Vaccination of non-transplanted patients with haematological malignancies: Guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7)

Companion paper 1/2

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Summary

Patients with haematological malignancies are at high risk of infection owing to various mechanisms of humoral and cell-mediated immune deficiencies, mainly depending on underlying disease and specific therapies. Some of these infections are preventable by vaccine. However, these malignancies are different from each other, and the treatment approaches are diverse and rapidly evolving, so it is difficult to have a common programme for vaccination in the haematology ward. In addition, owing to limited training on the topic, vaccination is an area often neglected by haematologists, additionally influenced by cultural differences, even among healthcare workers, in compliance to vaccines.

Several issues are encountered when addressing vaccination in haematology: the small size of the cohorts that makes it difficult to demonstrate the clinical benefits of vaccination, the subsequent need to rely on biological parameters, their clinical pertinence not being established in immunocompromised patients, lack of clarity on the optimal timing of vaccination in complex treatment schedules, and the lack of data on long-term protection in patients receiving treatments. In addition, the risk of vaccine-induced disease with live-attenuated vaccines strongly limits their use.

The European Conference on Infections in Leukaemia (ECIL) convened a group of experts in the fields of haematological malignancies and infections to address vaccination in haematology patients. This paper summarises a series of guidelines for non-transplanted patients, addressing the issue by the group – myeloid and lymphoid – of diseases, with a special consideration for children with acute leukaemia. A companion paper summarises the ECIL guidelines after haematopoietic stem cell transplantation.

INTRODUCTION

Patients with haematological malignancies are at increased risk for various infections, including some (e.g. influenza and invasive pneumococcal disease [IPD]) which are vaccine-preventable.¹⁻⁴

Vaccination has been widely pursued after haematopoietic stem cell transplantation (HSCT) to favour pathogen-specific immune reconstitution, and previous guidelines exist in this regard.⁵⁻⁸ Although HSCT recipients may be different, they share a time marker, which is the transplant date. In patients with haematological malignancies but who are not transplanted, both infectious risk and immune deficiencies are heterogeneous, including differences between adults and children, precluding a single vaccination programme.⁸ Patients with lymphoproliferative disorders (LPDs) and those with chronic myeloproliferative neoplasms (MPNs) suffer from distinct immune deficiencies and receive different treatments⁹⁻¹¹ variously impacting the vaccine response. Moreover, therapies have changed considerably over the last decades, making obsolete some conclusions from previous studies in patients treated with traditional approaches. Although haematology patients have lower responses than healthy individuals to most vaccines, vaccination may prevent infections in this population, decrease their severity, avoid hospitalisations, and save lives.

In 2017, the ECIL 7 group addressed the issue of vaccination in haematology patients. This paper summarises the guidelines in patients who are not transplanted. A companion paper summarises the guidelines for HSCT recipients.¹²

GUIDELINE DEVELOPMENT OVERVIEW

The ECIL is a joint venture of the Infectious Diseases Working Party of the EBMT, the Infectious Diseases Group of the EORTC, the ICHS, and the ELN. Its objective is to develop evidence-based guidelines for the management of infection in haematology and HSCT patients. The ECIL methodology has been previously described.¹³ Briefly, a group of ten experts, including

haematologists, infectious disease specialists, and paediatricians, was created. The relevant issues of vaccination in haematology were defined. The main desirable outcome was the evidence of reduction of vaccine-preventable infections due to immunization in different populations compared to those not vaccinated, while secondary outcomes included serological response, seroprotection, and safety.

MEDLINE (including MEDLINE In Process) searches were conducted (March-September 2017) to identify potentially relevant English-language studies. They included a combination of indexed terms and free text terms (chronic myeloproliferative disorder, chronic myeloid or myeloproliferative neoplasm, chronic myeloid leukaemia, acute leukaemia, myelodysplastic syndrome, chronic lymphoproliferative disorder, chronic lymphocytic leukaemia, myeloma, lymphoma, Hodgkin's disease, AND immunisation, vaccination, vaccine, immune response, AND/OR *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, tetanus, diphtheria, pertussis, influenza, hepatitis B, poliomyelitis, human papillomavirus, varicella, zoster, measles, mumps, rubella, yellow fever, rotavirus, BCG, and live-attenuated vaccine). References were screened for other potentially relevant papers. Full papers for all potentially relevant abstracts were shared with all co-authors.

