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Considerations on antimicrobial prophylaxis in patients with lymphoproliferative diseases: A SEIFEM group position paper

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ABSTRACT

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The therapeutic armamentarium for the treatment of patients with lymphoproliferative diseases has grown considerably over the most recent years, including a large use of new immunotherapeutic agents. As a consequence, the epidemiology of infectious complications in this group of patients is poorly documented, and even more importantly, the potential benefit of antimicrobial prophylaxis remains a matter of debate when considering the harmful effect from the emergence of multidrug resistant pathogens. The present position paper is addressed to all hematologists treating patients affected by lymphoproliferative malignancies with the aim to provide clinicians with a useful tool for the prevention of bacterial, fungal and viral infections.

1. Introduction

Infectious complications still represent one of the principal causes of morbidity and mortality for patients with lymphoproliferative diseases (Nørgaard et al., 2006; Di Blasi et al., 2018).

The immunocompromised condition of the host depending on the underlying disease and the severity of neutropenia secondary to the intensity of the chemotherapic regimens are well established risk factors for the development of infections in patients with lymphoproliferative disorders (Nørgaard et al., 2006; Pagano et al., 2017a). On the other hand, monoclonal antibodies targeting neoplastic cells bearing tumor antigens, inhibitors of BCR signaling, immunomodulatory drugs and cellular immunotherapy represent the most recent options for the treatment of patients with lymphoproliferative malignancies (Santos et al., 2017; Mehta-Shah and Younes, 2015). The preliminary results reported with the use of these immunological agents seem to be extremely promising, however, the precise effects of these agents on the adaptive immunity are not yet completely defined. Furthermore, these new treatments are given as single agent or in many circumstances in combination with conventional chemotherapy making the incidence and the management of infectious complications largely unknown.

Aim of present position paper is to provide readers with a reliable platform to guide an optimal anti-infective prophylaxis in patients with lymphoproliferative disorders

2. Methods

We conducted a comprehensive electronic literature search from January 2008 to June 2018, using the PubMed database. Only human studies published in English language were included. Our search terms and medical subject headings (MeSH) were: acute lymphoblastic leukemia (ALL) and infections, and/or bacterial, and/or fungal, and/or viral infections; chronic Lymphocytic Leukemia (CLL) and infections, and/or bacterial, and/or fungal, and/or viral infections; Non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) and infections, and/or bacterial, and/or fungal, and/or viral infections; multiple myeloma (MM) and infections, and/or bacterial, and/or fungal, and/or viral infections.

Results were screened based on titles and abstracts to determine suitability for inclusion in this scoping review. The attention was focused on the epidemiology, risk factors and prophylaxis of bacterial, fungal and viral infections. The evaluation of vaccination programs has not been taken into account in the present review. We considered all studies including controlled clinical trials, prospective and retrospective observational studies including at least ten patients. The proposed management of infectious complications has been highlighted in bold italic at the end of each chapter. The co-authors reviewed all the publications, identified and prepared a slide set comprising evidence-based statements and recommendations presented to the annual SEIFEM (**S**orveglianza **E**pidemiologica delle **I**nfezioni nelle **EM**opatie group) meeting held in Rome 2019, where experts of infectious complications in hematologic patients convened : after revision according to the results of the discussion, a summary report was made.

3. Acute lymphoblastic leukemia (ALL)

Treatment strategies of patients with ALL have changed over the last 10–15 years, with the extension of pediatric or intensive protocols to young and older adults and the introduction of tyrosine kinase inhibitors (TKI) for Philadelphia positive (Ph+) ALL. These different therapeutic approaches, and the availability of new immunological drugs, such as monoclonal antibodies, and CD19-targeted chimeric antigen receptor (CAR)–modified T cell immunotherapy, may be responsible for a different epidemiology of infectious complications. Overall, fatal infections during ALL induction therapy occur in 4.7 % of the patients (Di Blasi et al., 2018), although the incidence is reported to be higher in adults than in children or adolescents, and particularly in the elderly population (Ribera et al., 2008; Rijneveld et al., 2011; Daenen et al., 2012; Sive et al., 2012); the infection related mortality reaches 11.8 % in patients over 60 years treated with an intensive protocol (Martell et al., 2013). On the other hand, a chemotherapy-free approach or a reduced intensity chemotherapy for Ph + ALL led to a lower rate of infections (Ribera et al., 2016). The impact of Rituximab (R) on the predisposition to develop infections seems to be controversial: Thomas et al. (Thomas et al., 2010) showed a higher number of infection-related death in complete remission among patients treated with R + intensified HyperCVAD as compared to an historical control group of patients treated without R; by contrast, Maury et al. (Maury et al., 2016), did not find a significant increase of infections in the R arm. In a randomized trial for relapsed/refractory ALL, inotuzumab alone was associated with a reduced rate of febrile neutropenia episodes and invasive fungal infection (IFI) as compared to chemotherapy (24 % vs 49 % and 0% vs 2% respectively) (Kantarjian et al., 2016). However, the association of inotuzumab + reduced intensity chemotherapy as first line therapy in older patients resulted in a 10 % of fatal sepsis and a high incidence of infectious complications (Kantarjian et al., 2018; Jabbour et al., 2018). Similarly, the rate of grade 3–4 infections in patients who received blinatumomab was reduced when compared to the chemotherapy group (34.1 % vs 52.3 %); in particular, 1.5 % and 3% of IFI were reported in patients treated with blinatumomab and chemotherapy respectively (Kantarjian et al., 2017). Finally, a recent analysis of infectious complications during CAR-T cell immunotherapy in ALL revealed a close association with the presence of severe ($\geq$ grade 3) cytokine release syndrome (CRS), with a 6% of infection related mortality in a series of 53 adult patients with relapsed/refractory ALL (Park et al., 2018). In this study, the incidence of bacterial, fungal and viral infections within 30 days were 32 %, 7.5 % and 9.4 %, respectively. Similar findings have been reported by Hill et al. (Hill et al., 2018) (25.5 %, 4.5 % and 10.6 % in ALL patients respectively).

