Vaccination and haematological malignancies 1

Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7)

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Patients with haematological malignancies are at high risk of infection because of various mechanisms of humoral and cell-mediated immune deficiencies, which mainly depend on underlying disease and specific therapies. Some of these infections are vaccine preventable. 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 a haematology ward. Additionally, because of insufficient training about the topic, vaccination is an area often neglected by haematologists, and influenced by cultural differences, even among health-care 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 show the clinical benefits of vaccination, the subsequent need to rely on biological parameters, their clinical pertinence not being established in immunocompromised patients, scarcity of clarity on the optimal timing of vaccination in complex treatment schedules, and the scarcity of data on long-term protection in patients receiving treatments. Moreover, the risk of vaccine-induced disease with live-attenuated vaccines strongly limits their use. Here we summarise guidelines for patients without transplantations, and address the issue by the haematological group—myeloid and lymphoid—of diseases, with a special consideration for children with acute leukaemia.

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This paper is the first in a **Series** of two papers about vaccination and haematological malignancies

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Introduction

Patients with haematological malignancies are at increased risk for various infections, including some (eg, influenza and invasive pneumococcal disease) that are vaccine preventable.[1–4] Vaccination has been widely pursued after haemopoietic stem cell transplantation to favour pathogen-specific immune reconstitution, and previous guidelines exist.[5–8] Although transplantation recipients can be different, they share a time marker, which is the transplant date. In patients with haematological malignancies who are not transplanted, infectious risk and immune deficiencies are heterogeneous, including differences between adults and children; these differences preclude a single vaccination programme.[8] Patients with lymphoproliferative disorders and those with chronic myeloproliferative neoplasms (MPNs) suffer from distinct immune deficiencies and receive different treatments[9–11] that variously affect the vaccine response. Moreover, therapies have changed considerably over the past decades, which have made some conclusions from previous studies obsolete in patients treated with traditional approaches. Although patients with haematological disorders 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 European Conference on Infections in Leukaemia (ECIL 7) group addressed the issue of vaccination in patients with haematological disorders. Here we summarise the guidelines in patients who have not had a transplantation. In a companion report we summarise the guidelines for haemopoietic stem-cell transplantation recipients.[12]

Guideline development overview

ECIL is a joint venture of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation, the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer, the Immunocompromised Host Society, and the European Leukaemia Net. Its objective is to develop evidence-based guidelines for the management of infection in haematology and haemopoietic stem-cell transplantation patients. The ECIL method has been previously described.[13] 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 desired outcome was evidence of a reduction of vaccine-preventable infections due to different populations compared with those not vaccinated, and secondary outcomes included serological response, seroprotection, and safety.

We did MEDLINE (including MEDLINE In Process) searches from March to Sept, 2017, to identify potentially relevant English-language studies. The searches 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,

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The European Conference on Infections in Leukaemia (ECIL) group, a joint venture of the Infectious Diseases Working Party of the European Society for Blood and Marrow transplantation (EBMT), the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC), the European Leukaemia Net (ELN), and the Immunocompromised Host Society (ICHS)

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For the **ECIL website** see www.ecil-leukaemia.com

	Definition
Clinical efficacy	Significantly decreased frequency and severity of the disease in vaccinated patients when compared with non-vaccinated patients
Seroconversion	Either the development of vaccine-specific antibodies in seronegative patients or a predefined (two-fold, three-fold, etc) 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 1: **Definitions of response to vaccination**

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). We screened references for other potentially relevant papers. We analysed full papers for all potentially relevant abstracts, and paid particular attention to the study design, the population, the timing of immunisation, and the endpoints. On the basis of these analyses, we elaborated recommendations that we 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 Sept 21–23, 2017, and was attended by 52 experts in infections in haematology who were from 20 European countries, Israel, and Australia. In the plenary session, we presented our literature analysis and guideline proposals, which were discussed and revised until a consensus emerged. The final version was approved on Sept 23, 2017, and the slide set was made publicly available on the ECIL website on Oct 2, 2017. We wrote the final documents 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 in the tables (the definitions of response to vaccination are reported in table 1).

