

LITERATURE REVIEW

COVID-19 VACCINATION OPTIONS FOR IMMUNOSUPPRESSED CANCER PATIENTS

Opsi Vaksinasi COVID-19 untuk Pasien Kanker yang Mengalami Imunosupresi

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ABSTRACT

Background: Currently, many COVID-19 vaccine candidates are being developed to end the pandemic; however, immunosuppressed cancer patients have been excluded from the participating criteria. It is important that they are able to examine their options for achieving immunity against COVID-19. **Purpose:** This review aims to discuss the available options that can be taken to vaccinate immunosuppressed cancer patients when no vaccine is being developed for their safety. **Methods:** A literature study was conducted using Google Scholar, DOAJ, and GARUDA Library on November 2, 2020, focusing on articles examining vaccination guidelines for immunosuppressed cancer patients. **Results:** The search found 200 articles, which were curated to obtain 13 articles that satisfied all inclusion criteria. These consist of four guidelines, five reviews, and four research articles. Based on the literature, immunosuppressed cancer patients have the option to use the vaccines currently under development, with precautions set for live attenuated and potentially infectious vaccines. Vaccination timing also needs to be adjusted so as to fall at a certain time before or after the immunosuppressive condition. Moreover, a more complete COVID-19 immunity can be achieved through a synergy between individual vaccination and the construction of herd immunity. **Conclusion:** Most of the vaccines currently under development may be safe for cancer patients, being mindful of several considerations. Here, herd immunity can serve as a complement to individual immunity.

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ABSTRAK

Latar Belakang: Terdapat banyak kandidat vaksin COVID-19 yang

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saat ini sedang dikembangkan untuk mengakhiri pandemi, namun para penderita kanker yang mengalami immunosupresi tidak dimasukkan ke dalam kriteria penerima vaksin. Penting bagi mereka untuk mengevaluasi pilihan yang tersedia agar memperoleh kekebalan terhadap COVID-19. Tujuan: Kajian ini bertujuan untuk membahas pilihan yang dapat diambil untuk memvaksinasi pasien kanker yang mengalami immunosupresi ketika tidak ada vaksin yang diuji keamanannya untuk mereka. **Metode:** Studi literatur telah dilakukan di Google Scholar, DOAJ, dan GARUDA Library pada tanggal 2 November 2020 dengan fokus pada artikel mengenai pedoman vaksinasi untuk pasien kanker yang mengalami immunosupresi. **Hasil:** Pencarian tersebut berhasil menemukan 200 artikel yang kemudian dikurasi menjadi 13 artikel yang memenuhi semua kriteria inklusi. Artikel-artikel tersebut terdiri dari 4 pedoman, 5 ulasan, dan 4 artikel penelitian. Berdasarkan literatur utama ini, pasien kanker yang mengalami immunosupresi memiliki pilihan untuk menggunakan vaksin yang saat ini sedang dikembangkan dengan mewaspadaikan vaksin live attenuated dan yang berpotensi menginveksi. Waktu vaksinasi juga perlu disesuaikan pada waktu terbaik sebelum atau sesudah kondisi immunosupresif. Lebih dari itu, imunitas COVID-19 yang lebih lengkap dapat dicapai melalui sinergi antara vaksinasi individu dan konstruksi herd immunity. **Kesimpulan:** Sebagian besar vaksin yang sedang dikembangkan mungkin aman untuk pasien kanker dengan beberapa pertimbangan. Kemudian, herd immunity dapat berfungsi sebagai pelengkap untuk melengkapi kekebalan individu.

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INTRODUCTION

As at November 20, 2020, there have been approximately 57.30 million COVID-19 cases and 1.4 million deaths reported to the World Health Organization (World Health Organization, 2020a). Surveillance data provided by the Centers for Disease Control and Prevention (CDC) indicate that COVID-19 infection in America has a higher risk of leading to a severe outcome in people with underlying health conditions. These underlying conditions were found in 78% (358/457) of COVID-19 patients admitted to ICU and in 94% (173/184) of COVID-19 related deaths (CDC COVID-19 Response Team, 2020).