3.1. Bacterial infections

A large multicenter retrospective study by the SEIFEM group revealed that the rate of bacterial infections in patients with ALL ranged between 18.5 % and 28.5 %, according to the different phase of treatment (Di Blasi et al., 2018). Bacterial infections were observed in 34.3 % of the patients during induction in the GRAAL-2005 study, with an infection-related mortality of 2.8 % (Honeyman et al., 2016). Gram-positive bacteremias were predominantly found in the GRAAL-2005 study (Sulis et al., 2018), while gram-negative rods were

the leading cause of bacteremias in the SEIFEM study (Di Blasi et al., 2018), possibly due to the epidemiology of the different geographic areas in different period of time and the choice of prophylactic regimens.

Studies concerning antibacterial prophylaxis with fluoroquinolones (FQ) in ALL were mostly conducted in pediatric patients receiving intensive chemotherapy (Yousef et al., 2004; Widjajanto et al., 2013; Wolf et al., 2017; Sulis et al., 2018; Alexander et al., 2018); the majority of the studies demonstrated a reduction of febrile episodes, BSI incidence and hospitalization/intensive care unit admission, without a significant increase of multi-resistant bacteria or *C. difficile* infections, and no effect on survival.

Antibacterial prophylaxis in ALL is a matter of debate. it should be considered during induction/reinduction phase of treatment, with a ≥7 days expected severe neutropenia. Close monitoring of bacterial epidemiology should also be done, in order to detect early emerging antibiotic resistant strains.

3.2. Fungal infections

Data on IFI in ALL are rather limited: the incidence of IFI was 7.8 % in the GRAAL-2005 series (Mariette et al., 2017), whereas the SEIFEM study (Di Blasi et al., 2018) showed a lower incidence (4.3 %); the prospective randomized AmBiGuard study (Cornely et al., 2017) reported a rate of IFI up to 11.7 % in the placebo group, while a negligible incidence of IFI has been observed in Ph + ALL patients even in elderly patients receiving low-dose chemotherapy regimens + TKI or TKI alone (Chalandon et al., 2015; Foà et al., 2011; Vignetti et al., 2007; Rousselot et al., 2016). Mold infections, particularly *Aspergillus* spp, were prevalent in adult population (Di Blasi et al., 2018; Cornely et al., 2017): advanced age was a risk factor for IFI (Ribera et al., 2008; Daenen et al., 2012) and IFI-related mortality (Di Blasi et al., 2018), whereas a negligible incidence of IFI has been observed in Ph + ALL patients receiving low-dose chemotherapy regimens + TKI or TKI alone even in elderly patients (Chalandon et al., 2015; Foà et al., 2011; Vignetti et al., 2007; Rousselot et al., 2016).

Few data on primary antifungal prophylaxis (PAP) in ALL are available. Table 1 summarizes the main studies reporting epidemiologic data on PAP in ALL patients. According to a multicenter retrospective study evaluating PAP vs no PAP (Cattaneo et al., 2011) in ALL, the incidence of IFI (possible/proven/probable), was 2.6 % vs 21 % and similar results have been reported by Cornely et al. in the AmBiGuard study (Cornely et al., 2017) (no PAP vs L-AmB: 11.7 % vs 7.9 %, respectively). A recent phase II trial which analyzed the efficacy of micafungin as antifungal prophylaxis in 65 ALL patients, reported a 4.6 % rate of possible/proven/probable IFI (Park et al., 2019). It is noteworthy that a shift in epidemiology towards *non-albicans Candida spp*. has been recently observed (Mellinghoff et al., 2018) and surveillance studies aimed to assess antifungal susceptibilities are largely desirable in order to adopt the most appropriate regimen. In addition, prophylaxis of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis is universally accepted and recommended by different scientific society guidelines (Cordonnier et al., 2016; Green et al., 2007).

Although further studies should be performed in order to assess the actual risk of IFI in ALL, the current data support the utility of mold-active prophylaxis in ALL, at least in intensive regimen protocols and particularly in older patients. No clear benefit has been demonstrated for echinocandins and polyenes in ALL, but at present they are the only available drugs for ALL patients receiving vinca alkaloids.

Strategies for preventing PJP in ALL during the whole treatment course include trimethoprim/sulfamethoxazole (TMP/SMX); pentamidine by aerosol, atovaquone or dapsone may be considered as acceptable options for TMP/SMX intolerant patients.

3.3. Viral infections

Many studies reported a beneficial effect of acyclovir-based prophylaxis in reducing oral mucositis in HSV-seropositive patients (Saral et al., 1983; Bustamante and Wade, 1991). Therefore, antiviral prophylaxis with acyclovir during leukemia induction in HSV-seropositive patients is usually recommended with a moderate/high level of evidence (Styczynski et al., 2009).

Patients with ALL should be screened for HBV infection prior to starting immunosuppressive antineoplastic agents (Reddy et al., 2015; EASL, 2017). Patients with B ALL often receive anthracycline-based regimens and high-dose corticosteroids: consequently, a nucleoside analogue (entecavir 0.5 mg/day or tenofovir 245 mg/day) is employed in patients who are HBsAg positive (HBVreactivation >10 %), (Reddy et al., 2015), while lamivudine is preferred in HBsAg-negative/anti-HBc-positive patients (EASL, 2017). When R is part of the chemotherapy regimen, prophylaxis is strongly suggested (entecavir or tenofovir for at least 12 months if HBsAg positive) since patients are considered at high-risk of reactivation (Reddy et al., 2015).