All the relevant studies were analysed, with particular attention paid to the study design, the population, the timing of immunization and the endpoints. Based on these analyses, the group elaborated recommendations that were graded according to the ESCMID grading system (Appendix, Table 1)¹⁴ and, together with all analysed data, provided them to all ECIL participants before the meeting. The ECIL 7 conference was held in Sofia-Antipolis, France, on 21-23 September 2017 and attended by 52 experts from 20 European countries, Israel, and Australia, all experts in infections in haematology. In the plenary session, the group presented its literature analysis and guideline proposals, which were discussed and revised until a consensus emerged. The final version was approved on 23 September and the slide set was made publicly available on the ECIL website (www.ecil-leukaemia.com) on 2 October 2017. The final documents were written based on the initial

proposal, discussion during plenary session and final approval. To distinguish whether our proposals were based on clinical or on laboratory endpoints, we have added this information (“C” for clinical endpoint, “L” for laboratory endpoint) in the tables.

The definitions of response to vaccination are reported in Table 1.

OVERVIEW OF CRITICAL ASPECTS OF VACCINATION IN HAEMATOLOGY PATIENTS

Many issues need to be addressed when vaccinating haematology patients. Clinical efficacy is difficult to demonstrate owing to the small size of most studies and low incidence of some infections. Therefore, most of our recommendations are based on serological response. Seroprotection is defined using data from healthy individuals, which may not be relevant to immunocompromised patients. Data on long-term persistence of protection are lacking. Live-attenuated vaccines (LAVs) pose the risk of vaccine-induced disease, which is potentially life threatening, to immunocompromised patients.¹⁵ Only in specific circumstances, when there are no inactivated alternatives, they may be considered when the expected benefits outweigh the risk. Additionally, defining the optimal timing of vaccination is challenging: “Timing is crucial”.¹⁶ Some patients with chronic diseases may not need treatment for years after diagnosis, giving them time for vaccination, but once treatment is started, the persistence of the protection is unknown. Others, such as those with acute myeloid leukaemia (AML), require urgent chemotherapy, making vaccination futile at the time of diagnosis. Moreover, treatment (e.g. rituximab) often influences vaccine efficacy. While other guidelines recommend certain vaccines in immunocompromised patients in general, we considered not only different diseases but also different treatments and timings. Finally, in addition to the individual benefit of protection, vaccinating these patients could contribute to herd immunity, which is compromised in some countries.

VACCINATION IN MYELOID DISEASES

Myeloid malignancies (e.g. AML, myelodysplastic syndromes (MDS), chronic myeloid leukaemia (CML), and other MPNs) represent a heterogeneous group of diseases in which therapeutic approaches differ widely.

AML and MDS

The ECIL group recommends yearly administration of a single dose of inactivated influenza vaccine (IIV) from the end of intensive chemotherapy, hepatitis B (HBV) vaccination in case of high risk of HBV transmission during chemotherapy, and all other inactivated vaccines recommended according to age and country guidelines 3-6 months after the end of chemotherapy (Table2).

Most infections occurring during intensive chemotherapy for AML are not vaccine-preventable. Once at home, these patients may have an increased risk of community-acquired infections, and this may delay chemotherapy, finally affecting the outcome. However, the benefit of vaccination is difficult to estimate in AML patients as data are scarce and mostly derived from mixed haematology populations. The largest amount of data involves influenza and HBV.

Inactivated influenza vaccine

There is no recent data on the risk of influenza infection in AML patients. However, high rates of pneumonia and death were noted in previous studies.^{17,18} Although the seroconversion rates to one IIV dose is not higher than 20%^{19,20}, yearly vaccination is recommended after the end of intensive chemotherapy as long as the patient is considered immunocompromised (Table 2). There is no significant benefit of a second dose.²⁰

HBV vaccine

The risk of primary HBV infection in low-prevalence setting is very limited owing to the use of safe blood products and infection control policies in Europe²¹, but it exists in some countries with high

HBV prevalence. Since acute hepatitis B may delay chemotherapy, early vaccination in these countries could be considered in high-risk patients, e.g. those with high transfusion needs.^{22,23} Its benefit seems limited in other situations.²⁴

Others

Few data exist for other inactivated vaccines. However, some data could be extrapolated from paediatric studies. Immunity loss is lower in AML than in acute lymphoblastic leukaemia (ALL) children^{25,26} but revaccination with a booster from 3–6 months after the end of chemotherapy usually restores seroprotection for *S. pneumoniae*, tetanus, polio, measles, *N. meningitis C*, and *H. influenzae B*.²⁷⁻²⁹

For non-transformed MDS patients, there is no specific data, especially during treatment with 5-azacytidine. Moreover, MDS encompasses a heterogeneous group of diseases with different infection risks and therapies. Given the median age of MDS patients, it seems reasonable to recommend inactivated vaccines according to age, comorbidities, and country guidelines, especially against influenza and pneumococcus.

Chronic myeloid leukaemia (CML) and other MPNs

The ECIL group recommends in CML patients yearly single dose IIV and pneumococcal vaccination.

Patients with other MPNs should receive inactivated vaccines according to age and country recommendations (Table2).

