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Review

Prevention and management of infectious complications in patients with chronic lymphocytic leukemia (CLL) treated with BTK and BCL-2 inhibitors, focus on current guidelines

Malgorzata Mikulska [a,b,*], Chiara Oltolini [c], Emanuela Zappulo [d], Michele Bartoletti [e,f], Anna Maria Frustaci [g], Andrea Visentin [h], Candida Vitale [i,j], Francesca R. Mauro [k]

[a] Infectious Diseases Unit, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy
[b] IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[c] ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
[d] Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy
[e] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele Milan, Italy
[f] Infectious Disease Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano, 20089 Milan, Italy
[g] ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[h] Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua, Italy
[i] Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino, Italy
[j] Department of Molecular Biotechnology and Health Sciences, University of Turin, Italy
[k] Hematology, Department of Translational and Precision Medicine, Sapienza University, Rome, Italy

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ABSTRACT

CLL is associated with an increased risk of infectious complications. Treatment with BTK or BCL-2 inhibitors does not seem to increase significantly the risk of opportunistic infections, but the role of combination therapies including BTK and/or BCL-2 inhibitors remains to be established. Various infectious complications can be successfully prevented with appropriate risk management strategies. In this paper we reviewed the international guidelines on prevention and management of infectious complications in patients with CLL treated with BTK or BCL-2 inhibitors. Universal pharmacological anti-herpes, antibacterial or antifungal prophylaxis is not warranted. Reactivation of HBV should be prevented in HBsAg-positive subjects. For HBsAg-negative/HBcAb-positive patients recommendations differ, but in case of combination treatment should follow those for other, particularly anti-CD20, agent. Immunization should be provided preferably before the onset of treatment. Immunoglobulin therapy has favourable impact on morbidity but not mortality in patients with hypogammaglobulinemia and severe or recurrent infections. Lack of high-quality data and heterogeneity of patients or protocols included in the studies might explain differences among the main guidelines. Better data collection is warranted.

1. Introduction

Knowledge on the frequency and optimal prevention strategies of infectious complications in patients with hematological malignancies, including those with chronic lymphocytic leukemia (CLL) and treated with novel targeted agents, is extremely important. Prophylactic strategies are chosen, evaluated, and recommended based on the incidence of specific infections complications (e.g., viral reactivations, main bacterial infections, or fungal diseases), their severity as assessed through hospitalization and mortality rates, and availability, feasibility, and applicability of prevention strategies. Main difficulties in assessing the impact of infectious complications in case of treatment with targeted agents arise from the heterogeneity of the populations in which the risk is evaluated, with higher rates of infections in those with advanced disease compared with first-line treatment, and differences related to the presence of prior or concomitant therapies, patient comorbidities, vaccination status, and management strategies used [1]. Moreover, differences in reporting, e.g., incidence vs. rate per 1000 treatment

* Corresponding author at: Infectious Diseases Unit, IRCCS Ospedale Policlinico San Martino, L.go R. Benzi, 10, 16132 Genoa, Italy.
E-mail address: m.mikulska@unige.it (M. Mikulska).

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patient-days, make comparison between studies of limited utility in defining optimal prophylactic strategies, particularly in prolonged treatment courses.

Most of the data on infectious complications in patients with CLL treated with BTK inhibitors derives from studies on the first introduced agent - ibrutinib, which also has the longest follow up available. With more limited data available for newer agents (e.g. zanubrutinib, acalabrutinb), there are no clear signals of an increased infection risk. On the contrary, the impact on infectious complications might be increased if any of these targeted agents is used in combination rather than in monotherapy, but real-life data is still scarce.

While there is consensus on recommended prevention measures for some infections, for others international guidelines might differ significantly, depending on the data available at the time of writing and on cost-effectiveness evaluation.

In order to provide a comprehensive overview for physicians caring for patients with CLL treated with BTK and BCL-2 inhibitors, we reviewed the main studies and guidelines available, highlighting and commenting on discrepancies among them.

2. Methods

We considered for revision and recommendations' retrieval the guidelines on infections in patients with hematological malignancies, or specifically with CLL if available, from major international scientific societies, published during the last ten years, seeking balance between those of infectious diseases and hematology origin, together with hepatology societies for HBV infection. We additionally performed MEDLINE search looking for "guidelines/recommendations" and "CLL" and "infection" and we screen all papers' references to identified additional documents. Even though we did not review each national guideline, we included those that were recent, applicable to many of the issues reviewed and of clinical use (e.g. guidelines from countries with high prevalence of HBV).

2.1. Prevention and management of infectious complications

2.1.1. Viral

2.1.1.1. Herpes simplex and varicella zoster virus (HSV/VZV). International guidelines (Table 1) do not recommend the universal use of antiviral prophylaxis against Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) in all patients with CLL, but it should be considered in selected subjects with a history of recurrent HSV/VZV reactivations or additional risk factors, such as concomitant treatment with high-dose steroids or rituximab [2–8].

Observational studies on patients with chronic lymphoproliferative disorders treated with targeted agents, mainly ibrutinib, reported an incidence of serious viral infections of 2.5% in patients with CLL, and despite antiviral prophylaxis was not provided, only a minority of viral infections was due to HSV/VZV ($n = 2$, both disseminated VZV), and zoster reactivation occurred mainly in relapsed/refractory patients [9,10]. Conversely, in another study, acyclovir or valacyclovir prophylaxis was administered in 54% of patients and viral infections represented 19% of total episodes of serious infections; again, HSV/VZV infections accounted for a minority of episodes (three cases of HSV reactivation, for which the severity was not specified, nor whether they were breakthrough infections that occurred during prophylaxis) [11]. Notably, prior treatment with rituximab and fludarabine emerged as risk factor for viral infections [11].

Clinicians should be aware of the clinical spectrum of HSV and VZV reactivations in patients with CLL, especially disseminated VZV infection in heavily pre-treated patients [12], while also considering the possibility of VZV reactivation in untreated subjects [13], and the potential severity of primary HSV or VZV infection in immunocompromised hosts leading to hemophagocytic lymphohistiocytosis syndrome [14]. The adjuvanted recombinant zoster vaccine (RZV), approved also for immunocompromised patients, is recommended as a preventive strategy to reduce the incidence and severity of VZV reactivations and to potentially reduce the need for prophylaxis (please refer to paragraph "3. Vaccination strategies" for further details).

2.1.1.2. Cytomegalovirus. Cytomegalovirus (CMV) is a widely prevalent herpes virus which establishes a chronic infection state. T-cell exhaustion is a state of acquired T-cell dysfunction that arises not only during chronic viral infections, but also occurs in the presence of cancer. In CLL, CD8+ T cells exhibit features of exhaustion and impaired functionality, but reactivations of latent viruses such as CMV are uncommon in untreated patients. A study in patients with CLL demonstrated that despite defects in functionality in CD8+ T cells, the functionality of CMV-specific CD8+ T cells *in vitro* was intact in terms of cytokine production, cytotoxic capacity, and ability to form an adequate immune synapse, compared to age matched healthy controls [15]. Moreover, there was a concern that CMV infection was associated with reduced survival in the elderly and had a negative impact on clinical outcomes in patients with CLL. However, in a prospective cohort of 347 patients with CLL, it was shown by multivariate modelling that CMV seropositivity did not influence overall survival, unlike age and the presence of un-mutated immunoglobulin heavy chain [16].