Table 1
Main studies reporting epidemiologic data on PAP in ALL patients.

References	Type of study	Arms and number of Patients	Overall infection rate	Comments
Cattaneo, 201 (Nachbaur et al., 2015)	Prospective, Phase II (randomized comparison)	175 AML/ALL (138/37) Caspofungin (93) vs standard policy (82)	- p/p IFI: 5.7 % (AML: 6.5 %; ALL: 2.7 %) - p/p IFI caspofungin 7.5 % vs SP 3.7 %	No stratification according to PAP in ALL
Nachbaur, 2015 (Nachbaur et al., 2015)	Retrospective	100 pts with various HM; Micafungin during neutropenia (ALL 10 %)	-IFI breakthrough: 6% (proven), 3% (prob) -IFI proven: 4 molds e 2 Candida	Heterogeneous population and treatments
Koehler, 2017 (Koehler et al., 2017)	Prospective, observational	179 AML/ALL (87 %/13 %) Various PAP	-IA incidence: 3.8 %	No stratification according to PAP
Nicolato, 2016 (Nicolato et al., 2016)	Retrospective	350 febrile episodes in ALL pts Various PAP (27 %)	-IFI prevalence: 8.8 %	Different type of treatment; analysis only during neutropenia
Doan, 2016 (Doan et al., 2016)	Retrospective	98 ALL (including Ph pos, 27 %) PAP and no PAP	-IFI: 11 % (poss/prov/prob) -IFI during PAP: 2.6 % -IFI no PAP: 21 %	85 % of pts received PAP
Cornely, 2017 (Cornely et al., 2017)	Prospective, randomized phase III (induction)	L-Amb (237) vs placebo (118)	-p/p IFI: 7.9 % vs 11.7 % (NS)	Heterogeneous chemotherapic treatments
Wang, 2018 (Wang et al., 2018)	Retrospective	103 pts Fluconazole vs mold-active PAP	-IFI 17.6 % vs 15.9 % -IA fluconazole 11.8 % vs mold active PAP 1.4 %	Real life study, low sample size

Abbreviations: AMLAcute Myeloid Leukemia; ALLAcute Lymphoblastic Leukemia; p/pproven/probable; PtsPatients; HMHematological Malignancies; p/p IFIproven/probable Invasive Fungal Infection; IAInvasive Aspergillosis; PAPPrimary Antifungal Prophylaxis; L-AmBLiposomal Amphotericin B.

Epidemiology of other viral infections is largely underestimated, because of the lack of systematic monitoring of viral infections. In a retrospective Indian study, the incidence of CMV symptomatic reactivation was 11.3 %, occurring particularly in the later phases of treatment during high doses of steroids (Gulia et al., 2014). A study from the M.D. Anderson reported the occurrence of CMV pneumonia in 2.5 % of patients with ALL (Nguyen et al., 2001).

Antiviral prophylaxis is not recommended in ALL patients except for HSV prevention with acyclovir in seropositive patients at least during induction treatment. Anti HBV prophylaxis is strongly recommended in ALL patients (entecavir or tenofovir in HbsAg-positive patients and lamivudine in HBsAg-negative/anti-HBc-positive patients (expert opinion).

4. Chronic lymphocytic leukemia

The main risk factors of infection in patients with CLL include several immune defects (e.g. abnormal complement-dependent cytotoxicity, qualitative deficiencies of neutrophil function etc.) related to the disease and the use of immunosuppressive treatments (Forconi and Moss, 2015).

Disease-related defects include hypogammaglobulinemia, which occurs in virtually all patients with CLL and correlates with duration and stage of the disease (Wadhwa and Morrison, 2006; Ravandi and O'Brien, 2006). Quantitative and qualitative neutrophil and monocyte defects are found in CLL patients and although the absolute number of neutrophils is normal or slightly decreased in untreated patients, defects in phagocytic and bactericidal activity, have been demonstrated in a consistent number of subjects (Wadhwa and Morrison, 2006). Major infections occur in >50 % of CLL patients contributing to 30 %–50 % of deaths (Moreira et al., 2013; Morrison et al., 2001; Hensel et al., 2003). In addition to alkylating agents, purine analogues and monoclonal antibodies that have been used for the treatment of CLL for many years, new classes of highly effective drugs have been introduced in the clinical practice. These compounds act by inhibiting the Bruton Tyrosine Kinase (BTK) or the phosphatidylinositol 3-kinase (PI3K), key components of the B-cell receptor (BCR) signaling pathway, through which the growth, adhesion and survival of B cells are regulated (Tillman et al., 2018). The BTK is also present in neutrophils, monocytes and macrophages where it mediates pathways involving innate and adaptive immunity (Tillman et al., 2018). Therefore, the molecular targets of these agents are also found in normal cells and can be involved in the exertion of several deleterious off-target effects (de Weerdt et al., 2017).