CML patients are usually not considered at high risk of infection unless they develop neutropenia or acute transformation although, compared to healthy individuals, they have an increased risk of respiratory and skin infections³⁰ and of tuberculosis in areas of high endemicity.³¹ Tyrosine kinase inhibitors (TKIs), the standard of care for treatment of CML, were associated with an increased risk of

infections³², including tuberculosis and varicella-zoster virus (VZV) infections, as well as HBV reactivation.

Patients with MPN not receiving ruxolitinib do not seem to have an increased risk of infection.³⁰

Ruxolitinib, the first Janus kinase 1/2 inhibitor, used in patients with myelofibrosis³³, increases the risk of infection, especially of herpes zoster³⁴ although the risk for other infections – tuberculosis, HBV - is uncertain.³⁵⁻³⁷ Vaccine data in patients with CML or MPN are limited to IIV and pneumococcal polysaccharide 23-valent vaccine (PPSV23).

Inactivated influenza vaccine

The seroprotection rate of H1N1 adjuvanted vaccine, assessed in 32 CML patients receiving imatinib or dasatinib³⁸, was 85% after one dose, not different from that in healthy controls (100%), as was the CD8+ and CD4+ T-cell response and its functional quality.³⁹ However, the geometric mean concentrations (GMCs) of specific antibodies were significantly lower than those in controls. The second dose did not provide a significant benefit. Some IIV studies included patients with MPN but the response rate was not specifically assessed in this subgroup.^{19,20}

Pneumococcal vaccines

The response to one dose of PPSV23 was assessed in 51 CML patients treated with various TKIs and healthy controls.³⁹ IgG and IgM responses were impaired (75% versus 100% in healthy controls). The pneumococcal conjugate vaccines (PCVs) are more immunogenic than the PPSV23 owing to the T-cell dependent response induced by the conjugation with the CRM197 diphtheria protein. Although there are no data on PCV in CML patients, it seems reasonable, on the basis of data in other immunocompromised populations, to recommend one dose of PCV followed at least eight weeks later by one dose of PPSV23. In the case of MPN, there are no data with PPSV23 or with PCVs.

Despite the lack of data on LAV in CML or MPN patients, we do not recommend their use in patients on TKI or ruxolitinib. The ECIL guidelines for patients with myeloid diseases are summarised in Table 2.

VACCINATION IN LYMPHOPROLIFERATIVE DISEASES

Multiple myeloma (MM)

The ECIL group recommends in MM patients yearly single dose of IIV and pneumococcal vaccination, while other inactivated vaccines should be considered 3-6 months after the end of treatment according to age and country recommendations (Table 3).

MM patients are at high risk of infections due to B, T, NK, and dendritic cell dysfunctions, with a hazard ratio of infection of 7.1⁴⁰, and infections causing one-fifth of the deaths.^{40,41} Major advancements over the last decade have considerably changed therapeutic approaches.

Inactivated influenza vaccine

MM patients have a six-fold higher risk of influenza than the general population.⁴⁰ In most IIV studies, MM patients were not separately analysed. Extremely variable seroconversion rates have been reported from 0% to 83%, mostly between 20% and 25%, with no clear benefit of a second dose.^{19,20,42-46}

Pneumococcal vaccines

The risk of IPD in MM patients reaches 60 times that of general population^{4,47,48} and is associated with low specific antibody and opsonophagocytic activity (OPA) titres.⁴⁹ There are no recent data on pneumococcal vaccination in MM, particularly with PCV. The response rate to PPSV23 was reported between 33% and 57%^{45,49-52}, and was better in patients with complete response⁵² and

in those not hypogammaglobulinemic.⁴⁹ However, most patients were off therapy or during a plateau phase, and their treatments were not representative of current practice.^{45,50-52}

Additionally, the response rates to one dose of either PPSV23 or PCV7 were surprisingly similar, both around 60%, versus 100% in the controls.⁴⁹ As OPA assays did not correlate with antibody titres, it was suggested that MM patients could develop ineffective antibodies.⁵³

Lenalidomide could enhance the response to 2 doses of PCV7.⁵⁴

Given the high risk of IPD, the absence of safety concerns and data from other immunocompromised populations, vaccination with at least 1 dose of PCV, followed by 1 dose of PPSV23 at least 8 weeks later, is recommended, preferably before treatment or during maintenance.

Haemophilus influenza B (HiB) vaccine

The risk of HiB infection in MM, although expected, is unknown and there are conflicting data regarding the rate of seroprotection in non-vaccinated MM patients compared to the healthy controls.^{55,56} Thus, routine vaccination cannot be recommended. In the only available study, the vaccine response in the patients was similar to that in healthy individuals.⁴⁵

Herpes zoster vaccine

MM patients have a 4 to 14 higher risk of herpes zoster than the general population^{40,57}, especially during bortezomid treatment.⁵⁸ Valacyclovir prophylaxis is safe, effective, and recommended in this setting. Zoster LAV vaccine is contraindicated and no data are available in MM. Only 9 non-transplanted MM patients were included in a phase I study with the heat-inactivated vaccine and their specific response is unknown.⁵⁹ Given the high efficacy of a recently approved inactivated subunit zoster vaccine⁶⁰, data in MM patients are much awaited.