Considering the risk of opportunistic infections in patients with CLL receiving BTK-inhibitors, CMV reactivation and/or end-organ disease has been reported only anecdotally [17], and among viral infections, only few were due to CMV (4/28) [11]. A recent prospective study analyzed the rate and kinetics of CMV reactivations and CMV-specific T-cell immunity in 23 CMV-seropositive patients with CLL treated with ibrutinib monotherapy ($n = 14$ first-line therapy, $n = 9$ relapsed/refractory CLL) [18]. Overall, 7/23 patients (30%) developed CMV reactivation within 15–45 days after starting ibrutinib, but in most cases plasma CMV-DNA detection was a blip, with only two patients having repeatedly positive results. Notably, all reactivations cleared spontaneously, and no patient developed end-organ disease. At baseline, over 80% of patients had detectable CMV-specific T-cell immunity; during the first 6 months after starting ibrutinib, despite the decreased frequency of detectable CMV-specific T-cell responses, patients were still able to expand functional CMV-specific T cells upon antigenic stimulus, which likely accounted for the short duration of CMV reactivations [18].

In conclusion, clinically significant CMV reactivation is a rare condition in patients with CLL receiving BCL-2 or BTK-inhibitors and preemptive strategy is not recommended (Table 1) [2–6,19]. Therefore, a symptom-based approach to CMV testing, repeated testing to confirm whether CMV-DNA load is increasing, and appropriate diagnosis in case of suspected organ disease are warranted. However, based on the increased risk of CMV reactivation when combining bendamustine and rituximab compared with monotherapy, the impact of combination therapies with targeted agents and anti-CD20 antibodies on the risk of CMV reactivation will need to be carefully evaluated.

2.1.1.3. Hepatitis B virus. Almost all among 10 reviewed guidelines recognized the risk of Hepatitis B virus (HBV) reactivation in case of treatment with BTK and BCL-2 inhibitors in patients with positive HBsAg and absent or low HBV-DNA replication (< 2000 UI/ml), as detailed in Table 2 [6,7,20–28]. The risk of reactivation was considered lower for BCL-2-I than for BTK—I. If reactivation risk stratification was provided, this was estimated as <10% in two guidelines [21,28] and > 10% in one guideline for BTK-I [26], and < 1% in two guidelines for BCL-2-I [27,28]. All guidelines but one recommended pharmacological prophylaxis, while in one, ALT monitoring was considered a possible alternative only for patients without significant fibrosis, if a new agent is considered as carrying low risk of reactivation, although the authors stated that more evidence was required for ibrutinib [26]. High-barrier

Table 1
Overview of main recommendations on prophylaxis in patients with CLL treated with BTK-I or *BCL*-2-I.

Pathogens and intervention	Agent	ESCMID 2018 [2,8,31]	ECIL 2019 [3,19,32]	ESMO 2021 [4]	AGIHO/DGHO 2018, 2021, 2022 [5,30,33,34]	NCCN, V. 1.2023, V. 1.2024 [6,7]
HSV/VZV prophylaxis	BTK-I	Not recommended [2]	Not recommended [3]	Not recommended Consider secondary prophylaxis in patients with recurrent HSV/VZV reactivations [4]	Consider in patients with additional risk factors (CIIu) [5]: -Age > 60 years -High-dose steroids (planned to receive cumulative prednisone equivalent dose >2500 mg/m2 body surface area)	Consider in patients with additional risk factors and increased risk of opportunistic infections [6,7] Acyclovir 400–800 mg bid, Valacyclovir 500 mg bid
	BCL-2-I	Not recommended [2] If co-administration of anti-CD20 mAbs, consider prophylaxis depending on the underlying disease and concomitant therapy [8]	Not recommended [3]		-Advanced line of therapy -Type of therapy (maintenance with anti-CD20 mAbs, bendamustine) -History of febrile neutropenia or VZV/HSV reactivation. of benefit particularly in advanced lines of therapy. To prevent oral HSV disease: acyclovir 400 mg bid (AIIr), valacyclovir 250 mg bid or 500 mg bid (BI) To prevent recurrent genital HSV: acyclovir 400 mg bid (AI), valacyclovir 500 mg bid (BIIt) or famciclovir 500 mg bid (BIIt) To prevent HZ: acyclovir 400 mg qd, 400 mg bid or 400 mg tid (AII), valacyclovir (data more limited)	Not recommended [6] Consider if co-administration of anti-CD20 mAbs
CMV monitoring	BTK-I	Not recommended [2]	Not recommended [3] (DIII) [19]	Not recommended [4]	Not reported as recommended [5]	Not recommended [6]
	BCL-2-I	Not recommended [2] If co-administration of anti-CD20 mAbs, consider screening with a symptom-based approach [8]				
Antibacterial prophylaxis	BTK-I	Universal prophylaxis not recommended [2]	Not recommended [3]	Not recommended Consider in patients with recurrent infections [4]	No [30]	Not recommended [6]
	BCL-2-I	Not recommended [2] Not reported as recommended [8]	Universal prophylaxis not recommended [3]			Not recommended [6] Consider fluoroquinolone prophylaxis during neutropenia [7]
Antifungal prophylaxis, *Candida,* and *Aspergillus*	BTK-I	Universal prophylaxis not recommended [2] Not recommended (DIII) [31]	Universal prophylaxis not recommended Consider on case-by-case basis if [32]: -Prolonged neutropenia (>6 months) -Older age -Advanced or unresponsive disease	Universal prophylaxis not recommended [4]	No. Consider on case-by-case basis in patients with additional risk factors (recent treatment, neutropenia) [33]	Not recommended [6]
	BCL-2-I	Not recommended [2,8] Not recommended (DIII) [31]	Universal prophylaxis not recommended [3,32] Consider on case-by-case basis if [32]: -Prolonged neutropenia (>6 months) -Older age -Advanced or unresponsive disease Consider posaconazole prophylaxis during the first 3 months of therapy if grade 3–4 neutropenia [3]		No. If co-administration of anti-CD20 mAbs, consider on case-by-case basis in patients with additional risk factors [33] No drug reported	Not recommended [6] Consider prophylaxis during neutropenia [7] No drug reported

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Table 1 (*continued*)

Pathogens and intervention	Agent	ESCMID 2018 [2,8,31]	ECIL 2019 [3,19,32]	ESMO 2021 [4]	AGIHO/DGHO 2018, 2021, 2022 [5,30,33,34]	NCCN, V. 1.2023, V. 1.2024 [6,7]
Antifungal prophylaxis, PCP	BTK-I	Consider prophylaxis in patients with relapsed or refractory CLL and additional risk factors for PCP (i.e., alemtuzumab, purine analogue-based chemotherapy or prolonged high-dose corticosteroids) [2]	Not routinely recommended; its risk-benefit should be outweighed in the context of diminished T-cell immunity due to previous (e.g., fludarabine-cyclophosphamide-rituximab therapy) or concomitant therapy [3]	No data (not considered at risk) [4]	Not considered at significant risk [34]	Not recommended in monotherapy. Consider prophylaxis in patients at high risk for opportunistic infections (i.e., purine analogue-based chemotherapy or prolonged high-dose corticosteroids) [6]
	BCL-2-I	Not recommended, no benefit expected; continuous clinical surveillance is advisable [2]	No data (not considered at risk)		Not considered at significant risk	Not recommended [6]