Cancer is one such underlying condition (CDC COVID-19 Response Team, 2020; Dai et al., 2020; Mehta et al., 2020); cancer patients are more vulnerable to the severe effects of COVID-19 due to their impaired immune response. A study in a hospital in New York City showed that cancer patients have twice the case fatality rate (CFR) (28%) than non-cancer COVID-19 patients (14%) and more than four times the CFR than the

city's overall CFR (6%) (Mehta et al., 2020). This result is consistent at a larger scale. A multicenter study in China found that COVID-19 patients with cancer have a higher death rate, chance of ICU admission, chance of having at least one adverse symptom, and chance of needing invasive mechanical ventilation (Dai et al., 2020).

Vaccination is one of the most promising solutions to ending this pandemic. The race for the first-approved COVID-19 vaccine has produced 48 vaccines in clinical trials. In these trials, the immunosuppressed are excluded from the participating criteria (World Health Organization, 2020b). This may result in an inequity of access to COVID-19 vaccination, because no vaccine is being prepared for immunosuppressed cancer patients. Therefore, this review aims to discuss the options currently available for vaccinating immunosuppressed cancer patients when no vaccine is being tested for their safety. The generalized recommendation is synthesized by utilizing currently available knowledge about how to vaccinate immunosuppressed cancer patients.

METHODS

A literature study was conducted using Google Scholar, DOAJ, and GARUDA Library on November 2, 2020, excluding patents and citations. Keywords used were “immune-suppressed cancer vaccination” and “immunosuppressed cancer vaccination guideline”. The search was limited to the first 10 pages of each keyword to maintain relevancy. Other supporting studies were unrestricted. The inclusion criteria order used were as follows: articles written in English; articles that recommend vaccination guidance for immunosuppressed human cancer patients; articles that contain clearly distinctive vaccination guideline for immunosuppressed human cancer patients; and articles that are reviews, research articles, or official guidelines issued by a health organization. The workflow is illustrated in Figure 1.

The analysis of the literature obtained was conducted by summarizing all sources that fit within the pre-specified eligibility criteria. Both authors reviewed the literature independently, then combined the summary during the manuscript-writing process. All conflicts that arose were solved by discussion between the two authors.

RESULTS

From 200 pieces of literature found, 13 satisfied all inclusion criteria. These consisted of four guidelines, five reviews, and four research

articles (Table 1). Based on the main references, COVID-19 vaccination is also closely related to COVID-19 herd immunity. Since both are crucial to providing immunity for immunosuppressed cancer patients, herd immunity will also be briefly discussed in this article.

Immunosuppression in Cancer Patients

Cancer patients can be immunosuppressed either directly or indirectly. For example, a cancer causing direct immune suppression is acute myeloid leukemia (AML), where the expression and release of arginase II blasts results in the suppression of T-cell proliferation (Mussai et al., 2013). All cancer types needing chemotherapy treatment, such as gastric cancer, theoretically risk indirect immunosuppression. In gastric cancer, cytotoxic chemotherapeutic agent 5-fluorouracil (5-FU) upregulates exosomal PD-L1 expression, which results in immunosuppression (Zhang et al., 2020). Radiotherapy can also cause indirect immunosuppression, however, only total-body irradiation (TBI) seems to cause white blood cell count reduction. A report by (Hale et al., 2019) also shows that TBI causes years of delay in immune response recovery in rhesus macaques. TBI is typically given to hematological cancer patients before stem cell or bone marrow transplant to wipe out all of their cancer cells and suppress the immune system, so as to prevent implant rejection.

