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EDITORIAL

VACCINATIONS IN CANCER PATIENTS: A CALL TO ACTION

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Undoubtedly, oncology has evolved impressively in recent years, leading to a substantial improvement in patients' life expectancy. Major advances have been seen in diagnostic techniques, surgery (increasingly conservative), and radiotherapy (more precise and with fewer side effects). Medical therapies, administered both at an early stage and at a more advanced stage, have also helped to reduce recurrences and have increased the survival time even of patients with distant metastases, leading to the chronicity of cancer for many years. Attention to managing comorbidities must therefore be considered an integral part of care to improve quality of life.

About 50 percent of the causes of death in patients with solid tumors are related to infections (1). These are mainly bacterial infections, followed by fungal and viral ones. Infections are capable of drastically worsening the prognosis of patients, causing interruption of cancer treatments, altering the tumor microenvironment (TME) by increasing the proportion of pro-inflammatory cells, creating dysbiosis of the gut microbiota following the use of antibiotics, antimycotics and antivirals, and overall, negatively impacting the quality of life of patients (2).

Even though the risk of death from infectious causes is more than doubled in patients with cancer compared to immunocompetent individuals, oncologists still perceive these issues as being of little interest to them and not pertinent to themselves.

A recent survey sponsored by the Italian Association of Medical Oncology (Associazione Italiana di Oncologia Medica - AIOM) has confirmed low awareness of the infectious diseases, in particular of the vaccine preventable diseases (VPDs), and poor knowledge about vaccines. The management of VPDs in patients with cancer was considered very important for only 42% of respondents and slightly less than half of the respondents usually did not address vaccines to their patients. The survey also showed little confidence in the correct timing of vaccine administration and little willingness to engage in dialogue with patients to dispel doubts and fears about possible interactions with oncological therapies (3). We, as oncologists, have a key role to recommend vaccinations to our patients by educating them about the potential risks of being infected with one of these VPDs.

Influenza epidemics have been indicated as one of the potential causes of excess mortality. The trend in all-cause mortality, especially in the elderly and frail, shows a sinusoidal pattern with peaks in the winter months and troughs in the summer

periods. In Italy, deaths attributed to influenza according to the National Institute of Statistics (ISTAT) forms are "only" a few hundred. The main reason is that the influenza virus often worsens the otherwise impaired condition of patients suffering from other diseases, is not sought out and the death is attributed to general pneumonia. Using different statistical models, however, over 68,000 deaths attributable to influenza were estimated during the influenza seasons from 2013/14 to 2016/17 (4). In a recent paper, Angrini and colleagues pointed out that the influenza virus could alter TME, and thereby promote lung cancer progression thanks to sustained inflammation. The increased production of reactive oxygen species (ROS), NADPH oxidase (NOX), cyclooxygenase-2 (COX-2), and prostaglandin E(2) (PGE(2)) induces increased oxidative stress, which may ultimately lead to resistance to cancer therapies (chemotherapy, radiotherapy, and immunotherapy) (5). AIOM was the first scientific society to publish recommendations on seasonal flu vaccination in 2014 (6), and it is probably thanks to intensive and constant efforts to promote this vaccine that, even in the survey mentioned above, 96% of oncologists now recommend this vaccination to their patients (3). The immune exhaustion induced by flu can increase the risk of bacterial superinfections.

Pneumococcal pneumonia, the main pneumococcal disease worldwide, is caused by *Streptococcus pneumoniae*, a Gram-positive bacterium that colonizes the nasopharynx. It is responsible for a range of diseases such as pneumonia, bacteremia, and meningitis and the World Health Organization (WHO) stated that it is one of the high-priority pathogens due to growing antibiotic resistance (3). The widespread use of anti-pneumococcal antibiotics has led to the development of strains that are resistant to penicillins and ceftriaxone with the consequent need for antibiotics of later generations. One of the most intriguing new areas of research is the role of *Streptococcus pneumoniae* in the process of lung carcinogenesis. In mouse models, Li and colleagues demonstrated that the cancer cells infected by *Streptococcus pneumoniae* had high levels of pro-inflammatory cytokines and that the proliferative marker (Ki-67) was higher than the controls without infection. Moreover, the authors showed that *Streptococcus pneumoniae* in lung cancer cells can upregulate the phosphoinositide-3-kinase-AKT (PI3K-AKT) and nuclear factor-kB (NF-kB) signaling pathways that ultimately promote carcinogenesis, cell proliferation, and metastasis (7). AIOM recommends pneumococcal vaccination to all patients with cancer ≥65 years, and also in younger patients, especially with lung and/or head and neck cancer (8). Patients with cancer should receive the pneumococcal sequential vaccine program with the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) (8). It is well known that PPSV23 is immunogenic in patients undergoing chemotherapy (9), whereas data about the immunogenicity of PCV13 are still scarce in patients with cancer. A recent paper showed significantly higher levels of anti-pneumococcal antibodies in patients with early stages of non-small cell lung cancer (NSCLC) than in patients with advanced NSCLC (III-IV stages) and higher antibody levels after vaccination in NSCLC patients surviving 5-year follow-up (10). Despite AIOM recommendations, and growing scientific evidence, only 60% of respondents in the survey suggest pneumococcal immunization (3).