Lymphoma

The ECIL group recommends in lymphoma patients yearly single dose of IIV and pneumococcal vaccination, preferably before treatment or during maintenance. Other inactivated vaccines, including HPV, should be provided 3-6 months after the end of chemotherapy (6 months after the last dose of rituximab) according to age and country recommendations (Table3).

Patients with lymphoma have impaired T- or B-cell immunity, with the latter further affected by the use of anti-B cell antibodies. Lymphoma represents a wide, heterogeneous group of diseases. Aggressive lymphomas require prompt, intensive chemotherapy, making vaccination futile at that time. However, once these patients obtain remission, they are usually no longer at high risk of infections, except for those who received rituximab. On the other hand, patients with indolent lymphoma do not require immediate treatment and vaccination before treatment is usually feasible.

Inactivated influenza vaccine

Patients with lymphoma are at increased risk of influenza and its severe forms. The response to IIV was highly variable, in the median 30%, and usually lower than that in controls.^{21,44,46,61-66} The response rate to adjuvanted or non-adjuvanted H1N1 vaccines was similar.^{38,67-70} However, a second dose could be beneficial, particularly with an adjuvanted formulation.^{21,38,69,71} No data are available in patients receiving intensive regimens.^{65,71} Yearly IIV is recommended as long as the patient is considered immunocompromised, except during high-intensity treatment because the response is unlikely.

Pneumococcal vaccines

Lymphoma patients have a 5–10-fold increased risk of IPD.^{4,48} Most vaccine data came from splenectomised patients, mostly with Hodgkin's lymphoma, in whom good response to PPSV23 was reported before chemotherapy (36%-64%)⁷²⁻⁷⁴, similar to other splenectomised patients.⁷⁵ In

good responders, protection waned at 3 years ⁷⁴, and poor responders did not benefit from revaccination.⁷²⁻⁷⁴ However, these data do not reflect current practice, and only confirm good response before chemotherapy.

No specific data on PCV exist in lymphoma patients. However, based on data from other immunocompromised populations, the absence of safety concerns, and the potential benefit, pneumococcal vaccination is recommended (Table 3), except for patients receiving intensive chemotherapy or anti-B monoclonal antibodies as they are unlikely to respond.

Human papillomavirus (HPV) vaccine

Lymphoma patients are at increased risk of HPV-associated cancer, especially after pelvic irradiation.⁷⁶ Although no specific data exist on HPV vaccination in lymphoma patients, there were no safety issues in other immunocompromised patients.⁷⁷ We recommend following the country's age-specific recommendations for healthy adolescents and young adults after the end of treatment.

Chronic lymphocytic leukaemia

The ECIL group recommends in CLL patients yearly single dose of IIV, and pneumococcal vaccination preferably before treatment or during maintenance, while other inactivated vaccines should be administered 3-6 months after the end of treatment (6 months after the last dose of rituximab) (Table3).

The high rate and severity of pneumococcal and HiB infections in CLL are correlated with low IgG levels and specific antibody titres. In a cohort of 263 patients including 66 treated with ibrutinib, infection was observed at least once in 72%, with death in 38%.⁷⁸ This B-cell deficient population had suboptimal vaccine responses owing to impaired antibody production and antigen

presentation and increased plasma levels of histamine. The latter inspired studies on ranitidine to improve vaccination response.

Inactivated influenza vaccine

Despite the increased risk of influenza in CLL, vaccine studies are few and the old studies do not represent current practice.^{38,44,62,65} The response to IIV was usually low (5-30%)^{44,79}, except in treatment-naïve patients.⁶⁵

The benefit of a second dose seems limited to adjuvanted vaccines.^{38,62,79} In patients receiving ibrutinib, poor response was observed, even with high-dose IIV.^{80,81}

Pneumococcal vaccine

CLL patients have an increased, almost 30-fold, risk of IPD.⁴⁷ Overall, the response to PPSV23 was poor (0–21%), better in early-stage disease⁸²⁻⁸⁵, and not improved by ranitidine or GM-CSF.^{85,86}

The response to one dose of PCV was in general better, 20% and 58% in treatment-naïve patients or early-stage disease^{87,88}, but its duration was unknown. Thus, vaccination with PCV followed by PPSV23 is preferred before treatment. No response was observed in four patients receiving ibrutinib.⁸⁹

Haemophilus influenzae B vaccine

There are no recent data on the risk of HiB infection in CLL. The response rate to HiB vaccine was low, around 25%, and better in case of early-stage disease, normal immunoglobulin levels, and younger age.^{82,83,90} Two small-scale studies suggested a benefit of ranitidine co-administration.^{86,91} Although the extent of HiB burden in the current era of universal HiB vaccination is unknown, the efficacy of the vaccine can be expected.