4.1. Bacterial infections

The abnormal complement activity occurring in patients with CLL, may predispose patients to infections due to the lack of protection normally ensured by the opsonization process and subsequent neutrophil activation. *Staphylococcus aureus* and various gram-negative pathogens such as *Pseudomonas aeruginosa, Escherichia coli* and *Klebsiella pneumoniae* may cause infections during neutropenia and in patients with severe hypogammaglobulinemia (Nosari, 2012). Several studies showed a high rate of infections, mainly bacterial (18 %–36 %) in patients treated with fludarabine-cyclophosphamide (FC) alone or in combination with R (Joffe et al., 2018; Guillermin et al., 2018; Eichhorst et al., 2016; Strati et al., 2013; Tam Constantine et al., 2008), probably due to the severe and long-lasting T-cell depletion. Bacterial infections after FCR are common in patients older than 65 years (Eichhorst et al., 2016) and with absolute lymphocyte counts $\leq 1.0 \times 10^3$ cells/μL at 3 months after FCR (21.0 % vs 13.8 %) (Joffe et al., 2018). Overall, the infection risk is higher during the first year after therapy and rapidly declines to less than 1.5 % per year from the third year onward. Treatment with bendamustine monotherapy or in combination with R was less clearly associated with infections. Chlorambucil-treated patients, alone or in association with ofatumumab, show a very low infection rate ranging between 2 and 9% (Michallet et al., 2018; Knauf et al., 2009; Hillmen et al., 2015; Burger et al., 2015). Overall, the infection rate ranged from 11 to 14 % when chlorambucil was combined with R or obinutuzumab and the majority of the infections are reported of bacterial origin (Goede et al., 2014). The reported risk of infections following treatment with Ibrutinib or other BTK inhibitors, alone or in combination with other agents, ranges from 11,4%–29% (Varughese et al., 2018; Chanan-Khan et al., 2016; Burger et al., 2014; Byrd et al., 2014; Reinwald et al., 2018; Kim et al., 2008b) and only 5% have a bacterial origin. Most frequent adverse events reported in randomized trials with idelalisib, alone or in combination with other drugs, are pneumonia, pyrexia, and febrile neutropenia (Jones et al., 2017a; Zelenetz et al., 2017; Brown et al., 2014; Furman et al., 2014), but data on microbial aetiology are not always available. Table 2 reports the most relevant studies on bacterial infections in patients with CLL.

Specific antibacterial prophylaxis may not be recommended in patients with CLL, although FQ prophylaxis may be considered in FCR and BR regimes. Monitoring of local epidemiology should be considered mandatory to guide appropriate antibiotic treatment.

4.2. Fungal infections

The incidence of fungal infections in CLL patients ranges between 0.5–18% (Varughese et al., 2018; Williams et al., 2018; Nosari et al., 2014; Pagano et al., 2017b, a; Safdar et al., 2010; Stanzani et al., 2013; Sun et al., 2015; Teng et al., 2015; Tisi et al., 2017; Visentin et al., 2017; Francis et al., 2006) according to the treatment received and *Aspergillus spp*. is the most frequently isolated fungal pathogen (Raisch et al., 2016). Interestingly, CLL with an unfavorable prognostic profile were more often affected by IFI. In particular, CD38 expression, genetic profile (p53, ATM or 12+) and IgvH mutation status represented biological risk factors for IFI (Pagano et al., 2017b; Nosari et al., 2014, 2014; Pagano et al., 2017b, a; Safdar et al., 2010; Stanzani et al., 2013; Sun et al., 2015; Teng et al., 2015; Tisi et al., 2017; Visentin et al., 2017; Francis et al., 2006). Five cases with PCR-evidence of PJP were found in a cohort of 96 patients (Ahn et al., 2016). An open label trial comparing idelalisib and ofatumumab versus ofatumumab monotherapy in patients with relapsed CLL reported a PJP rate of 5% vs. 1% (Jones et al., 2017b). A retrospective analysis of 8 studies (front line/relapsed CLL and relapsed iNHL) included 2198 patients who received idelalisib alone or with R or bendamustine-R (BR) and patients treated with R ± bendamustine: the overall incidence of PJP infection was 2.5 % in patients receiving idelalisib ± combination therapy vs 0.2 % in patients receiving only R alone or BR alone (relative risk = 12.5) (Sehn et al., 2016).

At present, data available are not sufficient to expect benefit from universal use of antifungal prophylaxis, but as the indications for ibrutinib continue to expand, there is the need for further studies defining those patients who are candidates for close clinical monitoring and/or mold-active prophylaxis strategies. PJP prophylaxis is recommended for all patients receiving idelalisib for a period of 2–6 months after discontinuation of the treatment,

4.3. Viral infections

Viral infections are a relevant cause of morbidity in CLL patients (Merchardt et al., 2013). The incidence of CMV infections in CLL patients ranges between 0 and 46 %, according to the treatment received and the diagnostic strategy used for virus detection (Merchardt et al., 2013; Marchesi et al., 2018) (Table 3). While the treatment with fludarabine, bendamustine and R was not clearly associated with CMV reactivation (Chan et al., 2015; Munõz et al., 2014), recent data reported several cases of CMV infection following administration of idelalisib, with an estimated incidence of about 2% (Reinwald et al., 2018; Jones et al., 2017a; Ljungman et al., 2017). A very low rate of HSV and VZV infections has been reported in patients treated with chlorambucil, R and BCR inhibitors, while fludarabine should be considered as the most relevant risk factor for these viral infections (Table 3).

Table 2
Infection in Chronic Lymphocytic Leukemia (CLL). Clinical studies and other relevant recent references about bacterial infections published since 2008.