Overview of essential aspects of vaccination in patients with haematological disorders

Many issues need to be addressed when vaccinating patients with haematological disorders. Clinical efficacy is difficult to show because of 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 might not be relevant to immunocompromised patients. Data on long-term persistence of protection are scarce. Live-attenuated vaccines (LAVs) pose the risk of vaccine-induced disease, which can be life threatening to immunocompromised patients.[15] Only in specific circumstances, when there are no inactivated alternatives, they could be considered when the expected benefits outweigh the risk.

Additionally, defining the optimal timing of vaccination is a challenge: timing is crucial.[16] Some patients with chronic diseases might not need treatment for years after diagnosis, which gives 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, which makes vaccination futile at the time of diagnosis. Moreover, treatment (eg, rituximab) often influences vaccine efficacy. Although other guidelines recommend particular 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 (eg, 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 (table 2).

Most infections that occur during intensive chemotherapy for AML are not vaccine preventable. Once at home, these patients might have an increased risk of community-acquired infections, and this risk could delay chemotherapy, and affect the outcome. However, the benefit of vaccination is difficult to estimate in patients with AML as data are scarce and mostly derived from mixed populations with haematological disorders. The data that are available are mainly on influenza and HBV vaccination.

There are no recent data on the risk of influenza infection in patients with AML. 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]

The risk of primary HBV infection in low-prevalence setting is limited because of the use of safe blood products and infection control policies in Europe,[21] but it exists in some countries with high HBV prevalence. Since acute hepatitis B might delay chemotherapy, early vaccination in

	Inactivated influenza vaccine	Pneumococcal vaccines	Other inactivated vaccines	Comments
AML and MDS	At the end of intensive chemotherapy in patients with AML or MDS, a single dose is recommended yearly as long as the patient is considered immunocompromised (B II u)	3–6 months after the end of chemotherapy, patients with AML or MDS 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). 3–6 months after the end of chemotherapy, patients with AML or MDS should be (re) vaccinated according to age and country recommendations	Patients with MDS who do not receive any specific treatment should have their vaccine programme revised according to age and country recommendations
CML	Patients with CML should receive one dose yearly (B II u)	Patients with CML should be vaccinated against *Streptococcus pneumoniae* (C II t). Although there are no data on the response to PCV, it is recommended to give one dose of PCV followed 2 months later by one dose of PPSV23	According to age and country recommendation	The expected response rate during dasatinib or bosutinib treatment might be lower than with the other tyrosine kinase inhibitors
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

All the recommendations are based on laboratory endpoint—serological response, mainly seroconversion rate. ECIL 7=2017 European Conference on Infections in Leukaemia. HBV=hepatitis B virus. AML=acute myeloid leukaemia. MDS=myelodysplastic syndrome. CML=chronic myeloid leukaemia. PCV=pneumococcal conjugate vaccines. PPSV23=pneumococcal polysaccharide 23-valent vaccine. For the evidence-based medicine grading system (B II u, C II t, C II u) see appendix.

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

these countries could be considered in high-risk patients—for example, those with high transfusion needs.[22,23] Vaccination benefit seems scarce in other situations.[24]

Few data exist for other inactivated vaccines. However, some data could be extrapolated from paediatric studies. Immunity loss is lower in children with AML than with acute lymphoblastic leukaemia (ALL)[25,26] but re-vaccination with a booster 3–6 months after the end of chemotherapy usually restores seroprotection for *S pneumoniae*, tetanus, polio, measles, *N meningitidis* serogroup C, and *H influenzae* serogroup b (Hib).[27–29]

For patients with MDS who did not have a transformation, 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 patients with MDS, it seems reasonable to recommend inactivated vaccines according to age, comorbidities, and country guidelines, especially against influenza and *S pneumoniae*.

