved GC patients' knowledge about vaccination and vaccination coverage.[83]

Delacruz and colleagues with a quality improvement project reported similar good results. The authors improved their compliance with pneumococcal vaccination by 39% ($P < 0.001$) thanks to a dedicated nurse practitioner who was able to screen and prescribe vaccination to more patients with cancer before receiving chemotherapy.[84]

SARS-COV-2

SARS-CoV-2 is an enveloped single-stranded positive-sense RNA virus that belongs to the family Coronaviridae.[85] SARS-CoV-2 infects human cells expressing the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane serine protease 2 (TMPRSS2). ACE2 is expressed throughout the body such as the epithelial cells of the oral mucosa, lungs, heart, gut and kidneys.[86] This explains the wide range of clinical manifestations of COVID-19 (i.e. respiratory, cardiovascular and gastrointestinal system manifestations, hepatobiliary, kidney and neurological manifestations). Gao and colleagues reported that, even if many patients with COVID-19 are asymptomatic, they are able to transmit the virus to other subjects.[87] Different variants have been discovered beside the wild-type strain with different transmissibility, cellular tropism and severity of the disease.[88] SARS-CoV-2 Omicron is currently the predominant variant circulating.[89] Long COVID (or 'post-acute sequelae of COVID-19') is a multidimensional condition defined by the WHO as: 'A condition which occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis'.[90] It is associated with all ages and acute-phase disease severity with a worse quality of life. It is considered one of the main future challenges for oncologists that will be asked to distinguish between long COVID symptoms and the symptoms related to the oncological disease/oncological treatment.[91]

Diagnosis

Quantitative reverse transcription PCR (RT-qPCR) is the gold standard to carry out the diagnosis of COVID-19 also in low viral load in both symptomatic, pre-symptomatic and

asymptomatic subjects.[92,93] Antigenic assays evaluate directly the presence of the virus in the clinical sample through its proteins (antigens).[94] The result of the antigen—antibody reaction is directly visible to the naked eye or read by simple equipment without the need to be carried out in a laboratory. Serological tests can detect exposure to the SARS-CoV-2 virus, but are unable to confirm whether or not an infection is ongoing; so, in case of positivity, a molecular swab test is needed for confirmation. The asymptomatic screening may have the aim of reducing the risk of nosocomial transmission. However, the CDC currently does not recommend the asymptomatic screening on admission to most types of health care facilities except for periods of higher transmissibility.[95] A recent Italian retrospective study has evaluated this aspect. The authors evaluated the rate of SARS-CoV-2 positivity in a large cohort of consecutive asymptomatic patients with an antigen rapid diagnostic test. The low rate of SARS-CoV-2-positive patients (2.17%) does not seem cost-effective.[96] Reinforcing of existing levels of protection (e.g. switching to universal use of N95 respirators when carrying out certain procedures on any patient and active versus passive screening of HCWs for signs of COVID-19) seems to be a more practical and reasonable approach.[97]

Therapy

The latest COVID-19 treatment guidelines report monoclonal antibodies (i.e. sotrovimab) as drugs for preventing virus entry into host cells and antiviral drugs (i.e. tocilizumab, baricitinib and remdesivir) to use in the early stage of COVID-19 to act directly on viral replication.[98] In the out-of-hospital setting, the first-generation oral antiviral agents against SARS-CoV-2 (such as nirmatrelvir/ritonavir and molnupinavir), anti-spike monoclonal antibodies and remdesivir are used to treat high-risk outpatients with mild-to-moderate COVID-19.[99] In an Italian prospective study, these early anti-SARS-CoV-2 therapies in patients with cancer undergoing active treatment demonstrated to reduce the time of negative sample (73% versus 18%, $P = 0.0011$) and to shorten the symptoms' duration (94% versus 27%, $P < 0.0001$) compared to the absence of these therapies.[100] Finally, a systematic review and meta-analysis reported that tixagevimab/cilgavimab (TGM/CGM) used as pre-exposure prophylaxis was associated with lower COVID-19-related hospitalization rate (0.54% versus 1.2%, $P = 0.27$) and lower mortality rate (0.2% versus 1.2%, $P = 0.67$).[101]

Anti-SARS-CoV-2 vaccine

The first vaccine authorized by international regulatory bodies was the mRNA BNT 162b2 (Comirnaty—Pfizer/Biontech) vaccine based on mRNA technology that encodes the spike protein of SARS-CoV-2 present on the viral envelope. Based on the same technology, the mRNA-1273 (Spikevax—Moderna) was later approved. The other two licensed vaccines (ChAdOx1-S, Vaxzevria—Astrazeneca and Ad26.COV.2.S, Jcovden—Janssen) are both characterized by the presence of a recombinant viral vector based on adenovirus which contains the gene coding for the sequence complete with the spike protein.[102]