Herpes zoster vaccine

Patients with CLL have an increased risk of herpes zoster, and many of them, given their age, could be eligible for the recently approved subunit vaccine. However, no CLL-specific data exist, neither with this vaccine, nor with the heat-inactivated vaccine.^{59,92} There are no data on the safety of the zoster LAV in CLL.

Role of rituximab on the immune response to vaccination in CLL

Rituximab is widely used in both B-cell lymphoma and CLL. However, it strongly impairs, often annihilates, the response to IIV^{38,70,71,93}, even in case of two doses⁷¹ or ASO3-adjuvanted vaccine.^{38,67,70,71} When patients were vaccinated within 6–10 months^{38,67} or even within a median of 29 months⁶⁶ after the last rituximab dose, the response was 0–29%. Similar effects are expected with other B-cell monoclonal antibodies.

Moreover, there are no data on the duration of response after pre-rituximab IIV vaccination and there are very limited data on other vaccines.

Studies suggested that rituximab has stronger effect on the response to primary than to recall antigens^{94,95}, which, however, remains lower than in healthy controls.^{66,94} The exception to the deleterious effect of rituximab might be the heat-inactivated zoster vaccine.⁹⁶

As the vaccine response is null during rituximab treatment and suboptimal at least within 6 months thereafter for IIV, and assumed to be decreased with PCV on the basis of data in rheumatoid arthritis patients⁹⁷, other protective measures should be provided during rituximab treatment and in the following year, and vaccinations postponed. Blood lymphocyte counts and immunoglobulin levels may help in assessing the immune recovery. The impact of rituximab may sometimes last for more than 12 months and measuring vaccine response seems particularly helpful in these patients.

Whenever possible and after careful assessment of the risk-benefit ratio of postponing treatment to vaccinate the patient, patients should be vaccinated before treatment, although the persistence of the response once treatment is started is unknown.

After the active phase of treatment (i.e. during maintenance or plateau) or within 3–6 months after the end of treatment, the vaccine history should be reviewed in order to plan an individual vaccine programme according to age, comorbidities, and country recommendations. Antibody titres can help at this time in designing a tailored programme.

VACCINATION IN CHILDREN WITH ACUTE LEUKAEMIA

For children with acute leukaemia the ECIL group recommends during induction and re-induction chemotherapy only HBV vaccination in settings with high risk of HBV transmission; during maintenance therapy yearly IIV and PCV vaccination; LAV varicella vaccination in seronegative children is preferred at 3-6 months after the end of chemotherapy rather than during maintenance; after the end of chemotherapy, a booster dose of all vaccines in those previously vaccinated and a full vaccination course according to age and country recommendations in those never vaccinated (Table 4).

Currently, more than 80% of the children with ALL can be cured.⁹⁸ Vaccination in these patients aims at protecting them from infections as in healthy children. At the diagnosis of ALL, prompt chemotherapy usually postpones any vaccination.

During the intense chemotherapy phases, the prevention policies in most institutions include contact isolation, immunoglobulins, antimicrobials, and benefiting from cocooning and herd immunity. LAVs are contraindicated.⁹⁹⁻¹⁰¹ Conversely, although there is no safety concern regarding the inactivated vaccines, the response is suboptimal during these phases.¹⁰²⁻¹⁰⁶ The exception to the rule of not vaccinating prior to or during leukaemia therapy is HBV vaccination of seronegative children in areas of high HBV endemicity¹⁰⁷, which is feasible with the rapid schedule used for newborns to HBV-positive mothers (20 µg recombinant HBV vaccine at 0-14-28 days). This results in a seroconversion rate of 23.8%²³ and up to 30–35% after 1 or 2 additional doses¹⁰⁵, with no benefit of increasing the number of initial doses.^{108,109}

The last and longest phase of ALL treatment is maintenance. Influenza and pneumococcal vaccinations are recommended during this phase as patients are at increased risk for these infections^{110,111} and are usually back to day-care, kindergarten, or school.^{111,112} The response rate to IIV during maintenance was 30–80%^{1,81,112-115}, lower than that in healthy children^{113,116} but with minor adverse effects and no benefit of high-dose^{81,117} or of adjuvanted IIV.^{118,119}

During the maintenance phase or just thereafter, the seroprotection rate was 86–100% after 2 doses of PCV7²⁷ and higher than 70% for most serotypes after one dose of PCV13.¹²⁰