Abbreviations: AGIHO/DGHO, Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO); BCL-2-I, B-cell lymphoma 2 inhibitor; bid, bis in die (twice a day); BTK—I, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; ECIL, European Conference on Infections in Leukemia; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESMO, European Society for. Medical Oncology; HSV, Herpes Simplex virus; mAbs, monoclonal antibodies; NCCN, National Comprehensive Cancer Network®; PCP, Pneumocystis jirovecii pneumonia; qd, quaque die (once a day); tid, ter in die (three times a day); VZV, Varicella Zoster virus.

drugs were recommended in 8 guidelines, while one considered lamivudine acceptable in case of HBV-DNA < 2000 UI/ml or short-term cancer treatment (4–6 months) [19]. Prophylaxis should be started at the onset of treatment and continued for at least 6–12 months after its termination. ALT and HBV-DNA monitoring should be performed during prophylaxis, and at least 12 months after discontinuation of antiviral therapy [22].

In patients with resolved HBV infection (i.e., HBsAg-negative, HBcAb-positive, HBV-DNA-negative, and HBsAb positive or negative), five guidelines considered the risk of reactivation to be <10% or uncertain, suggesting no need for pharmacological prophylaxis but recommended regular monitoring of ALT and HBsAg (and HBV-DNA in some), every 1–3 months or every 3 months [20,22,24,25,28]. Two guidelines recommend antiviral prophylaxis [6,23], and an additional one only in case of BKT-I (considered as risk >10%) but not BCL-2-I [27], while one recommended prophylaxis only in case of advanced liver fibrosis or cirrhosis [26]. Notably, when BTK-I and BCL-2 I are used in combination with other immunosuppressive drugs, the additional risk due to the companion molecule should be carefully considered. In particular, in case of concomitant anti-CD20 treatment, prophylactic antiviral therapy is recommended for HBsAg-positive patients and is also preferred for HBsAg-negative/HBcAb-positive ones [6,21,25,28]. In such cases, prophylaxis, preferably with high-barrier agents, should be provided from the onset of treatment until hematological cure is obtained [21], and at least 12 months after the last anti-CD20 administration [6,21,25,28]. Alternatively, pre-emptive administration of antivirals upon detection of increasing viral load (HBV-DNA) could represent an option for HBsAg-negative/HBcAb-positive patients with concurrent high levels of HBsAb, although this is a less preferred strategy and it requires high level of compliance with repeated and prolonged monitoring [6,7]. AST levels and HBV-DNA should be monitored every 1–6 months during treatment, then every 3–6 months after completion of treatment, as many reactivations occur later post-chemotherapy [6,25].

2.1.1.4. Respiratory viruses othet than SARS-CoV-2. Community-acquired respiratory virus (CARV) infections were among the most frequent infections reported in trials with BTK and BCL-2 inhibitors. CLL-related or treatment-related hypogammaglobulinemia or lymphopenia might contribute to an increased susceptibility to CARVs, although severe pneumonia is rare [29]. Early and prompt treatment of influenza infection should be provided, while there are no robust data to recommend antiviral treatment outside of hematopoietic stem cell transplantation for other viruses, such as respiratory syncytial virus (RSV) or parainfluenza virus (PIV). The response to influenza vaccination may be significantly lower in case of treatment with BTK-I (see the dedicated paragraph), and no data are available on RSV vaccination in this population.

Being other CARVs, such as Rhinoviruses, Coronaviruses, PIV, even more frequent than influenza or RSV, individual preventive measures (e.g., handwashing, masking) should be actively encouraged. Furthermore, in healthcare facilities, infection control measures should be provided to prevent outbreaks, and the option of post-exposure prophylaxis of influenza with oseltamivir may be considered.

2.1.2. Invasive fungal infections

2.1.2.1. Yeast and molds. International guidelines do not recommend universal use of primary antifungal prophylaxis in patients with CLL, as the incidence of invasive fungal infections (IFIs) is quite low [2–8,19,30–34]. Indeed, according to data mainly deriving from observational studies in the era before the use of targeted agents, the overall incidence of IFIs was <2%, but increased up to 10% in heavily pre-treated patients, such as after ≥4 lines of chemo-immunotherapy [35,36].

However, the advent of BTK inhibitors initially had a major impact on the IFIs risk perception, with concerns about higher incidence based on data from early studies in patients with primary cerebral lymphoma treated with ibrutinib and high-dose steroids (in three studies: 5%, 11%, and 27% in case of ibrutinib monotherapy and 39% in all patients) [37–39]. Indeed, an unexpectedly high rate of any IFIs, and particularly high rate of cerebral involvement (22%) were reported in these studies, and also confirmed in other cohorts of ibrutinib-treated advanced patients with CLL with invasive aspergillosis (10–41%) [40–42].

Subsequent observational retrospective studies and surveys in patients with CLL diagnosed with IFIs after the widespread use of ibrutinib for relapsed/refractory CLL, reported a slight increase in the occurrence of proven-probable IFIs (2.4–12%, with 12% found in a small study of 33 patients with relapsed or refractory CLL). *Aspergillus* and yeasts infections mostly occurred during the first 6 months of ibrutinib therapy [40,41,43], while non-*Aspergillus* mold infections were reported as late-onset (>6 months after starting ibrutinib) [44]. The infection-related mortality in IFI cases was confirmed as 10–43% [10,40,41,43,44]. Thus far, the main suggestion has been to consider an individualized antifungal prophylaxis in BTK-I treated patients only in the presence of other risk factors, such as previous IFI, salvage treatment following

Table 2
Selected guidance recommendations for Hepatitis B screening and management in patients undergoing immunosuppressive treatments.