Chronic myeloid leukaemia (CML) and other MPNs

The ECIL group recommends a single dose of IIV every year and pneumococcal vaccination in patients with CML. Patients with other MPNs should receive inactivated vaccines according to age and country recommendations (table 2).

Patients with CML are usually not considered at high risk of infection unless they develop neutropenia or acute transformation although, compared with healthy individuals, they have an increased risk of respiratory and skin infections[30] and of tuberculosis in areas of high endemicity.[31] Standard treatment of CML with tyrosine kinase inhibitors was associated with an increased risk of infections,[32] including tuberculosis and varicella-zoster virus, and HBV reactivation.

Patients with MPNs not receiving ruxolitinib do not seem to have an increased risk of infection.[30] Ruxolitinib, the first Janus kinase 1 and 2 inhibitor, used in patients with myelofibrosis,[33] increases the risk of infection, especially of herpes zoster[34] although the risk for other infections—tuberculosis and HBV—is uncertain.[35–37] Vaccine data in patients with CML or MPNs are limited to IIV and pneumococcal polysaccharide 23-valent vaccine (PPSV23).

Inactivated influenza vaccine

The seroprotection rate of H1N1 adjuvanted vaccine, assessed in 32 patients with CML receiving imatinib or dasatinib,[38] was 85% after one dose, which was 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 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 MPNs 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 patients with CML who were treated with various

tyrosine kinase inhibitors and 24 healthy controls.[39] IgG and IgM responses in patients with CML were impaired (75% *vs* [versus] 100% in healthy controls). Pneumococcal conjugate vaccines (PCVs) are more immunogenic than PPSV23 because of the T-cell dependent response induced by the conjugation with the CRM197 diphtheria protein. Although there are no data on PCV in patients with CML, it seems reasonable, based on data in other immunocompromised populations, to recommend one dose of PCV followed at least 8 weeks later by one dose of PPSV23. In the case of MPNs, there are no data with PPSV23 or with PCVs.

Despite the absence of data on LAV in patients with CML or MPNs, we do not recommend their use in patients taking tyrosine kinase inhibitors or ruxolitinib. The ECIL guidelines for patients with myeloid diseases are summarised in table 2.

Vaccination in lymphoproliferative diseases

Multiple myeloma

The ECIL group recommends patients with multiple myeloma receive a yearly single dose of IIV and pneumococcal vaccination, and other inactivated vaccines should be considered 3–6 months after the end of treatment according to age and country recommendations (table 3).

Multiple myeloma patients are at high risk of infections because of B, T, natural killer, and dendritic cell dysfunctions, with a hazard ratio of infection of 7·1,[40] and infections causing a fifth of the deaths in Sweden and Asia.[40,41] Major advances over the past decade have considerably changed therapeutic approaches.

Inactivated influenza vaccine

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

Pneumococcal vaccines

Patients with multiple myeloma are 60 times more likely to get pneumococcal disease than the general population,[4,47,48] because of patients low specific antibody and opsonophagocytic activity titres.[49] There are no recent data on pneumococcal vaccination in patients with multiple myeloma, particularly with PCV. The response rate to PPSV23 was reported as between 33% and 57%,[45,49–52] and was better in patients with complete response[52] and in those not hypogammaglobulinaemic.[49] However, most patients were off therapy or in plateau phase, and their treatments were not representative of normal 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 control group.[49] As opsonophagocytic activity assays did not correlate with antibody titres, it was suggested that patients with multiple myeloma could develop ineffective antibodies.[53]

Lenalidomide could enhance the response to two doses of PCV7·[54]

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

Haemophilus influenza b vaccine

The risk of Hib infection in multiple myeloma, although expected, is unknown and there are conflicting data regarding the rate of seroprotection in patients with multiple myeloma that are not vaccinated compared with healthy controls.[55,56] Therefore, routine vaccination cannot be recommended. In the only available study,[45]