SARS-CoV-2 infection in patients with solid tumors

A multicenter case-control study reported a higher rate of complications and mortality in patients with cancer compared to patients without cancer during COVID-19, with poorer outcomes in hematologic malignancies and lung cancer.[103] OnCovid was the first multicenter observational study that described the natural history and outcomes from COVID-19 in European patients with cancer. Between 26 February and 1 April 2020, the authors identified 890 patients with confirmed COVID-19 and cancer across 19 European centers. More than half of the patients reported complications from COVID-19 with the mortality rate in excess of 70%. Moreover, active oncological treatment was not associated with worse mortality.[104] Not all types of cancers seem to have equal risks of morbidity and mortality, with a mortality range from 8% to 30%.[105] Patients with lung cancer present an increased risk of death compared with other cancers, probably due to the combination of the pathophysiological, clinical and treatment-related risk factors.[106] A systematic review and meta-analysis of the published literature showed that mortality in patients with lung cancer was significantly higher than that in patients with other malignancies (HR = 1.91, 95% CI 1.53-2.39, $P < 0.01$).[107]

The COVID-19 pandemic slowed or stopped cancer screening services worldwide. In Italy, 980 994 fewer invitations were done for mammography screening from January to December 2020 compared with 2021 and the screening tests for colorectal and cervical cancer decreased by 45.5% and 43.4%, respectively, in 2020 compared with 2019.[108]

Immunogenicity of anti-SARS-CoV-2 vaccination in patients with solid tumors

A meta-analysis demonstrated that patients with cancer had a suboptimal SCR rate after COVID-19 vaccination when compared with healthy subjects.[109] The CAPTURE study demonstrated a SCR rate of 44% after the first dose and 85% after the second dose of COVID vaccine in patients with cancer.[110] Two doses of mRNA anti-SARS-CoV-2 vaccines are able to prevent the symptomatic SARS-CoV-2 infection, but a decrease in humoral response was demonstrated 6 months after the vaccine, especially among the immunocompromised subjects.[111,112] Di Noia et al. noted that supportive therapies such as steroid therapy might reduce immunogenicity.[113] La Verde and colleagues demonstrated that the vaccine type (BNT162b2 or mRNA-1273) and the use of granulocyte colony-stimulating factor negatively affected the antibody response.[114] The type of oncological treatment seems to influence the humoral response with lower N-IgG levels during chemotherapy and

higher levels during ICIs.[115] Ariamanesh and colleagues highlighted that chemotherapy was associated with lower rates of immunogenicity (83.5%) compared to radiotherapy and hormone therapy (97%).[116] Figueiredo et al. observed an increased humoral response in patients with solid tumors on ICIs compared to chemotherapy; moreover, the reduction in antibody titer was more pronounced in patients who received the vaccine after initiation of ICIs compared with those who received it before.[117]

Booster dose

According to the evidence of a diminished immunogenicity 6 months after the second dose and the discovery of new variants of SARS-CoV-2 with a potential ability to escape vaccine-induced immunity, the CDC authorized a third dose of COVID-19 vaccine ('booster') for immunocompromised patients.[118] The Italian VAX4FRAIL study monitored humoral and T-cell immune response after three vaccine doses in 114 patients with solid tumor. The authors found a suboptimal immune response induced by two doses of BNT16b2 and mRNA-1273 vaccines in frail patients. However, the booster improved both humoral and T-cell responses.[119] The optimal boosting frequency and schedule are unknown. Computational modelling predicts that the booster provides sufficient protection for >12 months in healthy subjects, while in patients with cancer the booster effect seems to diminish and so it should be considered more frequently.[120] Real-world studies highlighted that regular booster of SARS-CoV-2 vaccines might maintain the optimal protection in these patients as routinely for other vaccinations.[121-123]

Anti-SARS-CoV-2 vaccines and adverse events during oncological treatment

Kian et al. revealed no significant differences in side effects in patients with cancer undergoing various anticancer therapies compared to the general population (31% versus 27%).[124] In the VAX4FRAIL study, the reported toxicities were clinically manageable and did not affect patient care.[125] The available data do not seem to demonstrate an increase in irAEs during ICIs,[126] although cases of hepatitis have been reported.[127] Local lymphadenopathy is a common side-effect after SARS-CoV-2 vaccination,[128] and it may be mistaken for metastases.[129] Consequently, it is preferable to postpone any type of instrumental re-evaluation of oncological disease with computed tomography (CT) or [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography-CT until 4 weeks after vaccination.[130]

Anti-SARS-CoV-2 vaccine hesitancy

A systematic review and meta-analysis investigated COVID-19 vaccine hesitancy among patients with cancer. The authors reported that the fear of vaccine-related side effects and the ongoing active anticancer therapies were the leading causes for vaccine hesitancy.