Society, year	AGIHO, 2015 [20]	ECIL, 2015 [21]	EASL, 2017 [22]	IwCLL, 2018 [23]	AASLD, 2018 [24]	ASCO, 2020[1] [25]	APASL, 2021 [26]	AUSTRALIAN, 2022[2,3] [27]	KOREAN, 2022[2,3] [28]	NCCN, V. 1.2023, V. 1.2024 [1] [6,7]
HBsAg+/HBV-DNA-negative or positive										
Prophylaxis	Yes	Yes	Yes	Yes	Yes	Yes	Yes, in all cases of presence of liver fibrosis (≥F2) (if considered as low risk group). ALT monitoring every 3 months in others.	Yes	Yes	Yes
Drug preferred	LAM is appropriate in short-term cancer treatment (4–6 months) or in patients with HBV-DNA <2000 IU/ml. ETV or TDF/TAF if IST >12 months or HBV-DNA >2000 IU/ml.	ETV or TDF/TAF	ETV or TDF/TAF	ND	ETV or TDF/TAF	ETV or TDF/ TAF	ETV or TDF/TAF	ETV or TDF	ETV or TDF/ TAF (alternative: besifovir)	ETV
Start	At treatment onset	At treatment onset	ND	At treatment onset	Before or at treatment onset	Before or at treatment onset	Before or at treatment onset	ND	Before or at treatment onset	At treatment onset
Stop[4]	6–12 months after the end of IST	Until hematological cure and 12 months after the end of IST	Patients with chronic infection but no hepatitis: at least 12 months after cessation of IST and discontinued only if the underlying disease is under remission	End of IST	At least 6 months after the end of IST	At least 12 months after the end of IST	At least 6 months after the end of IST for HBsAg positive patients without advanced liver fibrosis or cirrhosis and with low level of HBV DNA (<2000 IU/ ml) before initiation of NUCs	ND	At least 6 months after the end of IST	At least 12 months after the end of IST and in consult with hepatologist
Comments			Liver function tests and HBV DNA should be tested every 3 to 6 months during prophylaxis and for at least 12 months after NUC withdrawal	No difference based on HBsAg presence; only high HBV-DNA levels determine duration of antiviral treatment			The risk group for patients treated with ibrutinib is still uncertain, no routine prophylaxis recommendation until further evidence			
HBsAg-negative and HBcAb-positive (resolved infection)										
Prophylaxis	No	Uncertain. Recommended in patients treated with biological agents and risk of reactivation ≥10%	No	Yes, as for HBsAg+, during IST	No	No	Yes, with ETV or TDF/ TAF, in patients with advanced liver fibrosis or cirrhosis, for 6 months after the end of IST. No prophylaxis in those without advanced fibrosis or cirrhosis	BTK-I: Yes BCL-2 I: No	No	Yes, preferred. Maintain prophylaxis up to 12 months after the end of IST. ETV is preferred. If high HBsAb levels – monitor with HBVDNA
Monitoring (for starting pre-	ALT and HBsAg every 1–3 months	Not reported	Pre-emptive approach based upon monitoring HBsAg	ND	Careful monitoring with ALT, HBV DNA,	Careful monitoring with ALT, and	If no prophylaxis, serum ALT should be	ND	Serum HBsAg and HBV DNA should be	HBV-DNA if no prophylaxis

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Table 2 (*continued*)

Society, year	AGIHO, 2015 [20]	ECIL, 2015 [21]	EASL, 2017 [22]	IwCLL, 2018 [23]	AASLD, 2018 [24]	ASCO, 2020[1] [25]	APASL, 2021 [26]	AUSTRALIAN, 2022[2,3] [27]	KOREAN, 2022[2,3] [28]	NCCN, V. 1.2023, V. 1.2024[1] [6,7]
emptive treatment)			and/or HBV DNA every 1–3 months during and after IST is recommended		and HBsAg every 3 months, for up to 12 months after cessation of IST	HBsAg every 3 months, during treatment	monitored every 3 months.		monitored during IST	

Abbreviations: ETV, entecavir; IST, immunosuppressive treatment; IwCLL, International Workshop on Chronic Lymphocytic Leukemia; LAM, lamivudine; ND, not discussed; NUC, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil.

[1] When used in combination with other immunosuppressive drugs, consider the additional risk due to the companion molecule.

[2] Guidelines which mention specifically BKTI.

[3] Guidelines which mention specifically BCL-2 inhibitors.

[4] Unless antiviral treatment is needed independently from IST.

fludarabine-based therapy or alemtuzumab (within 3 months), concomitant corticosteroids, recurrent/recent neutropenia, and for the first 6 months of BTK-I therapy, counting on a subsequent IFI risk reduction due to the beneficial impact of BTK-I on disease control [10,45,46]. Analyzing two recent retrospective studies which included over 200 ibrutinib-treated patients, mainly with CLL, and in whom antifungal prophylaxis other than anti-pneumocystis was provided only in <1.6% of patients, the incidence of proven or probable IFIs was low (1.3–2.8%) [9,11]. Details on the abovementioned and additional studies on the risk of IFI in BTK-I treated patients are reported in Supplementary Table S1 [9,11,35,36,40,41,43,44,47–50].

Overall, there are currently no data to suggest the need for routine use of mold-active anti-fungal prophylaxis in patients with CLL managed with ibrutinib (and likely other BTK-Is) in the absence of other risk factors, also considering the significant drug-drug interactions with azole agents through inhibition of the CYP3A4 metabolic pathway, leading to an increase in ibrutinib levels and potential toxicities. As BTK-Is are increasingly used in treatment-naïve patients, a diagnosis-driven strategy using clinical monitoring and early diagnostic workup (blood cultures, cryptococcal antigen, lung CT scan, serum and bronchoalveolar lavage (BAL) fluid galactomannan and fungal PCR), with careful evaluation of potential dissemination into the central nervous system (through brain magnetic resonance imaging, MRI, and lumbar puncture) should be appropriate to mitigate the risk of IFI.

2.1.2.2. Pneumocystis jirovecii. Despite an early single-center study reporting atypical cases of *Pneumocystis jirovecii* pneumonia (PJP) at a rate of 5% in ibrutinib-treated patients, subsequent studies in patients receiving monotherapy with ibrutinib reported an incidence of pneumocystosis <3% [51–53]. The clear benefit of pharmacological prophylaxis in non-HIV setting was documented in a meta-analysis for a population with the risk of PJP of 6% [54]. Therefore, for both BTK-I and BCL-2-I monotherapy, PJP prophylaxis is not routinely recommended, unless the patient has previously received or is concomitantly receiving agents associated with increased risk, such as corticosteroids (prolonged, high-dose), purine analogues, or idelalisib (see Table 1 for guidelines on prophylaxis).

Clinical surveillance and prompt appropriate diagnostic approach (through lung CT scan, PCR for pneumocystis-DNA in sputum or BAL fluid, and serum beta-D-glucan) and treatment are mandatory.

2.1.3. Bacterial

2.1.3.1. Antibiotic prophylaxis. Antibiotic prophylaxis is not routinely recommended for patietns with CLL treated with targeted therapies, and even in case of neutropenia, only the US NCCN guidelines recommend consideration of fluoroquinolones, while the European ESMO guidelines suggest prophylaxis only in case of recurrent infections (Table 1). Given prolonged treatment, possible toxicity and negative impact on induction or selection of resistant bacteria of fluoroquinolones are of concern. Moreover, drug-drug interactions between BTK-I and BCL-2-I and certain antibiotics should always be considered. For example, ciprofloxacin, which is a moderate inhibitor of CYP450 3A4, may significantly increase the plasma concentrations of ibrutinib or venetoclax. Indeed, their dosage should be adjusted according to the indication in the product labelling whenever it is used in combination with a moderate or strong CYP450 3A4 inhibitor.

Even though pneumonia is one of the most frequent severe infections in this population, early clinical suspicion, rapid appropriate diagnosis and therapy, rather than antibiotic prophylaxis, are warranted. The first line diagnostic approach to patients with CLL with suspected pneumonia includes chest X-ray (or CT scan, if rapidly available, since it is more sensitive and allows precise evaluation of type and extension of lung compromise), inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT), urinary antigens for *Legionella pneumophila* and

pneumococcus, two sets of blood cultures, nasopharyngeal swab for respiratory viruses, including SARS-CoV-2, sputum culture, if present, and serum galactomannan and beta-D-glucan if, respectively, aspergillosis and pneumocystosis, are suspected. The second line diagnostic approach includes CT scan, and, in the absence of documented etiology, lack of response or suspected coinfection, bronchoalveolar lavage (BAL) with microbiological assays performed directly in BAL fluid (e.g. with addition of molecular analysis of atypical bacterial or rapid molecular assays also for typical bacteria, CMV-DNA, and fungi such as *Aspergillus* or *Pneumocystis*).