Reference	Type of study	Arms and number of patients	Overall infection rate	Comments
Varughese, 2018 (Varughese et al., 2018)	Retrospective	Ibrutinib CLL 165 pts (as 1st-line treatment: 33 % and as monotherapy: 95 %)	12 %	Bacterial infections: 5 % (9/165). Staphylococcus aureus is the most common bacterial pathogen identified. Among the cases of bacterial infection were 10 cases of pulmonary or pleural space infections and 7 of bloodstream infection.
Michallet, 2018 (Michallet et al., 2018)	Prospective, phase III	R-Benda vs R- CLB in Fluda-ineligible CLL pts 357 pts	19 % vs 8%	Bacterial infections: data not available. Febrile neutropenia: 6% vs 4%. Any infection were significantly more frequent with R-Benda than with R-CLB.
Joffe, 2018 (Joffe et al., 2018)	Retrospective	FCR frontline, 99 pts	NA	For bacterial infections evaluable 92 pts. Bacterial infections: 18,7%. Bacterial infections after FCR based on ALC levels at 3 months were significantly more frequent if ALC levels $\leq 1.0 \times 10^3$ cells/μL (21.0% vs 13.8%) (p .596).
Guillermin, 2017 (Guillermin et al., 2018)	Retrospective	FC-based first-line treatment (79 % FCR);76 pts	16.4 %	Bacterial infections (any grade): 35.9 %.
Jones, 2017 (Jones et al., 2017a)	Prospective, Phase III	Idela + O vs O in R/R CLL; 261 pts	NA	Higher incidence of severe infection in the idela group: pneumonia (13 % vs 10 %) and sepsis (6% vs 1%)
Eichhorst, 2016 (Eichhorst et al., 2016)	Prospective, Phase III	FCR vs R-Benda in TN advanced CLL 561 pts	39 % vs 25 % (grade ≥3)	The incidence of bacterial infections (grade 3 and 4) between treatment group was similar: 2%. Increased frequency of severe infection in FCR arm and in older than 65 years.
Zelenetz, 2017 (Zelenetz et al., 2017)	Prospective, Phase III	Idela vs placebo in combination with R-Benda in R/R CLL; 416 pts	39 % vs 25 % (grade ≥3)	Bacterial Infections: data not available. The frequency of infections was higher in the idela group than in the placebo group and most infections such as pneumonia and upper respiratory tract infections were bacterial (data on rate not shown)
Chanan-Khan, 2016 (Chanan-Khan et al., 2016)	Prospective, Phase III	IBRU vs placebo in combination with R-Benda in R/R CLL 578 pts	29 % vs 25 % (grade ≥3)	Bacterial Infections: data not available
Hillmen, 2015 (Hillmen et al., 2015)	Prosepctive, Phase III	CLB vs O-CLB 447 pts	9% vs 12 % (grade ≥3)	The most common infections were respiratory tract infections. 27 % vs 31 %. Similar frequencies of sepsis (3% O-CLB vs 2% CLB). Bacterial Infections: data not available
Burger, 2015 (Burger et al., 2015)	Prosepctive, Phase III	CLB vs IBRU frontline CLL 269 pts	2%	Bacterial Infections: data not available
Goede, 2014 (Goede et al., 2014)	Prosepctive, Phase III	G–CLB or R–CLB vs CLB in TN CLL with comorbidities; 781 pts	11 %-14 % (grade ≥3)	Bacterial Infections: data not available. Most reported infections were of bacterial origin (data on rate not shown)
Burger, 2014 (Burger et al., 2014)	Prosepctive, Phase II	R- IBRU in High-risk CLL; 40 pts	13 % (grade ≥3)	Bacterial Infections: data not available. There were: two lung infections, one upper respiratory tract infection, one sepsis, and one mucositis.
Byrd, 2014 (Byrd et al., 2014)	Prosepctive, Phase III	IBRU vs O in R/R CLL/SLL; 391 pts	24 % vs 22 % (grade ≥3)	Bacterial Infections: data not available. There were: pneumonia, including Pseudomonas aeruginosa, Urinary tract infection, Cellulitis, Stenotrophomonas ae. infection and Sepsis
Strati, 2013 (Strati et al., 2013)	Retrospective	FCR frontline Total 207 pts : 72 cytopenic at 3 months, 45 cytopenic at 6 months and 24 cytopenic at 9 months	21 % (15/72) 22 % (10/45) 38 % (9/24)	This study compares pts with and without cytopenia after frontline FCR. Late infections were more common in patients who were cytopenic at 9 months (38 %) and were mostly bacterial (6 pts-67 %). No differences in infection rates were reported when patients who were cytopenic at any time were compared with patients who were noncytopenic at any time
Knauf, 2009 (Knauf et al., 2009)	Prosepctive, Phase III	Benda vs CLB in TN advanced CLL; 319 pts	8% vs 3%	Infections occurring during Benda treatment may be related to transient neutropenia, and are prevalently bacterial (data on rate not shown)
Tam, 2008 (Tam Constantine et al., 2008)	Prosepctive, Phase II	FCR frontline 224 pts	NA	The risk of late infection was 10 % and 4% for the first and second years of remission, respectively, and less than 1.5 % per year for the third year onward. From the third year predominantly bacterial infection (data on rate not shown)

Abbreviations: Pts: patients; **R:** Rituximab; **CLB:** chlorambucil; **Fluda**: Fludarabine; **Benda**: Bendamustine, **IBRU:** Ibrutinib; **Idela:** Idelalisib; **O** Ofatumumab; **G (GA101):** obinutuzumab; **FCR**: fludarabine, cyclophosphamide, and rituximab; **FC:** fludarabine, cyclophosphamide; **TN and R/R CLL:** treatment-naıve and relapsed/refractory chronic lymphocytic leukemia; **SLL:** small lymphocytic lymphoma **ALC:** absolute lymphocyte count.

HBsAg-positive patients with CLL and indolent lymphomas who receive treatments based on R or obinotuzumab, in association with bendamustine, fludarabine or cyclophosfamide should receive entecavir 0.5 mg/day or tenofovir 245 mg/day for at least 12 months after discontinuation of immunosuppressive therapy (Reddy et al., 2015), while lamivudine 100 mg/day is recommended in HBsAg negative/anti-HBc-positive patients (expert opinion) (41). A warning from EMA PRAC was issued in June 2017 for a risk of <1% for HBV reactivation in patients receiving ibrutinib. The recommendation is to monitor and manage according to local medical standards of care.