Previously, varicella LAV for ALL patients during maintenance was a subject of controversy.^{121,122}

Vaccination during maintenance resulted in seroprotection in 80% and 90% after 1 and 2 doses, respectively, with a lower incidence of herpes zoster after vaccination than after natural varicella infection.^{123,124} However, although varicella LAV has sometimes been safely administered to ALL patients with short withdrawal of chemotherapy^{125,126}, the major criticisms to this policy are the potential need to postpone therapy for three weeks and the risk of vaccine-induced complications of up to 50%. Considering the low mortality of VZV during maintenance and the availability of effective antivirals¹²⁷, vaccinating is an easier and safer option after completion of chemotherapy than during chemotherapy.^{5,121} The zoster LAV, which contains 15–20-fold higher titres of attenuated virus than the varicella LAV, is contraindicated.

After the end of treatment, impairment of immune response, affecting both *de novo* and recall antigens, persists for 3–6 months^{128,129}, especially in younger children, owing to the detrimental effect of chemotherapy on the developing B-lymphocyte pool, memory B-, and plasma cells.¹³⁰ As a result, seroprotection rate variably decreases for diphtheria (2–83%), pertussis (18–73%), tetanus (2–80%), poliomyelitis (0–58%), HiB (0–65%), HBV (46%), varicella (17–35%), mumps (8%–71%), measles (40–71%) and rubella (8–28%).^{1,25,29,130-135} Importantly, the vaccine memory is not fully abrogated and the restoration of seroprotection was usually obtained with a booster dose, to 100% for tetanus, diphtheria, pertussis, HiB and 80–100% for HBV, measles, mumps, and rubella.^{29,130,132,135} Therefore, in centres having difficulties in assessing antibody titres, the systematic administration of booster

doses is a simple and cost-effective measure in children fully vaccinated before chemotherapy

^{29,130,132,134,135}, starting from at least 3 and, preferably, 6 months after the end of chemotherapy.

^{5,134,136} Despite the lack of precise data, we recommend that patients who were not vaccinated at all

before chemotherapy benefit from a full immunisation program according to country

recommendations, and those partially vaccinated before ALL complete the programme without

repeating the previous dose(s) (Table 4). ^{5,136,137} Although there are no specific data in AML, the same

recommendations are proposed for children with AML and ALL.

SAFETY OF VACCINATION IN NON-TRANSPLANTED PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

There are no safety concerns with inactivated vaccines. There may be mild adverse events, mostly local reactions at the site of injection, similar to immunocompetent hosts. There is no evidence of an increased rate of relapse of the haematological disease.

In acute leukaemia, postponing varicella LAV after completion of chemotherapy is a safer option than vaccinating during chemotherapy. ^{5,121} There is one report of a paediatric ALL patient who erroneously received MMR during maintenance and developed persistent rubella infection. ⁹⁹ Other LAVs should also be avoided during therapy and six months from the end of chemotherapy because of the potential risk and lack of safety data.

RECOMMENDATIONS FOR VACCINATION OF THE HEALTH-CARE WORKERS IN THE HAEMATOLOGY WARD

Hospital haematology staff should receive IIV annually (A II h). This measure reduced the proportion of nosocomial influenza infections in cancer patients. ¹³⁸ They should additionally be vaccinated according to country and hospital guidelines. Care holders who are seronegative for measles or VZV

should be vaccinated. In case of post-VZV vaccine rash, they should avoid contact with patients until resolution.

FUTURE DIRECTIONS AND AREAS OF RESEARCH

Owing to the increasing life expectancy of patients with MPNs, and the use of new drugs with potential immunosuppressive effects such as ruxolitinib ^{34,37} and new drugs for AL and MDS patients (e.g. midostaurin or venetoclax), studies on vaccine response in different diseases and under different therapies, including bispecific antibodies (eg, blinatumomab) or anti-CD19/20/22 CAR T cells which might have negative impact on vaccine response as well, are warranted. In most non-aggressive LPDs, the main issue is to determine the optimal timing of vaccination especially before and/or after anti-CD20 monoclonal antibody treatment. If patients are vaccinated before treatment, the duration of this response and the need for boosters should be assessed. For pneumococcal vaccination, the benefit of more than one PCV dose in the initial regimen, the duration of protection, and the need for subsequent PPSV23 dose(s) should be explored. The benefit of HPV vaccination in preventing HPV-related cancer should be evaluated in patients not included in the usual age-based recommendation. Finally, the inactivated zoster vaccines should be assessed in haematological patients, both adults and children. In paediatrics, the main issue is whether children who did not fully complete primary vaccinations would benefit from a full revaccination programme or only from boosters.

The implementation of these guidelines should be based on education of patients and caregivers on the benefits of vaccination. Since the risk of certain vaccine-preventable infections might vary according to local epidemiology and herd immunity, the optimal implementation should always take into consideration country recommendations, age (e.g. for HPV or meningococcus) and the availability of co-formulated vaccines.