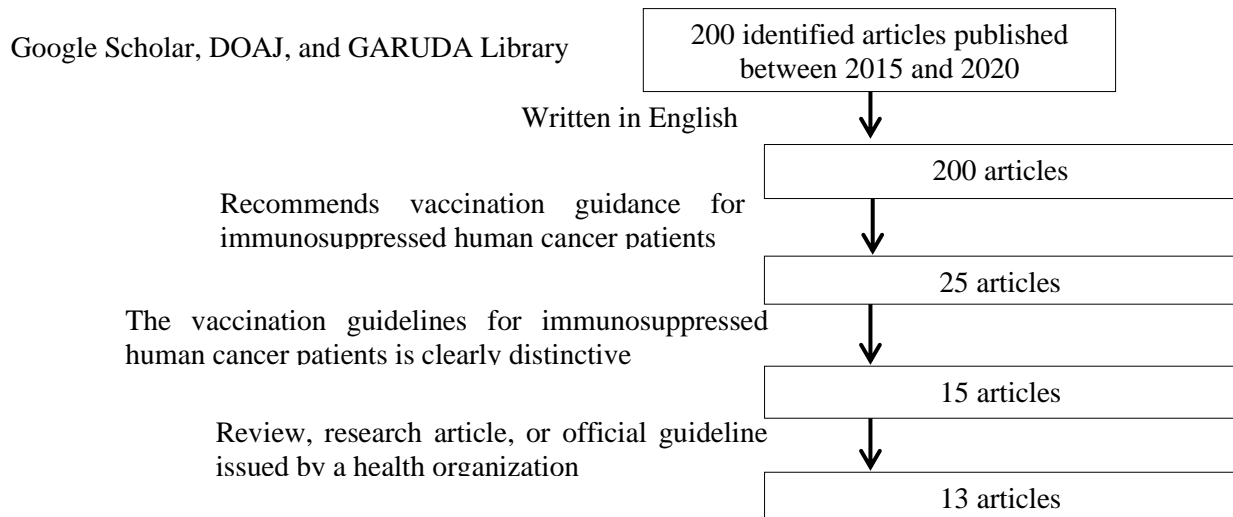


Figure 1. The literature selection process based on the inclusion criteria.

Table 1

Main Literatures Obtained

Title	Author	Type	Findings
Live zoster vaccination in an immunocompromised patient leading to death secondary to disseminated varicella zoster virus infection	Alexander et al (2018)	Research article	Live attenuated varicella zoster vaccination to an immunocompromised patient led to death
Safety of Influenza Vaccine in Patients With Cancer Receiving Pembrolizumab	Failing et al (2020)	Research article	Influenza vaccination is safe for cancer patients receiving pembrolizumab
Influenza vaccination in patients with lung cancer receiving anti-programmed death receptor 1 immunotherapy does not induce immune-related adverse events	Wijn et al (2018)	Research article	Influenza vaccination is safe for lung cancer patients receiving anti-PD-1 immunotherapy
Immunogenicity and clinical effectiveness of the trivalent inactivated influenza vaccine in immunocompromised children undergoing treatment for cancer	Kotecha et al (2016)	Research article	Influenza vaccination is safe for the immunosuppressed children undergoing cancer treatment
Influenza vaccination in adult patients with solid tumours treated with chemotherapy	Vollaard et al (2017)	Review	Influenza vaccination is safe for patients with solid tumors receiving chemotherapy both before and during treatment
Influenza vaccines in immunosuppressed adults with cancer	Bitterman et al (2018)	Review	Influenza vaccination resulted in lower mortality and infection-related outcomes in immunosuppressed adult cancer patients according to limited evidence
Vaccination recommendations for the adult immunosuppressed patient: A systematic review and comprehensive field synopsis	Lopez et al (2017)	Review	General vaccination guideline especially using inactivated and live vaccines for adult immunosuppressed patient
Practical review of immunizations in adult patients with cancer	Ariza-Heredia & Chemaly (2015)	Review	General vaccination guideline for adult cancer patients especially upon health improvement
Recommended immunization schedules for adults: Clinical practice guidelines by the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid)	Esposito et al (2016)	Guideline	General vaccination scheduling guide for adults in various conditions, including the immunocompromised

(Continue)