Finally, some cases of progressive multifocal leuco-encephalopathy (PML) caused by *JC* virus have been reported in CLL patients treated with BCR inhibitors (Reinwald et al., 2018). Clinicians should be aware of this severe viral complication, even though risk factors and treatment are not known so far.

A specific antiviral prophylaxis against CMV is not recommended in CLL patients treated with Fludarabine, bendamustine and rituximab. Due to the emergence of CMV infections in patients treated with idelalisib, there is a strong recommendation to monitor patients with a PCR-based diagnostic strategy for CMV reactivation.

5. Lymphomas

Conventional chemotherapy leading to profound neutropenia represents the risk factor for infectious complications in patients with lymphomas. Monoclonal antibodies, namely R, obinotuzumab and brentuximab-vedotin, alter immune response by modulating B-/T-cell interactions rather than directly affecting humoral immunity (Podhorecka et al., 2014). In addition, B-cell depletion exerts a deleterious impact on the induction, maintenance and activation of cell-mediated immunity (Nosari et al., 2014; Teng et al., 2015; Podhorecka et al., 2014). Table 4, reports the main studies analyzing infectious complications in patients receiving therapy for NHL and HL.

Table 3
Viral infections in Chronic Lymphocytic Leukemia (CLL).

Reference	Type of study	Arm and number of patients	CMV Infection rate	Comments
Demitrovicova, 2017 (Demitrovicova et al., 2017)	Retrospective	Fluda, ALZ, Bendamustine, BCRi 110 pts	8.14 %	Lower risk of infectious complications in patients treated with novel targeted agents
Jones, 2017	Randomized	Idela + Ofa *vs* Idela 201 pts	2%	Higher rate of infections in patients treated with Ofa + Idela including CMV
Ghiridhar et al., 2017	Case report	BCRi 2 pts	–	Disseminated VZV in two patients treated with BCRi (Idelalisib and Ibrutinib). None of these patients received antiviral prophylaxis
Sutton, 2016	Case report	None 1 pt	–	Disseminated VZV in a patient with severe hypogammaglobulinemia. No specific treatment for CLL
Chan, 2015	Retrospective	Fluda plus Rituximab 138 pts	3.6 % (CMV retinitis)	Five cases of CMV retinitis. Treatment was based both on intravitreal and systemic Ganciclovir and Foscarnet
Munõz, 2014	Retrospective	Rituximab plus Bendamustine 18 pts(*)	5.5 %	Once case of asymptomatic CMV reactivation detected by PCR
Freedberg, 2013	Case report	Fluda 1 pt	–	First case of visceral VZV infection in a patient with CLL treated with Fluda. No antiviral prophylaxis was given

Abbreviations: Pts: patients; **CMV:** Cytomegalovirus; **Fluda:** Fludarabine**; ALZ:** Alemtuzumab; **BCRi:** B-cell receptor inhibitors; **Idela:** Idelalisib; **Ofa:** Ofatumumab; **CLL:** chronic lymphocytic leukemia; **PCR:** polymerase-chain reaction; **VZV:** Varicella Zoster virus; **HSV:** Herpes simplex virus.

5.1. Bacterial infections

Bucaneve et al, and Cullen et al. (Bucaneve et al., 2005; Cullen et al., 2005) demonstrated in randomized, double blind studies including NHL patients, that antibacterial prophylaxis with levofloxacin was effective in reducing infection rate, but not mortality.

(Gafter-Gvili et al. (2016)) reported that 34.6 % of 153 NHL patients who received bendamustine developed infections, resulting in a higher mortality when compared to non-infected patients (22 % vs. 8%). Antibacterial prophylaxis policy was not reported.

Varughese et al. (Varughese et al., 2018) found a 7% rate of bacterial infections in patients treated with ibrutinib for B-cell NHL, mostly due to gram-positive bacteria (48 %): main risk factors were the number of prior therapeutic lines > 3 and neutropenia, occurring in 2% of NHL patients. In patients with refractory or relapsed follicular lymphoma, idelalisib was associated with a non-negligible incidence of fever (35 %), neutropenia (24 %) and upper respiratory infections (21.6 %), but a low rate of pneumonitis (3%) associated with a prevalence of gram-positive bacteria (Salles et al., 2017). The ESCMID 2018 guidelines do not recommend antibiotic prophylaxis in patients treated with ibrutinib or idelalisib (Reinwald et al., 2018).

Obinutuzumab seems to be associated with a higher incidence of febrile neutropenia and infections as compared to R (Byrd et al., 2014). Brentuximab-vedotin is associated to 55 % incidence of infections when combined with AVD (adriamycin, vinblastine and dacarbazine) regimen (Drgona et al., 2018; Connors et al., 2017) while the combination with bendamustine resulted in a 14 % rate of grade 3 lung infection and 25 % rate of grade 3–4 neutropenia (O'Connor et al., 2018). There are very few data about adaptive immunotherapy with CAR-T cells. Hill JA et al. evaluated 62 patients who received CAR-T cells for relapsed/refractory NHL, showing a 9.7 % incidence of bacterial infections, mostly gram-positive bacteria thereby supporting anti-gram positive prophylaxis with levofloxacin (Hill et al., 2018).