	Inactivated influenza vaccine	Pneumococcal vaccines	Other inactivated vaccines	Comments
Multiple myeloma	Yearly vaccination (one dose) is strongly recommended (A II u) as long as the patient is considered immunocompromised	One dose of PCV13 followed by one 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 3–6 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 (one dose) is strongly recommended (A II u) as long as the patient is considered immunocompromised, except in patients receiving intensive chemotherapy or who are receiving or have received anti-CD20 antibodies in the previous 6 months	One dose of PCV13 followed by one dose of PPSV23, at least 8 weeks later, is recommended (B II t), preferably before treatment or during maintenance, except in patients who are receiving high-dose chemotherapy or who are receiving or have received anti-CD20 antibodies in the previous 6 months	Human papillomavirus vaccine is recommended in healthy adolescents and young adults according to country recommendations for age after the end of treatment (B II t). Other inactive vaccines should be considered 3–6 months after the end of treatment, according to age, comorbidities, and country recommendations	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 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 one 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 might significantly impair the vaccination response

All the recommendations are based on laboratory endpoint—serological response, mainly seroconversion rate. ECIL 7=2017 European Conference on Infections in Leukaemia. LAVs=live-attenuated vaccines. PCV13=pneumococcal conjugate 13-valent vaccine. PPSV23=pneumococcal polysaccharide 23-valent vaccine. For the evidence-based medicine grading system (A II u, B II u, B II t, D III) see appendix.

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

the vaccine response in the patients was similar with that in healthy individuals.

Herpes zoster vaccine

Patients with multiple myeloma are four to 14 times more likely to get herpes zoster than the general population,[40,57] especially during bortezomid treatment.[58] Valacyclovir prophylaxis is safe, effective, and recommended in patients with myeloma. Zoster LAV is contraindicated and no data are available in multiple myeloma. Only nine patients with multiple myeloma who did not have transplantations were included in a phase 1 study with the heat-inactivated vaccine and their specific response is unknown.[59] Given the high efficacy of an approved inactivated subunit zoster vaccine,[60] data in these patients are much awaited.

Lymphoma

The ECIL group recommends patients with lymphoma receive a yearly single dose of IIV and pneumococcal vaccination, preferably before treatment or during maintenance. Other inactivated vaccines, including human papillomavirus (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 (table 3).

Patients with lymphoma have impaired T cell or B cell immunity, and B cell immunity is further affected by the use of anti-B cell antibodies. Lymphoma represents a wide, heterogeneous group of diseases. On one hand, aggressive lymphomas require prompt, intensive chemotherapy, making vaccination futile at that time. However, once these patients obtain remission, they are usually no longer at a 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, with a median of 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 about patients receiving intensive regimens.[65,71] IIV vaccine is recommended yearly as long as the patient is considered immunocompromised, the only exception is when they receive high-intensity treatment because the response to the vaccine is unlikely.

Pneumococcal vaccines

Lymphoma patients have a five to ten fold increased risk of invasive pneumococcal disease than the general population.[4,48] Most vaccine data came from splenectomised patients with Hodgkin's lymphoma, in whom good response to PPSV23 (36–64%) was reported before chemotherapy;[72–74] this finding is similar to other splenectomised patients.[75] In good responders, protection waned after 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 patients with lymphoma. However, based on data from other immunocompromised populations, the absence of safety concerns, and the potential benefit, pneumococcal vaccination is recommended for patients (table 3), except for those receiving intensive chemotherapy or anti-B monoclonal antibodies as they are unlikely to respond to the vaccination.

Human papillomavirus vaccine

Patients with lymphoma are at increased risk of HPV-associated cancer, especially after pelvic irradiation.[76] Although no specific data exist on HPV vaccination in patients with lymphoma, there were no safety issues in other patients who were immunocompromised.[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 patients with CLL receive a yearly single dose of IIV, and pneumococcal vaccination, preferably before treatment or during maintenance, and other inactivated vaccines should be administered 3–6 months after the end of treatment (6 months after the last dose of rituximab, table 3).