The proposal for shingles vaccination is even lower: just 42%! (3). Herpes Zoster (HZ), the infectious reactivation of the Varicella-Zoster Virus (VZV), negatively impacts the quality of life of patients with cancer, with burning pains and sensory disturbances that can last even years. The clinical and economic implications of VZV reactivation should lead to greater awareness by the oncologist. Patients with cancer may also have more than one episode of HZ, not only during chemotherapy cycles but also during immunotherapy (11). Head and neck and lung cancer present a higher risk of VZV reactivation, but in truth, no type of tumor can be said to be risk-free for HZ. Hansson and colleagues reported that the risk of HZ was higher within the first two years after the oncological diagnosis and increased with a younger age for both hematological and solid malignancies (12). Data on the immunogenicity of the adjuvanted glycoprotein E (gE)-based recombinant vaccine (RZV) demonstrated acceptable humoral and cell-mediated responses both during chemotherapy (13) and immunotherapy (14). Based on these data, AIOM is actively involved in recommending this vaccination for patients with cancer (15).

Despite anti-SARS-CoV-2 vaccination being recommended by 93% of oncologists (3), vaccine hesitancy for this type of vaccine in patients with cancer represented a serious issue since the beginning of the vaccination campaign. Vaccinations are

estimated to have prevented 14.4 million deaths from COVID-19 worldwide in the period from December 2020 to December 2021 (16). Patients with cancer expressed strong concerns about potential vaccine-induced adverse events and interactions with anti-cancer therapies notwithstanding these data (17). Although some vaccination-induced adverse events have been reported, overall advantages significantly exceed the risks of injury. Nevertheless, even though hundreds of millions of vaccine doses are administered each year, the prevalence of vaccine-related immune reactions is below 1:10,000. In a previous paper, we strongly pointed out that the incidence of vaccine-induced immune reactions is lower than the incidence of infection-induced immune reactions, and that these vaccine-induced immune reactions usually have a milder clinical course (18). As already mentioned for pneumococcal infections, the COVID-19 pandemic exacerbated antimicrobial resistance (AMR). AMR is one of the top public health problems worldwide with clinical implications (increased morbidity, mortality, hospitalization days, potential development of complications, epidemic possibilities, gut microbial dysbiosis), and economic implications (additional cost of more and more expensive drugs and procedures, longer hospital stays and possible invalidity) (2). Despite the importance of the issue, considerable knowledge gaps continue to hinder effective management against AMR. AMR is impairing health and development outcomes and represents a challenge to the entire global health system.

Finally, antibiotic-induced gut dysbiosis seems to have negative therapeutic effects in various tumor types and seems to be responsible for the occurrence of immune-related adverse events (irAEs). Antibiotics are able to decrease the diversity of gut microbiota, impair the host-microbe relationship and disrupt the homeostasis of the immune system. They can interfere with the adaptive immunity in the gut, stimulate sustained T-cell-mediated dysfunction, and ultimately lead to a higher susceptibility to infections (19).

Awareness of the importance of prevention of infections is essential for us oncologists. Only if we are the first believers in prevention, we can transmit an unequivocal signal to our patients. Oncologists are actively called to counteract the vaccination hesitancy of patients. The literature shows that patients with cancer are more confident about vaccinations if their oncologist proposes them. It is imperative to increase knowledge on this topic and to continue to be updated about the national and international recommendations. CDC regularly updates vaccine-by-vaccine recommendations (one of the latest examples − July 2024 − is the pneumococcal vaccination) (20). This provides an easy-to-consult tool for all physicians. Although studies show that the efficacy of vaccines is only partially reduced if they are administered during cancer treatment, it would be desirable to offer vaccinations before starting any type of oncological treatment. There is also a need for a network of specialists (infectious disease specialists, virologists, microbiologists, hygienists, general practitioners, pharmacists) to manage patients with cancer in the best possible way.

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