CONCLUSION

Patients with CML have usually good responses to influenza and pneumococcal vaccines. In patients with other MPNs, considering safety and the expected benefit of inactivated vaccines, influenza and pneumococcus vaccination should be provided. Patients with CLD have a low response to most vaccines, but owing to the high risk of infection, they can potentially benefit most from vaccine protection. Once the treatment is over, haematology patients should benefit from the vaccine programme proposed for the healthy population in a given country, including LAVs, when they are no longer considered immunocompromised.

Contributors

CC and PL recruited the experts. MM, CC and PL compiled the recommendations. All authors were involved in the literature search, development of recommendations and conception of the manuscript. All authors revised the manuscript and gave final approval.

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Declaration of interests

MM has been a scientific adviser for Biotest and has received payment for lectures and travel expenses from MSD, Janssen, Pfizer, Astellas and Gilead. RDB has received personal fees from Gilead and Merck. CC has received grants from Merck and Astellas and has been a scientific adviser for Merck. TL has received grants from Gilead, and non-financial support and personal fees from Gilead, Astellas, MSD and Basilea. PL has received grants from Merck and Astellas and has been a scientific adviser for Merck. SC, HDL, SE, GG, CK and DE declare that they have no conflict of interests.

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Table 1: The definitions of response to vaccination.

Term	Definition
Clinical efficacy	Significantly decreased frequency and/or severity of the disease in vaccinated patients when compared to non-vaccinated patients
Seroconversion	Either the development of vaccine-specific antibodies in seronegative patients or a predefined (x2, x3, x4...-fold) increase in vaccine-specific antibody titres in seropositive patients
Seroprotection	Minimal vaccine-specific antibody titre providing an estimated clinical protection (50-100%) according to the results of studies in healthy individuals.

Table 2: ECIL 7 recommendations for vaccination of patients with myeloid diseases

Haematological disease	Inactivated influenza vaccine (IIV)	Pneumococcal vaccines	Other inactivated vaccines	Comments
Acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS)	At the end of intensive chemotherapy in AML/MDS patients, a single dose of IIV is recommended yearly as long as the patient is considered immunocompromised (B II u).	Three to six months after the end of chemotherapy, AML/MDS patients should be (re)vaccinated according to age and country recommendations.	In countries with high HBV prevalence where a high risk of HBV transmission during chemotherapy exists, HBV vaccination starting before and continuing during chemotherapy can be administered (C II u). Three to six months after the end of chemotherapy, AML/MDS patients should be (re)vaccinated according	Patients with MDS who do not receive any specific treatment should have their vaccine programme revised according to age and country recommendations.

			to age and country recommendations.	
Chronic myeloid leukaemia	CML patients should receive one dose of IIV yearly (B II u).	CML patients should be vaccinated against pneumococcus (C II t). Although there are no data on the response to PCV, it is recommended to give 1 dose of PCV followed 2 months later by one dose of PPSV23.		The expected response rate during dasatinib or bosutinib treatment might be lower than with the other TKIs.
Other chronic myeloproliferative neoplasms	According to age and country recommendation.	According to age and country recommendation.	According to age and country recommendation.	There are no data on the vaccine response under ruxolitinib.

Note: All the recommendations are based on laboratory endpoint - serological response, mainly seroconversion rate.

Table 3: ECIL 7 recommendations for vaccination of patients with lymphoproliferative diseases

Haematological disease	Inactivated influenza vaccine (IIV)	Pneumococcal vaccines	Other inactivated vaccines	Comments
Multiple myeloma	Yearly vaccination with IIV (1 dose) is strongly recommended (A II u) as long as the patient is considered immunocompromised.	One dose of PCV13 followed by 1 dose of PPSV23, at least 8 weeks later, is recommended (B II u) , preferably before treatment or during maintenance.	Other inactive vaccines should be considered from 3 to 6 months after the end of treatment, according to age, comorbidities, and country recommendations.	LAVs are contra-indicated until at least 3 months after the end of chemotherapy (D III) .
Lymphoma	Yearly vaccination with IIV (one dose) is strongly recommended (A II u) as long as the patient is considered immunocompromised, except in patients receiving intensive	One dose of PCV13 followed by 1 dose of PPSV23, at least 8 weeks later, is recommended (B II t) , preferably before treatment or during maintenance,	Human papillomavirus vaccine is recommended in healthy adolescents and young adults according to country recommendations for age after the end of	In patients who are receiving or have received anti-CD20 antibodies in the previous 6 months, any inactivated vaccine should be delayed for at least 6