Immunization against pneumococcus, influenza and SARS-CoV-2, together with immunoglobulin supplementation, if warranted, might contribute to lowering the risk of respiratory tract infections.

2.1.3.2. Tuberculosis: screening and prophylaxis. Screening and treatment of latent tuberculosis infection (LTBI) are not routinely recommended in all patients with CLL treated with BTK or BCL-2 inhibitors. However, they should be performed on a case-by-case basis in patients with known epidemiological risk factors, i.e. contacts of persons with pulmonary or laryngeal TB disease, persons born in endemic countries, persons with marginal housing or homeless, persons with prolonged (>1 month) or frequent (≥ twice/year) travel to TB endemic countries, employees or residents of congregate settings, such as hospitals, dialysis units, correctional facilities, homeless shelters, nursing homes or substance abuse treatment centers [55–60].

A detailed background history (including previous exposure to individuals with TB) and evaluation of risk factors are the first steps to identify patients in whom microbiological assessment of exposure is indicated [60–62]. Chest X-ray and an IGRA (Interferon-Gamma Release Assays) test, which is preferred over tuberculin skin test (TST), should be performed. Patients with properly treated previous TB do not require additional therapy [34].

Currently, short-term rifamycin-based treatment regimens of 3- or 4-months for latent TB infection are generally proposed over 6- or 9-month isoniazid monotherapy [56]. However, significant interactions are expected with both rifampin and, to a lesser extent, isoniazid and some targeted agents. Specifically, rifampin is a strong inducer of CYP3A and significantly reduces BTK-I or BCL-2 I levels, thus co-administration should be avoided [63,64]. On the other hand, isoniazid is an inhibitor of CYP450 3A4 and increases plasma concentrations of BTK-I and BCL-2 I. In patients receiving isoniazid, a dose reduction of venetoclax of at least 75% is advised. In these patients, the use of alternative drugs for the treatment of active or latent TB might be preferred [65]. Consultation with TB specialist and case by case evaluation is mandatory.

3. Management for hypogammaglobulinemia in CLL

Current guidelines and evidence-based expert opinions suggest that immunoglobulin replacement therapy (IgRT) should be considered in patients with CLL with hypogammaglobulinemia with IgG levels <400–500 mg/dL and severe or repeated infections (i.e., at least 3 events/year) [7,23,30,66–68]. Indeed, a meta-analysis of randomized trials in patients with CLL and multiple myeloma showed that the use of prophylactic IgRT was associated with a significant decrease in major and clinically documented infections, although no significant impact on overall survival was observed [69].

Treatment of CLL with BTK-I could represent an additional risk factor for secondary hypogammaglobulinemia in these patients. A multicenter retrospective study from Germany reported that the introduction of IgRT significantly reduced the risk of severe infectious complications in hematologic patients, including those receiving BTK-I for CLL (HR: 0.47; $p = 0.003$) [70]. In another study, a reduction in IgG levels was observed during ibrutinib treatment, leading to severe hypogammaglobulinemia during which all patients developed recurrent infections [71]. A ROC curve analysis (with AUC 0.87) identified IgG levels of 650 mg/dL at the start of ibrutinib treatment as the best predictive value for subsequent development of secondary hypogammaglobulinemia, suggesting that the cut off for IgRT could be increased to 650 mg/dl from the traditional 400–500 mg/dL [71].

Considering BCL-2-Is, unless combined with anti-CD20 antibodies, the risk of hypogammaglobulinemia during treatment is not expected to be increased. Consequently, currently available guidelines do not recommend tailored IgRT strategies in these patients, but careful evaluation of future combination treatments is required.

An increasingly used therapeutic option in patients with hypogammaglobulinemia is represented by subcutaneous immunoglobulin therapy (SCIg). Recently, in a cohort of 116 patients with CLL (25% receiving ibrutinib and 3.4% venetoclax), the administration of SCIg was associated with higher increase in IgG levels compared with intravenous Ig (IVIg), and a significant reduction in infectious episodes from 2.59 (pre-SCIg) to 1.43 events/patient/year, particularly when patients were able to reach at least 600 mg/dL of IgG. However, there was no reduction of infectious complications in the IVIg group in that study, making the results controversial [36]. In 10 patients with CLL (4 treated with a BTK—I, 1 with venetoclax) receiving SCIg, there was a significant increase in IgG median titers, no infectious events, and a subjective benefit in quality of life [72]. A recent expert consensus provided recommendations and discussion on secondary hypogammaglobulinemia in CLL and multiple myeloma patients, with particular attention to the benefits of SCIg [73].

In conclusion, monitoring of serum immunoglobulin levels and use of intravenous immunoglobulin replacement (0.2–0.4 g/kg body weight) every 3 to 4 weeks (or equivalent dose of SCIg, administered usually one or twice a week) is recommended in patients with CLL with hypogammaglobulinemia and recurrent or severe infections in order to reach a target trough of 600–800 mg/dL and improve clinical outcomes [7,66,74]. Future studies should evaluate the optimal timing, preferred route of administration, dosing, frequency of administration and duration of the IgRT.

4. Vaccination strategies

The efficacy of vaccines in patients with CLL can be significantly reduced due to the inherent complex immune dysfunction associated with the disease. The impact of the novel drugs on vaccine response rate is fascinating but far from being fully understood. With these limitations, in Table 3 we provide updated data regarding vaccination strategies in patients with CLL receiving BTK and BCL-2 inhibitors [2,4–7,75–77].

Live vaccines are contraindicated in all immunocompromised subjects, including those with leukemia and those treated with chemotherapeutic or immunosuppressive agents [6,7,75,77], until at least 3 months after treatment discontinuation, and 6 months in case of co-administration of anti-CD20 mAbs [75]. No specific data on BTK or BCL-2 inhibitors is available.

In case of all vaccines, better immune responses are expected if administered before starting chemotherapy. Preferably, vaccinations should be administered at timepoints other than <2 weeks prior to, during, or up to 3–6 months after chemotherapy due to low probability of response [6,77]. In patients treated concomitantly with anti-CD20 agents, the serological response to vaccines is very poor and postponing vaccinations 6–12 months from the last administration should be considered if aiming at long-term protection. However, there are no safety concerns in case of vaccines other than live attenuated (i.e. inactivated, recombinant, subunit, conjugate, mRNA, etc.), and cellular response could be elicited even in the absence of serological protection, thus vaccination against influenza, COVID-19 or pneumococcus during treatment might be offered. In such cases, additional protective measures should be still applied (hygiene, vaccination of household contracts, etc.). Finally, in patients treated with BTK—I, assessment of antibody titers and revaccination (if needed) can be considered, but additional studies are warranted.