The high rate and severity of pneumococcal and Hib infections in patients with 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% of patients, and caused death in 38%.[78] This B-cell deficient population had suboptimal vaccine responses due to impaired antibody production, antigen presentation, and increased plasma levels of histamine. The increased plasma levels of histamine inspired studies on ranitidine to improve vaccination response.

Inactivated influenza vaccine

Despite the increased risk of influenza in patients with CLL, vaccine studies are few and the past studies do not represent current practice.[38,44,62,65] The response to IIV was usually low (5–30%),[44,79] except in treatment-naive patients (68–92%).[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 vaccines

Patients with CLL have an increased, almost 30-fold, risk of invasive pneumococcal disease compared with the general population.[47] Overall, the response to PPSV23

	ECIL 7 recommendation	Timing and dose	Comments
During induction and re-induction phases			
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 three to five doses can be used	Co-administration of HBV-specific immunoglobulins might improve protection (C II u)
LAVs	Contraindicated (D II u)	..	..
During maintenance therapy			
IIV	A yearly vaccination with an IIV is recommended (A II u)	One dose, except for children aged 9 years or younger who should receive two doses (A II t)	..
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 1 week before and 1 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 3–6 months after the end of chemotherapy is a better option. Alternative measures (acyclovir, isolation, and 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 younger who should receive two doses	..
Patients fully vaccinated before acute leukaemia diagnosis			
DTaP, inactivated poliovirus vaccine and Hib vaccine	Patients should receive one dose of DTaP, inactivated polio, and Hib vaccine, irrespective of antibody titres (A II u)	Booster dose	In high-risk patients, suboptimal response to one dose might occur
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 serotype C or ACWY	Patients should receive one dose of meningococcal C monovalent or tetravalent vaccine (B III)	Booster dose	..
Meningococcal B	Patients should receive one dose of meningococcal B vaccine (C III)	Booster dose	..
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 antibody 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 second dose 4–6 weeks later if the patient is still seronegative 4 weeks after the first dose)
Measles, mumps, and rubella LAV	Patients should receive one dose of the vaccine if they have been previously vaccinated, irrespective of antibody titres (A II u)	One dose	Same comment as for varicella LAV
Patients not vaccinated before chemotherapy			
..	Patients never vaccinated should be vaccinated with full courses according to country recommendations (A II u). Patients whose vaccination programme was withdrawn for chemotherapy should resume the programme starting from the suspended dose without repeating the previous dose(s)	..	..

All the recommendations are based on laboratory endpoint—serological response, mainly seroconversion rate. ECIL 7=2017 European Conference on Infections in Leukaemia. HBV=hepatitis B virus. IIV=inactivated influenza vaccine. PCV=pneumococcal conjugate vaccines. LAVs=live-attenuated vaccines. HPV=human papilloma virus. DTaP=diphtheria, tetanus, acellular pertussis. Hib=*Haemophilus influenzae* serotype b. For the evidence-based medicine grading system (A II u, A II t, BIII, B II u, B II t, C III, C II u, D II u) see appendix.

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

was poor (0–21%), and better in early-stage disease,[82–85] and not improved by ranitidine or granulocyte-macrophage colony stimulating factor.[85,86] The response to one dose of PCV was 20%, which was generally better, and 58% in treatment-naive patients or early-stage disease,[87,88] but its duration was unknown. Therefore, 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 patients with 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[86,91] suggested a benefit of ranitidine co-administration.

Although the extent of Hib burden in the era of universal Hib vaccination is unknown, the efficacy of the vaccine can be expected to be effective.

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 chronic lymphoproliferative diseases

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 doses[71] or ASO3-adjuvanted vaccine.[38,67,70,71] When patients were vaccinated at 6–10 months[38,67] or even within a median of 29 months[66] 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 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, suboptimal at least 6 months thereafter for IIV, and assumed to be decreased with PCV based on data in rheumatoid arthritis patients,[97] other protective measures should be provided during rituximab treatment and in the following year, and vaccinations should be postponed. Blood lymphocyte counts and immunoglobulin levels could help in assessing the immune recovery. The impact of rituximab might sometimes last for more than 12 months and measuring vaccine response seems particularly helpful in these patients.