Bacterial prophylaxis should be tailored on an individual basis, considering multiple variables: type of disease (HL, NHL); biological characteristics (indolent vs aggressive); treatment strategy, including conventional chemotherapy with lymphodepleting agents, platinum-based regimens, dose escalated schedules, immunotherapy, number of previous lines of treatment. It should be underscored that antibacterial prophylaxis does not have a clearly demonstrated impact on attributable mortality to infection, while the issue of resistant strains selection is an emerging aspect. A new field of investigation is represented by patients who received adaptive immunotherapy with CD 19-targeted chimeric antigen receptor T cells (CAR-T), in whom prophylaxis with levofloxacin 750 mg/day is recommended in the case of ANC < 500/mm^3,.

5.2. Fungal infections

Several studies raised concern that the BTK inhibitor ibrutinib may increase the risk for IFI. In this respect, different mechanisms by which ibrunitib may favor the occurrence of IFI have been described, including impaired function of alveolar macrophage, neutrophil, T-cell, and platelets as well as alterations in the chemotaxis and cytokine environment. According to these findings, a recent study analyzing ibrutinib treatment for primary CNS lymphoma reported a 39 % rate of invasive aspergillosis in patients concurrently receiving steroids even in the absence of neutropenia, while others studies have reported a lower incidence of IFI around 3–4% (Carson et al., 2014). Conversely, the risk of IFI with the use of idelalisib, seems to be restricted to *PJP* only; accordingly, the ESCMID 2018 guidelines recommend prophylaxis for PJP until 2−6 months after discontinuation of idelalisib (Reinwald et al., 2018). Very few clinical data on IFI are available regarding patients treated with different strategies such as CD30-targeted agents and obinotuzumab. Preliminary data have been recently reported on adaptive immunotherapy with CAR-T cells (Hill et al., 2018). All categories of infectious complications initially occurred after a median of 6 days from CAR-T cell infusion; fungal infections were recorded in 4.8 % of NHL patients.

In the case of first-line antineoplastic therapy with R−CHOP or ABVD regimens no antifungal prophylaxis is recommended. In the case of further line of treatment TMP/SMX is recommended in patients with HL > 60 years old until 2−6 months after chemotherapy discontinuation, while Fluconazole is used in patients with NHL. Mold-active antifungal prophylaxis is not recommended in patients receiving ibrutinib or idelalisib (Wang et al., 2018). PJP prophylaxis is mandatory in patients treated with Brentuximab-vedotin (expert opinion) as consolidation or salvage therapy following ASCT, as well as in patients treated with idelalisib. Based on the preliminary results of the CAR-T cells studies, immunoglobulin repletion and antifungal prophylaxis are needed for these high-risk patients.

5.3. Viral infections

According to the 2015 guidelines of the American Gastroenterological Association (AGA) Institute, immunosuppressants are categorized into low-, moderate-, or high-risk groups based on estimates of HBV reactivation (HBVr) as per available evidence. Among patients with aggressive B lymphomas, the high-risk group (incidence of HBVr >10 %)

Table 4
Studies analyzing infections in patients with NHL.

FUNGAL INFECTIONS				
Reference	**Type of study**	**Arms and number of patients**	**Overall infection Rate**	**Comments**
Cytotoxic agent-based antineoplastic therapy				
Wongso, 2013 (Wongso et al., 2013)	Retrospective multicentric	3402 patients (advanced-stage classic HL) BEACOPP escalated	0.35 % (12/3402 cases) PJP, candidiasis, IA	TMP-SMZ in patients with HL > 60 years until 2–6 months after chemotherapy discontinuation
Takaoka, 2014 (Takaoka et al., 2014)	Retrospective monocentric	124 patients (refractory/relapsed NHL) Salvage therapy with ESHAP, VIM or MPV	12.9 % Proven/Probable IFI (16/124 cases)	Fluconazole 400 mg PO/IV daily
Tisi, 2017 (Tisi et al., 2017)	Retrospective monocentric	638 patients, NHL 450 (70.5 %), HL 188 (29.5 %)] R-CHOP, ABVD	2.5 % Proven/Probable IA (16/638 cases); 2.2 % in NHL; 3.2 % in HL	No prophylaxis recommended
Small-Molecule Inhibitors				
Varughese, 2018 (Varughese et al., 2018)	Retrospective	213 NHL; Ibrutinib	2.8 % (6/213 cases) IA 2 cases, PJP 2 cases, IA + PJP 1 case, cryptococcosis 1 case	
Cheah, 2016 (Cheah and Fowler, 2016)	Review	NA; Idelalisib	IFI <1%	PJP prophylaxis during treatment. Interrupt idelalisib when PJP is suspected and discontinue when confirmed
Engineering immune cells				
Hill, 2018 (Hill et al., 2018)	Open-label single-institution	62 NHL; CAR-T	4.8 % (3/62 cases)	Immunoglobulin repletion; antifungal prophylaxis for high-risk patients
BACTERIAL INFECTIONS				
Reference	**Type of study**	**Arms and No. patients**	**Rate of infection**	**Comments**
Cytotoxic agent-based antineoplastic therapy				
Dendle, 2017 (Dendle et al., 2017)	Retrospective Monocentric	325 DLBCL, R-CHOP	15.3 % (50/325) Gram-neg, 39 cases; Gram-pos, 11 cases	Recommend primary prophylaxis with G-CSF in patients older than 65 years and/or with comorbidities. No antibiotic prophylaxis is recommended
Gafter-Gvili, 2016 (Gafter-Gvili et al., 2016)	Retrospective multicentric	153 NHL, Bendamustine	7.8 % of BSI (12/153)	No antibiotic prophylaxis is recommended
Small-Molecule Inhibitors				
Salles., 2017 (Salles et al., 2017)	Retrospective monocentric	125 F L, Idelalisib	2.4 % (3/125 g-pos)	No antibiotic or GCSF prophylaxis is recommended
Varughese, 2018 (Varughese et al., 2018)	Retrospective monocentric	213 NHL, Ibrutinib	7% (14/213) Gram-pos, 7 cases; Gram-neg, 5 cases; Other, 2 cases	No antibiotic or G-CSF prophylaxis is recommended
Engineering immune cells				
Hill JA, 2018 (Hill et al., 2018)	Open-label single-institution	62 NHL CAR-T	9.7 % (6/62) Gram-pos, 3 cases; Gram-neg, 2 cases; Mycoplasma, 1 case	Prophylaxis with Levofloxacin 750 mg/die if ANC < 500/m^3
VIRAL INFECTIONS				
Reference	**Type of study**	**Arms and No. patients**	**Overall infection rate**	**Comments**
Cytotoxic agent-based antineoplastic therapy				
Reddy., 2015 (Reddy et al., 2015)	Guidelines	60 patients with DLBCL and HBsAg + in prophylaxis with lamivudine R-CHOP	30 % (18/60)	Prophylaxis with Entecavir 0.5 mg die for at least 6 months after discontinuation of immunosuppressive therapy.
Reddy., 2015 (Reddy et al., 2015)	Guidelines	39 patients with NHL and HBcAb + with no antiviral prophylaxis R-CHOP	18 % (7/39)	Prophylaxis with Entecavir 0.5 mg per os/ die for at least 6 months after discontinuation of immunosuppressive therapy
Chung, 2015 (Chung et al., 2015)	Guidelines	131 patients with LNH HCV+, R-CHOP, R-CEOP	27 % (36/131) 12.7 % (214/1677)	Treat HCV-infected patients with antiviral therapy with the goal of achieving SVR before chemotherapy