Table 1

Continued

Title	Author	Type	Findings
Antiviral prophylaxis in patients with solid tumours and haematological malignancies—update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO)	Sandherr et al (2015)	Guideline	Guideline to use vaccine as an antiviral prophylaxis in patients with solid tumors and hematological malignancies
Prevention and Treatment of Cancer-Related Infections	Baden et al (2016)	Guideline	Vaccination guideline and schedule as prophylaxis treatment for cancer patients
Immunization in cancer patients: Where we stand	Robin, Beckerich, & Cordonnier (2015)	Review	The rationalization and consideration behind vaccination programs for cancer patients
Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7)	Mikulska et al (2019)	Guideline	General vaccination guideline for patients with hematological malignancies including children with acute leukemia

Available Options

Patients with different cancer types show different susceptibilities to COVID-19, as shown in the Lee et al (2020) study. Their study compares patients across tumor subtypes, age groups, and genders, finding that the CFR of COVID-19 patients with hematological cancers is notably higher than that of their solid organ tumors in both genders and across all age groups. The researchers also show that older patients tend to have a higher CFR in both genders. In this review, the possible options discussed will be generalized to all cancer types, genders, and age groups. The possibility of developing herd immunity will also be discussed.

Vaccines Currently Under Development

When discussing the vaccination of the immunosuppressed, it is necessary to consider whether the recipients will experience reduced protection or increased adverse effects from the vaccine. These are closely related to the vaccine type and mechanism. The immunosuppressed are not advised to take live vaccines of any kind, since they may expose them to vaccine-related diseases via transmission of the live pathogen in the vaccine (Alexander et al., 2018; Ariza-Heredia & Chemaly, 2015; Lopez et al., 2017)..

A study by Alexander et al (2018) has reported that the administration of live attenuated varicella zoster vaccine to an immune-

compromised patient with chronic lymphocytic leukemia resulted in varicella zoster virus infection, hospitalization, and death. Some studies using the live attenuated vaccine have contradicted this result. The live attenuated influenza vaccine, in particular, seems to be beneficial and well tolerated in cancer patients, with no detectable sign of prolonged viral shedding. However, none of these studies have dared to vaccinate severely immunosuppressed individuals (Carr et al., 2011; Leung et al., 2004). In such cases, an inactivated vaccine might offer better safety, since it contains no live viral element. Inactivated vaccines have been proven to provide benefit without any harmful effects in immunosuppressed adults and immune-compromised children with cancer (Bitterman et al., 2018; Failing et al., 2020; Kotecha et al., 2016; Wijn et al., 2018). Patients with hematological malignancies have even already been advised to be vaccinated with several inactivated vaccines (Mikulska et al., 2019).

Fortunately, most vaccines currently under development do not employ a live virus. Exceptions are only made for non-replicating and replicating viral vector-based vaccines (World Health Organization, 2020b). Other vaccine types (inactivated, nucleic acid, protein subunit, virus-like protein) are relatively safe for the immunosuppressed. These vaccine types generally exert reduced protection and thus demand more

than a normal dose in order to achieve better seroconversion (Ariza-Heredia & Chemaly, 2015; Lopez et al., 2017). This lower seroconversion has been observed when inactivated influenza vaccine is administered to cancer patients compared to its healthy control (Vollaard et al., 2017). It is suggested that it would be beneficial to administer a second influenza vaccine dose in order to increase the seroconversion (Sandherr et al., 2015).

Vaccination timing for the immunosuppressed must also be adjusted (Mikulska et al., 2019). Generally, a vaccine should be administered prior to the immunosuppressive chemotherapy. Inactivated vaccines, in particular, should be administered two weeks prior to or three months following the completion of the immunosuppressive therapy. If the immunosuppressed is vaccinated during chemotherapy, they should be re-immunized after the treatment, since the inactivated vaccine response might be suboptimal (Papp et al., 2019).

The use of a live attenuated vaccine is generally contraindicated until the patient has regained his/her immune competency. It can be administered four weeks prior to the immunosuppressive treatment and at least three months after the cessation of the therapy (Ariza-Heredia & Chemaly, 2015). In some treatments, such as in CAR T-cell therapy, live vaccines may be contraindicated for at least a 6–12-month period after the treatment is finished (Baden et al., 2016; Esposito et al., 2016).