In conclusion, in patients with chronic lympho-proliferative disorders 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 (ie, during maintenance or plateau) or 3–6 months after the end of treatment, the vaccine history should be reviewed to plan an individual vaccine programme according to age, comorbidities, and country recommendations. Antibody titres can help during this phase to design 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, a yearly IIV and PCV vaccination; varicella LAV in seronegative children preferably at 3–6 months after the end of chemotherapy rather than during maintenance; and 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] The aim of vaccination in these patients is to protect them from infections just like healthy children would be. At the diagnosis of ALL, prompt chemotherapy usually postpones any vaccination.

During the intense chemotherapy phases, prevention policies in most institutions include contact isolation, immunoglobulins, antimicrobials, 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 before or during leukaemia therapy is HBV vaccination of seronegative children in areas of high-HBV endemicity,[107] which is feasible with the rapid schedule used for newborn babies to HBV-positive mothers (20 µg recombinant HBV vaccine at 0, 14, and 28 days). This results in a seroconversion rate of 23·8%[23] and up to 30–35% after one or two additional doses,[105] 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, pre-school, 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 two doses of

PCV7[27] 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 one and two 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 patients with ALL with short withdrawal of chemotherapy,[125,126] the major criticisms of this policy are the potential need to postpone therapy for 3 weeks and the risk of vaccine-induced complications of up to 50%. Considering the low mortality of varicella-zoster virus during maintenance and the availability of effective antivirals,[127] vaccinating seronegative patients 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 and 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, and 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 limited data, we recommend that patients who were not vaccinated at all before chemotherapy benefit from a full immunisation programme according to country recommendations, and those partly 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 patients with haematological malignancies who did not have a transplantation

There are no safety concerns with inactivated vaccines. There might be mild adverse events, mostly local reactions at the site of injection, which are similar with 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 patient with ALL who erroneously received the measles-mumps-rubella vaccine during maintenance and developed a persistent rubella infection.[99] Other LAVs should also be avoided during therapy and 6 months from the end of chemotherapy because of the potential risk and scarcity of safety data.

Recommendations for vaccination of health-care workers in a 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. Caregivers who are seronegative for measles or varicella-zoster virus should be vaccinated. In case of a rash post varicella-zoster virus vaccine, they should avoid contact with patients until resolution.

Future directions and areas of research

Studies on vaccine response are warranted in different diseases and under different therapies that might have negative effect on vaccine response. For example, patients with MPNs have an increasing life expectancy but they often receive ruxolitinib, which has potential immuno-suppressive effects. Similarly, the vaccine response of patients with acute leukaemia and MDS receiving new therapies (eg, blinatumomab, anti-CD19/20/22 CAR T cells, midostaurin, and venetoclax) should be assessed. In most non-aggressive lymphoproliferative disorders, the main issue is to determine the optimal timing of vaccination especially before 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 adult and child patients with haematological disorders. In paediatrics, the main issue is whether children who did not fully complete primary vaccinations would benefit from a full revaccination programme or only boosters.

The implementation of these guidelines should be on the basis of 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, optimal implementation should always take into consideration country recommendations, age (eg, for HPV or meningococcus), and the availability of co-formulated vaccines.

Conclusion

Patients with CML usually have good responses to influenza and pneumococcal vaccines. In patients with other MPNs, considering safety and the expected benefit of inactivated vaccines, influenza, and *S pneumoniae* vaccination should be provided. Patients with chronic lymphoproliferative diseases have a low response to most vaccines, but because of the high risk of infection, they can potentially benefit most from vaccine protection. Once the treatment is over, patients with haematological disorders should benefit from the vaccine programme proposed for the healthy population in their 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.

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 was 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 was a scientific adviser for Merck. All other authors declare no competing interest.

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