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Review

Immunization in cancer patients: Where we stand

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ABSTRACT

An increasing proportion of cancer patients benefit from new treatment strategies. However, infection remains a main cause of morbidity and mortality, either due to the underlying diseases, to treatment, or both. Although most opportunistic infections are sofar not routinely preventable by vaccines, community infections such as invasive pneumococcal disease and influenza may be avoided by vaccines in many instances. The immune response of cancer patients to vaccines is almost constantly depressed when compared to the one of healthy individuals of the same age range. However, they may, in many cases, reach seroprotection. This article addresses the rationale to develop and implement immunization programs in cancer patients, including patients with hematologic malignancies and recipients of stem cell transplantation, and the main specificities of this patient population regarding vaccines, and the potential approaches to improve the immune response. The Infectious Diseases Society of America has recently published guidelines for vaccination of the immunocompromised hosts. Although many questions remain to be clarified, oncologists and hematologists should be encouraged to implement these guidelines in their therapeutic programs and to develop prospective studies covering unsolved issues.

Contents

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Center for Diseases Control; CMV, Cytomegalovirus; CLL, chronic lymphocytic leukemia; EBMT, European Group for Blood and Marrow Transplantation; GM-CSF, granulocyte-macrophage colony-stimulating factor; GMT, geometric mean titer; GVHD, graft-versus-host disease; HiB, *Haemophilus influenzae* B; HIV, human immunodeficiency virus; HPV, human papillomavirus; IDSA, Infectious Diseases Society of America; IPD, invasive pneumococcal disease; MMR, measles-mumps-rubella; MMWr, morbidity and mortality weekly report; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; SCC, squamous cell carcinoma; SCT, stem cell transplantation; TDP, tetanus-diphteria-poliomyelitis.

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Introduction

Cancer patients are at high risk of infectious morbidity and mortality, varying according to the underlying disease and therapeutic approach, and the infectious risk may compromise the benefit of the cancer treatment. Some of these infections are vaccine-preventable. As more and more cancer patients are cured, or at least have an increased life-expectancy, they should be protected from side effects of treatment as far as possible, including from the community-infection risk as other individuals of the same age range. In this paper, we will analyze the medical need for immunization in cancer patients, including patients with hematological malignancies and recipients of stem cell transplantation (SCT), the available data on vaccination in these settings, and the obstacles which should be overcome in the routine practice in order to improve the immunization programs in oncology. We limit here our analysis to currently available vaccines, as future vaccines are addressed in the article of JA Lapinet et al. in this issue.

Why to vaccinate cancer patients?

During the active phase of cancer treatment, many components of the B- and T-immune system are deficient [1]. However, the deepness of these deficiencies greatly varies according to numerous factors, mainly underlying disease and status, age, type and timing of specific therapy, nutritional status, and comorbidities. Some of the infections complicating cancer – so-called "opportunistic" – are specific of such setting, like CMV reactivation or *Pneumocystis jirovecii* pneumonia, infections which are exceptionally observed in non-immunocompromised hosts. For other pathogens, the cancer patients have an increased risk of getting a community infection when compared to healthy individuals. For example, in Canada, the risk of invasive pneumococcal disease (IPD) has been shown to be 143 cases/100,000 persons per year in lung cancer, more than 10 times the risk of the healthy adult population (11 cases/100,000 persons), and still worst (673 cases/100,000 persons) in multiple myeloma [2]. Similarly, the risk of getting influenza infection is higher in cancer patients than in the healthy population, with an estimated age-specific rates for influenza-related hospitalization and death of 219 and 17.4 per 100,000, respectively, for patients age <65 years, and of 623 and 59.4 for patients age ≥65 years [3].

Not only the cancer patients have a higher risk for community infections than the non-cancer patients, but they have also a higher risk for infection-related hospitalization, respiratory failure, intensive care unit stay, ventilation and case-fatality rates. Indeed, the risk of death due to influenza infection was estimated in the US to be 166 per 100,000 for cancer patients older than 65 years, especially high in patients with lung cancer and hematology malignancies, 9 and 12% respectively, and roughly twice the one of the general population [3]. Additionally, any infectious episode may indirectly weight on the efficacy of the cancer treatment by disrupting the timing of chemotherapy courses [4] or delaying surgery.

Finally, although infections such as IPD or influenza are usual in the community, the fact that the risk is increased in cancer patients makes this excess of risk a health-care related complication and it is not acceptable that this risk be not prevented by vaccination each time vaccination may be protective and safe.

Specific concerns about immunization in cancer patients

Many specificities in the cancer patient population in regards to vaccines deserve consideration, and support specific guidelines [5–8]. The main paradox is that while the cancer patients are those with the higher need for protection, they are mostly those with the lower immune response to vaccines. In the rare studies comparing oncology or hematology patients to healthy individuals of similar age, the immune response to the vaccine was mostly lower [9–12], and rarely comparable [9,13] in the cancer patients. This may have discouraged many oncologists to have immunization strategies for their patients. However, although the response rate is mostly lower than in the healthy individuals, this does not mean that the cancer patients do not benefit from the vaccine since they may, however, reach a protective seroconversion [11]. Additionally, there is no evidence that vaccines could have more vaccine-induced adverse effects in cancer patients than in healthy individuals. Similarly, there is no evidence that vaccine could induce or reactivate graft versus host disease (GVHD) after allogeneic SCT, as well as there is no evidence that vaccines may significantly trigger or exacerbate disease flares in auto-immune inflammatory diseases [14].

A large heterogeneity in cancer patients

Although there are common features in some cohorts of patients with different diseases regarding to immune defect (i.e. chronic lymphocytic leukemia (CLL), myeloma, and B-cell lymphoma), there is a large heterogeneity in cancer patient populations. For example, a patient who benefits from surgery for prostate cancer without complementary treatment is extremely different from a patient with acute myeloid leukemia ongoing induction chemotherapy. The more immunodepressed patients are probably the allogeneic SCT recipients, and especially those of them who develop GVHD. These patients usually exhibit complex deficiencies of cell-mediated immunity, chemotaxis, phagocytosis, and immunoglobulin production [15] which may last several years in case of persistent chronic GVHD. As timing is crucial in immunization of immunocompromised patients, this heterogeneity does not facilitate the transfer of specific data from one cancer population to another, and it enlights the importance of prospective studies in well-defined populations. In an attempt to take this heterogeneity in account, the recent Infectious Diseases Society of America (IDSA) guidelines [7] proposed a definition of different levels of immunosuppression:

- *high-level* including in the cancer population: patients receiving chemotherapy, patients receiving daily corticosteroid therapy with a dose ≥20 mg (or >2 mg/kg/day for patients who weigh <10 kg) or prednisone or equivalent for >14 days, and those receiving certain biologic immune modulators such as tumor necrosis factor-alpha (TNF-α) blocker or rituximab, or SCT recipients (but with various degrees of immunodepression according to transplant characteristics, timing and GVHD)