	chemotherapy or who are receiving or have received anti-CD20 antibodies in the previous 6 months.	except in patients who are receiving high-dose chemotherapy or who are receiving or have received anti-CD20 antibodies in the previous 6 months.	treatment (B II t) . Other inactive vaccines should be considered from 3 to 6 months after the end of treatment, according to age, comorbidities, and country recommendations.	months after the last dose (B II u for IIV) . LAVs are contra-indicated until at least 3 months after the end of chemotherapy (D III) .
Chronic lymphocytic leukaemia	Same recommendation as for lymphoma patients	One dose of PCV13 followed by 1 dose of PPSV23, at least 8 weeks later, are recommended (B II u) , preferably before treatment.	Same recommendation as for lymphoma patients.	Same recommendation as for lymphoma patients. Novel drugs may significantly impair the vaccination response.

Note: All the recommendations are based on laboratory endpoint - serological response, mainly seroconversion rate.

Table 4: ECIL7 recommendations for vaccination of children with acute lymphoblastic leukaemia

Vaccine	ECIL 7 recommendation	Timing and dose	Comments
During induction and re-induction phases			
Hepatitis B virus (HBV) vaccine	In the setting of high HBV prevalence and high risk of acquiring HBV infection during chemotherapy, HBV vaccination is recommended as soon as possible from the start of treatment (B II u) .	Double dose. Different accelerated schedules of 3–5 doses can be used.	Co-administration of HBV-specific immunoglobulins might improve protection (C II u) .
Live attenuated vaccines (LAVs)	Contraindicated (D II u) .		
During maintenance therapy			
Inactivated Influenza vaccine (IIV)	A yearly vaccination with an IIV is recommended (A II u) .	One dose, except for children aged 9 years or below who should receive 2 doses (A II t) .	
Pneumococcal conjugate vaccine (PCV)	PCV vaccination is recommended during maintenance treatment (B II u) .	One dose (boost). In case the patient has not been	

		vaccinated before acute leukaemia, a full programme should be given.	
Varicella LAV	A vaccination with the varicella LAV can be given during maintenance if seronegative (C II u) .	One dose. Chemotherapy should be suspended one week before and one week after, but longer in case of vaccine-related rash.	Considering the potential risk of suspending chemotherapy for varicella vaccination on leukaemia relapse, postponing varicella vaccination 3 to 6 months after the end of chemotherapy is a better option. Alternative measures (acyclovir, isolation, vaccination of household contacts) and specific passive protection after exposure should be proposed during maintenance and until vaccination.
Other LAVs	LAVs other than varicella vaccine are contraindicated (D II u) .		

From at least 3 but preferably 6 months after the end of chemotherapy			
IIV	A yearly vaccination is recommended as long as the patient is considered immunocompromised (B II u) .	One dose, except for children aged 9 years or below who should receive 2 doses	
<i>Patients fully vaccinated before acute leukaemia diagnosis</i>			
DTaP**, inactivated poliovirus vaccine and <i>HiB</i> vaccine	Patients should receive one dose of DTaP, inactivated polio, and <i>HiB</i> vaccine, irrespective of antibody titres (A II u) .	Booster dose	In high-risk patients, suboptimal response to one dose might occur.
Hepatitis B Virus vaccine (HBV)	Patients should receive HBV vaccination, irrespective of antibody titres (A II u) .	Booster dose	
PCV	Patients should receive one dose of PCV (A II u) .	Booster dose	
Meningococcal conjugate C/ACWY	Patients should receive one dose of meningococcal C monovalent or tetravalent vaccine (B III) .	Booster dose	
Meningococcal conjugate	Patients should receive one dose of	Booster dose	

B	meningococcal B vaccine (C III) .		
Human papilloma virus (HPV)	Patients should be vaccinated according to country recommendations and age (B III) .	Booster dose	
Varicella LAV	Patients should receive one dose of the vaccine if they have been previously vaccinated, irrespective of the Abs titres (A II u) .	One dose	An alternative option is to check the serum titres and to proceed with one boost dose only in seronegative children (and with a 2 nd dose 4–6 weeks later if the patient is still seronegative 4 weeks after the 1 st dose).
Measles, mumps, and rubella LAV	Patients should receive one dose of the vaccine if they have been previously vaccinated, irrespective of the Abs titres (A II u) .	One dose.	Same comment as for varicella LAV.
<i>Patients not vaccinated before chemotherapy</i>			
	Patients never vaccinated should be vaccinated with full courses according to country		

	<p>recommendations (A II u).</p> <p>Patients whose vaccination programme was withdrawn for chemotherapy should resume the programme starting from the suspended dose without repeating the previous dose(s).</p>		
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*HiB, *Haemophilus influenzae* B; DTaP: Diphtheria, tetanus, acellular pertussis

Note: All the recommendations are based on laboratory endpoint - serological response, mainly seroconversion rate.

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