Herd Immunity and Infection Control

At least 65–70% of the population needs to be vaccinated to build herd immunity (Marco-Franco, Guadalajara-Olmeda, Julián, & Vivas-Consuelo, 2020). Herd immunity is the state in which little to no transmission can occur within the population due to a lack of pathogen-transmitting individuals. This goal is more likely to be handled by the government (Dwipayana, 2020). Until then, citizens are advised to avoid public places and to restrict their activities to COVID-19-free surroundings. This restriction will build a contact isolation zone that can act as a protective bubble against SARS-CoV2 infection. The same method is also being recommended as measles management for immunosuppressed cancer patients (Pergam et al., 2019).

Once a vaccine is available, people around the immunosuppressed must be immunized (Mikulska et al., 2019; Robin et al., 2015). All types of vaccine currently under clinical trial may

be safe, with extra caution taken regarding vaccines employing non-replicating and replicating viral vectors, because both vaccine types are still infectious at a certain level. Non-replicating viral-vector vaccines work by infecting recipient cells, causing them to express the delivered gene. All the non-replicating viral-vector vaccines currently in clinical trial use the adenovirus vector, except one that uses the modified vaccinia virus Ankara (MVA) vector. On other hand, It is worth noting that replicating viral vectors are inherently able to replicate. There are three replicating viral-vector vaccine types currently under clinical trial: the measles vector, vesicular stomatitis virus (VSV) vector, and influenza vector, respectively (van Riel & de Wit, 2020; World Health Organization, 2020b).

The transmission risk of both non-replicating and replicating viral-vector vaccines is unknown, however, there are factors that might influence this risk: the type of vaccine and the immunosuppression level of the cancer patient (Robin et al., 2015). Since the exact safety of any COVID-19-vaccine candidate for the immunosuppressed is hardly known, unwanted transmission may pose unforeseen, potentially deleterious, effects. Precautions must be taken before administering these vaccines to people surrounding the immunosuppressed cancer patient until the vaccine is proven to be safe. Direct treatment of cancer patients in the hospital must be minimized and replaced by telemedicine or phone calls. Cancer cases requiring intravenous and subcutaneous drug administration should be adjusted to allow treatment to take place at home. If possible, intravenous drugs should be replaced by oral drugs and dosed in a way that reduces the need for hospital visits. Unavoidable hospital visits, such as for radiotherapy, must be preceded and followed by strict monitoring for COVID symptoms (You et al., 2020). All healthcare personnel in contact with the patient are also advised to be vaccinated as soon as possible, so as to reduce the risk of viral circulation within the treatment facility (Mikulska et al., 2019; Sandherr et al., 2015).

Equal access to the potentially life-saving COVID-19 vaccine should be encouraged by both scientists and policy makers. Scientists can include immunosuppressed cancer patients in their clinical trials. If this approach seems too risky, animal models can be used first during the *in vivo* preclinical trial. Injecting tumor-bearing mice with the vaccine can serve as a representative model in order to assess the immunosuppressed's immune

response and any subsequent adverse effect(s) that may occur. Meanwhile, policy makers could ensure vaccine safety for immunosuppressed cancer patients by funding relevant research.

CONCLUSION

Immunosuppressed cancer patients may be safe to be vaccinated using most of the vaccines currently under development (namely, the inactivated and subunit vaccines) while extra precautions must be taken against the live attenuated, non-replicating and replicating viral-vector vaccines. Vaccination timing must be adjusted to ensure a sufficient immunocompetence that can exert the proper immune response. Vaccination of cancer patients and the people surrounding them can induce herd immunity, which is crucial to providing a more complete COVID-19 immunity. It is hoped that future studies will meticulously tailor COVID-19 vaccines so that they are safe for the immunosuppressed, so that they will not be left behind.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare for this study.

AUTHOR CONTRIBUTIONS

IDAPD and IDAAS contributed equally during the conceptualization and final approval of this study. IDAPD took part in the methodology, data curation, formal analysis, and writing of the original draft. IDAAS took part in reviewing, editing, and revision.

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