Table 3
Overview of main recommendations on vaccination in patients with CLL treated with BTK-I or *BCL*-2-I.

Pathogen	ESCMID 2018 [2]	ECIL 2019 [75]	AGIHO/DGHO 2021 [5,76]	ESMO 2021 [4]	NHS 2021 [77]	NCCN, V. 1.2023, V. 1.2024* [6,7]
Influenza	Recommended	Inactivated vaccine recommended annually [75]	ND	Seasonal Flu vaccination is recommended in early stage CLL	Inactivated flu vaccine annually at the start of the flu vaccination season. A second dose a month later should be offered if possible.	Recommended annually
Pneumococcus	ND	Vaccination with PCV followed by PPSV23, preferably before treatment [75] Consider vaccinating patients before the initiation of BTK-I therapy	ND	Recommended in early stage CLL	At diagnosis: -Patients with no previous pneumococcal vaccination: single dose of PCV13 followed by a dose of PPSV23 at least two months later. -Patients with history of previous PPSV23 vaccination: single dose of PCV13 at least one year after last dose of PPSV23, followed by a dose of PPSV23 at least two months later. All patients: PPSV23 every five years	PCV20 or PCV15 at CLL diagnosis; if PCV15 used, it should be followed by PPSV23 at least 8 weeks later. For patients who have previously received PPSV23, the PCV20 or PCV15 dose should be given at least 1 year after the last PPSV23.
HZ	Not reported as recommended [90] If co-administration of anti-CD20 mAbs, LAIV should not be provided until at least 6 months after completion of therapy [8]	ND	RZV recommended, due to safety and immunogenicity, although data on clinical efficacy in certain malignancies are preliminary and long-term protection rates are limited; until more data available, it is suggested to continue acyclovir prophylaxis in high-risk patient groups	ND	RZV is recommended (adults ≥50 years, adults ≥18 years at increased risk for zoster disease), 2 doses, ≥2–6 months apart (a shorter schedule is allowed for high-risk adults, second dose 1–2 months after the first one). If previous vaccination with ZVL, RZV should be given at least 2 months after the last ZVL dose [77]	RZV recommended for all patients treated with BTK-I

Abbreviations: ND, not discussed; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent polysaccharide pneumococcal vaccine; RZV, recombinant zoster vaccine (Shingrix); ZVL, zoster live attenuated vaccine.

Indeed, due to the increased risk of infective complications from capsulated bacteria and Influenza, most guidelines recommend vaccination against pneumococcus and yearly against influenza(Table 3).

4.1. *Influenza*

Regarding influenza vaccination, response to the inactivated vaccine in patients with CLL has generally been reported to be low (5–30%) [77,78], except in treatment-naive subjects (68–92%) [79]. Some trials have shown better response when a second dose was administered. The NHS guidelines recommend administering a second dose whenever possible in patients with CLL [80–82]. Few, outdated, and conflicting information on the specific effect of ibrutinib on the immune response to influenza vaccination are available. Although a study in 19 ibrutinib-treated patients from the US showed seroprotective titers after vaccination with inactivated trivalent influenza vaccine in up to 74% of patients [83], another experience from Australia found a very poor response rate to influenza trivalent vaccination in 14 ibrutinib-treated patients of whom many received prior intensive treatment, although only 14% with anti-CD20 antibodies [84]. Due to the poor response rate, the NCCN guidelines encourage patients with CLL to be careful and to avoid potential CARV exposure during influenza season, even after vaccination [7].

4.2. *Pneumococcus*

When evaluating the response rate to pneumococcal vaccination, protective antibody titers are more likely to develop after administration of conjugated pneumococcal vaccine (PCV) compared to polysaccharidic one (PPSV23) [75,85]. With recent introduction of 15 and 20-valent PCV vaccines, the schedules might differ based on availability and local recommendations. For instance, CDC states that also for immunocompromised patients there is no need for PPSV23 if PCV20 is used [86]. On the other hand, recent NIH guidance suggests boosting anti-pneumococcal immunity in all patients with PPSV23 every five years, including those who had previously received PCV20 [77].

Recent data support vaccinating the patients before starting BTK-I/BCL-2-I treatment, since the serological response to PCV vaccine could be extremely low in patients receiving these agents [87–89].

4.3. *Herpes Zoster*

While live zoster vaccine was not recommended for immunocompromised patients, recombinant zoster vaccine (RZV) has proved to induce robust and persistent both humoral and T-cell-mediated immune responses in adults with various hematological malignancies who were receiving immunosuppressive treatments. However, the proportion of patients with CLL enrolled was limited ($n = 42$ in vaccinated cohort, $n = 41$ in placebo cohort) and they were excluded from the analysis of the primary confirmatory immunogenicity objectives, being, as expected, a disease group with the lowest proportion of humoral response rate (approximately 20% in the vaccinated cohort, both at one month and one year after the second dose) [90]. Further studies on RZV in patients with CLL were performed, trying to delineate the impact of targeted drugs on vaccine response. Initially, data on vaccine response in patients on BTK-I therapy seemed encouraging. In one study, the response rate to

RZV did not differ significantly between BTK-I-treated and treatment-naïve cohorts (41% vs. 59%); moreover, the type of BTK- inhibitor (ibrutinib vs. acalabrutinib) and its indication (frontline treatment vs. relapsed CLL) did not influence the response rate [91]. A prospective study also confirmed that patients with CLL or Waldenstrom macroglobulinemia ($n = 32$) responded to RVZ while on BTK-I therapy for ≥3 months, achieving a humoral immune response in 75% of cases, with a concomitant T-cell response in 87% [92]. However, subsequent studies raised concerns about the efficacy of RZV during BTK-I treatment. Indeed, a study involving 62 patients ($n = 37$ monoclonal B-cell lymphocytosis/untreated CLL, $n = 25$ BTK-I treated patients with CLL) who received RZV documented an antibody response at 3 months in only 45% of participants, with a trend towards a lower response in BTK-I treated subjects (36% vs. 51%), a T-cell response of 54% (lower in BTK-I treated: 32% vs. 73%), and a combined antibody and cellular response in only 29% of participants [93]. Similarly, a recent trial which evaluated humoral and cellular immunogenicity of RZV in patients with CLL who were treatment-naïve ($n = 56$) or receiving BTK-inhibitors therapy ($n = 50$), favored the vaccination at CLL diagnosis, reporting how both antibody (76.8% vs. 40%) and cellular (70% vs. 41.3%) response rates were significantly higher in the treatment-naïve cohort versus the BTK-I cohort. Moreover, antibody titers and T-cell responses did not show correlation with age, absolute B- and T-cell counts, or serum immunoglobulin levels [94]. Therefore, available evidence suggests that RZV should be offered at CLL diagnosis to optimize the chance of an effective response by reducing the burden of VZV infection during CLL treatment, although in case of BTK-I or BCL-2-I treatment the VZV burden appears limited even without prophylaxis.

4.4. Other vaccines

Decisions on other vaccinations need to be made on a case-by-case basis, according to age, comorbidities, and country recommendations.