Female sex and undergoing active anticancer treatments were significantly related to COVID-19 vaccine hesitancy, while a good compliance with prior influenza vaccinations was significantly associated with COVID-19 vaccine acceptance.[131] However, Di Noia and colleagues reported that among 914 cancer patients, only 102 (11.2%) refused vaccination and this rate was lower than that in the general population.[132] In our opinion, tailored COVID-19 vaccine communication can be of great value to resolve doubts and increase the acceptance of the vaccine.

Twin-demic

During the first phase of the COVID-19 pandemic, the influenza virus had a very low prevalence, probably due to the mask-use ratio, social distancing and stringency of measures taken by authorities.[133] This fact, together with the fear of cumulative adverse events by combining the two vaccines (anti-SARS-CoV-2 and anti-seasonal flu), may explain patients' hesitation to undergo vaccination. Actually, the review of reports to VAERS after co-administration of mRNA COVID-19 and seasonal influenza vaccines did not reveal any unusual or unexpected patterns of AEs.[134] These results support the safety of co-administration of the two vaccines. A population-based cohort study demonstrated that the influenza vaccination was associated with a 22%-

Table 1. Recommendations and statements on the use of vaccination for seasonal flu, pneumococcal infection and SARS-CoV-2 in patients with solid tumors

1. Seasonal flu, pneumococcal and anti-SARS-CoV-2 vaccinations in patients with cancer are safe, minimally invasive and inexpensive.
2. Seasonal influenza and anti-SARS-CoV-2 vaccination should be widely recommended in every patient with cancer candidate to oncological active therapy, irrespective of the type of anticancer treatment (chemotherapy, ICIs, targeted therapy, hormonotherapy or a combination of these therapies).
3. Pneumococcal vaccination is recommended to all the patients ≥65 years with cancer, but also in younger patients, in particular if they have lung and/or head and neck cancer.
4. The ideal time to administer the vaccine in the patients undergoing active treatment is unclear. Preferably, vaccination should be scheduled before the start of the oncological therapies in order to avoid the phase of leucopenia in case the treatment has already begun. Recent papers have demonstrated the efficacy and safety of these vaccines also during active chemotherapy.
5. They can be co-administered.
6. Quadrivalent or trivalent influenza vaccines are recommended. The booster dose in the same influenza season or high-dose vaccines may be used in elderly immunocompromised patients during chemotherapy.
7. The optimal boosting frequency and schedule of anti-SARS-CoV-2 vaccine is unknown. It is probably better not to wait >12 months between boosters.
8. It is preferable to postpone any type of instrumental re-evaluation of oncological disease until 4 weeks after vaccination.
9. Cocoon vaccination is strongly recommended for the seasonal influenza and anti-SARS-CoV-2 vaccines.
10. HCW should habitually recommend vaccination to patients, dispelling doubts and worries, in their clinical practice, particularly during the first oncological visit. It is essential to provide a vaccine education and promote vaccine administration.
11. AIOM recommends influenza and anti-SARS-CoV-2 vaccinations to all HCW.

AIOM, Associazione Italiana di Oncologia Medica; HCW, health care workers; ICIs, immune checkpoint inhibitors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

24% lower risk of SARS-CoV-2 infection, a 17%-32% lower risk of SARS-CoV-2—associated hospitalization and a 27%-42% lower risk of SARS-CoV-2—associated mortality during the first 2 years of the COVID-19 pandemic.[135]

AIOM RECOMMENDATIONS

According to the above reported evidences, AIOM recommendations about the seasonal influenza, pneumococcal and anti-SARS-CoV-2 vaccinations are reported in Table 1.

CONCLUSIONS

Patients with cancer are more likely to get influenza, pneumococcal disease and COVID-19 and their complications with a consequent worsening of clinical conditions and delay in treatment of the underlying tumor. The AIOM recommends comprehensive education on the issue of VPDs. Continued surveillance, implementation of preventive practices and future well-designed immunological prospective studies are essential for better management of our patients with cancer.

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