***Haemophilus influenzae* B** (HiB) vaccination is controversial in patients with CLL. According to ECIL-2019 guidelines, the expected benefit of vaccination is uncertain [75,95,96]. The NHS guidance recommends HiB vaccination at diagnosis only if a patient has not received a HiB-containing vaccine in the previous five years and suggests a single booster dose if the post-vaccination antibody level is non-protective [77]. After treatment, re-immunization could be proposed.

Most guidelines do not recommend **meningococcal** vaccinations in CLL. However, some countries offer it to all immunocompromised patients, including those with CLL, while other only to those with functional asplenia or anti-complement treatment [6]. Local recommendations, which also include recommendations for epidemic and outbreaks settings, should be followed.

The NHS guidance document recommends vaccination against **tetanus** at CLL diagnosis, with a booster dose of the vaccine if it has not been administered in the previous 10 years and a further single booster dose if seroprotective titers are not reached after vaccination [77]. Additionally, patients should be up to date with diphtheria and pertussis vaccination status, but no additional vaccination or boosters are recommended [77], while the US guidelines recommend a booster every 10 years [6].

Immunization against **HBV** for those unvaccinated also differs between the countries: for example, it is recommended in the US but not in most European countries [7,77]. Notably, in an open-label, single-arm clinical trial including 58 patients, Pleyer et al. found a lower response rate to recombinant HBV vaccine in patients receiving BTK-I (3.8%; 95% confidence interval [CI], 0.7–18.9) compared to patients who were treatment-naïve (28.1%; 95% CI, 15.6–45.4; $p = 0.017$), suggesting that HBV vaccination should be planned early in the disease course and before starting BTK-I in order to ensure adequate protection [91].

Lastly, vaccination against SARS-CoV-2 is reported in the following dedicated paragraph.

5. COVID-19 in patients with CLL: clinical presentation, prevention and management

Patients with CLL may face an increased risk of severe illness and mortality if infected with SARS-CoV-2 virus, not only due to CLL-related immunodeficiency and chemotherapy, but also due to the frequent presence of risk factors identified in a general population, such as advanced age or cardiovascular comorbidities.

During the first and second pandemic waves, most patients with CLL with COVID-19 developed severe disease, and 30-day mortality rate was 31%–50% for hospitalized patients [97]. Later studies performed during Omicron predominance found an improved outcome also in patients with CLL, which may be explained by the improved prevention and management of COVID-19 with the availability of vaccines, monoclonal anti-spike protein antibodies, and antivirals, or lower viral virulence.

The course of COVID-19 in patients with CLL may vary considerably. While some patients present mild symptoms or are asymptomatic, others develop severe respiratory complications, including acute respiratory distress syndrome (ARDS). In addition, patients with CLL, as well as other immunocompromised categories, may present with some unique features of COVID-19. Cases of protracted illness with intermittent flare-ups or relapses of clinically symptomatic COVID-19 have been described, especially in patients after B-cell depletion. These syndromes may require hospital admission and may be characterized by high rate of mortality. The most accepted definitions of persistent inflammatory COVID-19 in these patients are those proposed by Belkin et al. [98]

Table 4
Diagnostic criteria of persistent inflammatory seronegative COVID -19[a] (adapted from Belkin et al. [98]).

1. Host criterion	B-cell depleting disease or therapy, including the following: Primary immunodeficiency causing hypogammaglobulinemia (X-linked agammaglobulinemia, common variable immunodeficiency, other primary hypogammaglobulinemia). Secondary immunodeficiency - anti-CD20 treatment in the past year; chronic lymphoblastic leukemia, non-Hodgkin lymphoma, multiple myeloma accompanied by hypogammaglobulinemia or receiving immunotherapy directed against B cells (bi-specific antibodies or antibody-drug conjugates against CD19, CD20 or BCMA); chimeric antigen receptor T-cell therapy or allogeneic or autologous hematopoietic stem cell transplantation within 1 y.
2. Clinical criterion	Prolonged or remitting fever (total > 7 d) with elevated CRP levels plus either one of the following: prostration, non-resolving cough, and dyspnea (total > 14 d), abnormal chest imaging showing pneumonitis (bilateral ground glass opacities).
3. Virological criterion, defined as either of the following	Persistent or intermittent positive SARS-CoV-2 RT-PCR result over >21 days.[b] Positive SARS-CoV-2 RT-PCR result in the last 90 days + sero-negativity for SARS-CoV-2 14 d after the initial infection in monoclonal antibody-naïve patients.[c]

Abbreviations: BCMA, B-cell maturation antigen; CD, cluster of differentiation; COVID, coronavirus disease; CRP, C-reactive protein; RT-PCR, Real-time PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Being sero-negative before and at the time of the onset of acute infection (regardless and despite vaccination) is a characteristic of this entity. It was not comprehensively included in the criteria for diagnosis because of practical reasons; the diagnosis can be made without a specialized blood test.

[b] A positive SARS-CoV-2 result from either a nasopharyngeal swab or lower-respiratory specimen demonstrating the same variant using sequencing supports the diagnosis but is not mandatory.

[c] Undetectable levels or low titres according to a local serology platform; patients who were treated with monoclonal antibodies for prevention may have higher titers.

(Table 4). The optimal management of these patients remain to be defined, but several experiences focused on repeated or combined treatment strategies [99,100].

5.1. Prevention of COVID-19

Vaccination against COVID-19 is strongly recommended for patients with CLL as it plays a vital role in preventing severe illness and reducing the risk of hospital admission. However, the response to vaccines is diminished in patients with CLL compared to the general population due to immune dysfunction [101]. In selected studies on COVID-19 vaccination in patients with CLL (Table S2), the overall serological response varied from 5% to 90% with higher rate of response seen in treatment-naïve patients and lower rate in anti-CD20-treated recipients [102–111].

In particular, in treatment-naïve patients, the rates of seroconversion after 2 doses varied between 55% and 94% [105,107–111]. In four studies, the rate of response in BTK-I recipients was approximately 30% (21% - 37%) [107,108,110,111], similar to what is reported for patients receiving BCL-2-I (i.e., 29%) [108]. Apart from one study which reported 51% response rate [103], patients with CLL previously treated with anti-CD20 had very low response rates (0%–14%) [105,109–111], with 0% in case of in case of combination of BTKi and anti-CD20 or venetoclax [107], and, only in one study, 51% in all anti-CD20 treated patients (24% in those treated within 12 months) [108]. Of note, one study reported the highest rates of response (79%) in patients in complete remission after CLL treatment [105], while in another, failed seroconversion occurred in 36.6% of treatment-naïve patients, 78.1% in those on therapy, and 85.7% in those receiving ibrutinib [102].

The role of booster doses was also evaluated. In a study from the US, the seroresponse increased from 56% to 68% after the booster dose in 117 patients with CLL [103]. In a cohort of 258 patients (of whom 215 with CLL), response to several booster doses was evaluated, increasing the seroconversion from 55% after the second dose to 73.4% after the third and 81.7% after the fourth dose. Among patients who were seronegative after the previous dose, seroconversion occurred in 40.6% post 4th dose, 46.2% after the 5th dose, 16.7% after the 6th dose, and 0% after doses 7 or 8 [104]. Considering the difficulties to obtain seroconversion in these patients, it is also crucial to promote vaccination among close contacts of patients with CLL, to create an added layer of protection.

Importantly, despite the lack of serological response, T-cell immunity has been reported in various anti-CD20 treated populations, highlighting that even in the absence of anti-S antibodies, cellular immunity might still provide some protection against severe COVID-19, as demonstrated by approximately 80% T-cell response despite serological response being detected in 55% [102].

Interestingly, in a small study of 9 zanubrutinib-treated patients with CLL who received 5 doses of COVID-19 vaccine, there was no detectable IgA mucosal immunity, which likely compromises the primary defense barrier against infection; systemic IgG responses were also impaired, whereas T-cell responses were normal [112].

5.2. Pharmacological prophylaxis of COVID-19

Prophylaxis with anti-spike monoclonal antibodies has been shown of benefit in immunocompromised patients, particularly if no serological response to vaccine has been observed, provided it is performed with antibodies active against the circulating strains [113]. However, the benefit of this strategy (on infection rate, severe infections and mortality rates) should be re-evaluated for novel active antibodies, considering that currently almost all patients are vaccinated with multiple doses, many have experienced previous SARS-CoV-2 infections, and the virulence of circulating strains appears to be lower than the original one.

5.3. Management of COVID-19

Managing COVID-19 in patients with CLL requires a multidisciplinary approach. Physicians must balance the risks and benefits of continuing or modifying CLL treatment regimens, considering disease stage, overall health status, and individual patient factors. In some cases, it may be necessary to postpone or modify treatment to minimize immunosuppression and optimize COVID-19 outcomes. From a therapeutic point of view, for the initial management of COVID-19 in the early phase of the disease (e.g., within 5–7 days after the onset of symptoms) guidelines recommend antiviral treatment [100,114]. The use of monoclonal antibodies against the Spike protein should be evaluated based on their activity against the predominant SARS-CoV2 variants and sub-lineages. At present (November 2023), there are no commercially available monoclonal antibodies that have *in-vitro* efficacy against the circulating variants [115]. The optimal treatment of severe and persistent cases in this setting is under debate, but combined and/or prolonged treatment with antivirals (2 or even 3), and monoclonal antibodies, if active, or high titer convalescent plasma (CVP), has been shown effective in cases and case series of immunocompromised patients [116].

Drug-drug interactions (DDIs) of nirmatrelvir/ritonavir with numerous agents, including BTK and BCL-2 inhibitors, should be evaluated and managed appropriately. The effect of ritonavir is similar to the effect of other strong CYP3A4 inhibitors such as ketoconazole. Indeed, in case of ibrutinib or venetoclax, a significant increase in ibrutinib/venetoclax concentrations is expected. Therefore, either other anti-SARS-COV-2 therapy should be provided (e.g. there are no DDIs with remdesivir) or, based on case-by-case evaluations, ibrutinib/venetoclax should be discontinued or its dose reduced until 3 days after the end of nirmatrelvir/ritonavir therapy. The European label of nirmatrelvir/ritonavir gives the possibility reduction of ibrutinib dose to 140 mg/daily or venetoclax by 75% in patients who completed the ramp-up phase (ref label). Interestingly, in a recent PK modelling study performed to predict DDIs of ibrutinib, zanubrutinib and acalabrutinib with ritonavir (100 mg twice daily for 5 days), ritonavir was predicted to increase, respectively, Cmax and AUC of ibrutinib 33- and 54-fold, of zanubrutinib 2.6- and 3.2-fold, and of acalabrutinib 3.9- and 6.5-fold. Based on these simulations, even more important dose-reduction strategies may be appropriate in case of coadministration with nirmatrelvir/ritonavir: ibrutinib 25 mg every 48 h, zanubrutinib 80 mg twice daily and acalabrutinib at 25 mg twice daily with nirmatrelvir/ritonavir [117].

Online databases, such as for instance the one provided by University of Liverpool (https://www.covid19-druginteractions.org/checker), which differentiates also the recommendations for short (5 days) and extended (10 days or more) administration of nirmatrelvir/ritonavir might be useful.

6. Conclusions and future considerations

CLL is typically associated with an increased risk of infectious complications. However, the new targeted monotherapies with BTK-I and BCL-2-I do not seem to be associated with a significantly higher risk of infections. The lack of high-quality data and the heterogeneity of patients included in observational studies might explain the differences in recommendations among the main guidelines. Overall, specific prophylaxis protocols in case of treatment with BTK-I and BCL-2-I are generally considered necessary only in patients with additional risk factors, such as neutropenia, steroid therapy or advanced diseases. The impact of novel combination therapies which include BTK-I and/or BCL-2-I with different agents (mainly anti-CD20 antibodies), in particular, the rate and optimal management of infectious complications, require further careful evaluation and dedicated studies.

Practice points

- CLL is associated with an increased risk of infectious complications, and prevention through immunization against pneumococcus, influenza, herpes zoster, and COVID-19, provided preferably before starting treatment, is recommended.
- Treatment with new targeted agents: BTK or BCL-2 does not seem to warrant specific prophylactic strategies other than prevention of HBV hepatitis in all HBsAg positive patients, and in HBsAg-negative/HBcAb-positive patients if treated with combinations containing targeted agents and anti-CD20 antibodies.
- Universal anti-*Pneumocystis* and anti-VZV/HSV prophylaxis are only recommended when additional risk factors are present.
- A slightly increased rate of invasive fungal infections (but still <3%), including those involving central nervous system, has been reported in case of BTK-I therapy and clinical attention and early diagnostic workup are recommended.
- Immunoglobulin replacement therapy is warranted in case of hypogammaglobulinemia and recurrent or severe infections, particularly respiratory.
- There is no data to suggest any potential benefit of antibacterial prophylaxis, but appropriate rapid diagnostic work up and treatment are required in case of pneumonia.

Research agenda

- Implementing standardized reporting of infectious complications, including etiology, localization, severity, outcome and rate per months of treatment.
- Identifying the rate of severe infectious complication within a predefined time frame of treatment with targeted agents and combinations.
- Defining optimal management strategies for most frequent and for severe infectious complications.
- Evaluation if recommended and applied infectious risk mitigation strategies (prophylaxis, screening, vaccination, early diagnosis) result in improved outcomes and higher rate of continuing targeted therapies.
- The use of novel rapid diagnostic methods for the diagnosis of pneumonia in CLL outpatients, particularly treated with BCL-2 inhibitors, should be studied.

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CRediT authorship contribution statement

Malgorzata Mikulska: Conceptualization, Methodology, Supervision, Writing – original draft, Data curation, Visualization, Writing – review & editing. **Chiara Oltolini:** Data curation, Visualization, Writing – review & editing. **Emanuela Zappulo:** Data curation, Visualization, Writing – review & editing. **Michele Bartoletti:** Data curation, Visualization, Writing – review & editing. **Anna Maria Frustaci:** Data curation, Visualization, Writing – review & editing. **Andrea Visentin:** Data curation, Visualization, Writing – review & editing. **Candida Vitale:** Data curation, Visualization, Writing – review & editing. **Francesca R. Mauro:** Conceptualization, Methodology, Supervision, Writing – original draft, Data curation, Visualization, Writing – review & editing.

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Appendix A. Supplementary data

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