(*continued on next page*)

Table 4 (*continued*)

FUNGAL INFECTIONS				
Cho, 2015 (Cho et al., 2015)	Nation wide population-based study	1677 NHL, R-CHOP/ RCEOP		Prophylaxis against herpes zoster might be considered in pts undergoing immune-chemotherapy
Small molecules inhibitor				
Cheah, 2016 (Cheah and Fowler, 2016)	Review	NA Idelalisib	<1% CMV infection	If seropositive regular clinical or laboratory monitoring is mandatory. If symptomatic infection: stop idelalisib and preemptive ganciclovir.
Raisch D., 2016 (Raisch et al., 2016)	FDA's adverse event reporting system of PML. Case Report	NA Ibrutinib	0.35 % (10/2860 total AE per drug)	New-onset signs and symptoms of central nervous system abnormalities: Consultation with a neurologist, brain MRI, and lumbar puncture.
Engineering immune cell				
Hill, 2018 (Hill et al., 2018)	Prospective	133 Relapsed/Refractory CD19 + ALL, CLL, or NH CAR T Cell	9% (13/133) Rhinovirus: 4; Parainfluenza: 3 Influenza A: 1; Metapneumovirus: 1 Coronavirus: 1; CMV viremia:1 EBV viremia: 1; EBV in cerebrospinal fluid of unclear clinical significance, n = 1	Patients with greater immunosuppression and CAR-T cell associated toxicities had the highest risk for infection, identifying a targeted group to study improved prophylactic strategy.
Other agents targeting lymphoid cell surface antigens				
Gopal, 2012 (Gopal et al., 2012)	open-label, nonrandomized multicenter trials.	25 Relapsed HL CD30+ Brentuximab	0.2 % (5/25) CMV	Monitor periodically CMV viremia especially with a positive or unknown history of CMV serology or viremia.
Raisch, 2016 (Raisch et al., 2016)	FDA's adverse event reporting system of PML. Case Report	NA Obinutuzumab/ Brentuximab	Obinutuzumab: 3/655 total AE 0.46 % Brentuximab: 15/1017 total AE 1.47 %	New onset signs and symptoms of central nervous system abnormalities. Consultation with e neurologist, brain MRI and lumbar punction

Abbreviations: HL: Hodgkin Lymphoma; NHL: Non Hodgkin Lymphoma; DLBCL: Diffuse Large B Cell Lymphoma; FL: Follicular Lymphoma; ALL: Acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; CNS: Central Nervous System; IFI: Invasive fungal infection; IA: Invasive aspergillosis; TMP-SMZ: trimethoprim sulfamethoxazole.
PJP: Pneumocystis jiroveci pneumonia; R: Rituximab; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; R-CEOP: Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone;ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine; BEACOPP-escalated: Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone; ESHAP: Etoposide, Metilprednisolone, Cytarabine, Cisplatin; VIM: Etoposide, Ifosfamide, Methotrexate; MPV: Methotrexate, Procarbazine, Vincristine; CAR-T chimeric antigen T cell; G-CSF: granulocyte cell stimulating factor ; HBV: Hepatitis B virus; HCV: Hepatitis C virus; VZV: Varicella Zoster Virus; CMV: Cytomegalovirus; AE: adverse event; FDA: Food and Drug Association; EMA: European Medical Agency; PRAC: Pharmacovigilance Risk Assessment Committee; AE: adverse Event.

consists of the following: B cell depleting treatments in either HBsAg-positive and HBsAg-negative/anti-HBc–positive patients, anthracycline-based treatments in HBsAg-positive patients, and HBsAg-positive patients receiving prednisone at a dose >20 mg/day for 4 weeks. HBsAg-positive patients with lymphoma receiving anti-CD30 agents such as brentuximab are also included in the high-risk group. The moderate-risk group (incidence of HBVr 1–10 %) includes HBsAg-negative/anti-HBc-positive patients receiving prednisone at moderate- or high- dose and anthracycline derivatives. For the high-risk group with HBsAg positivity, antiviral prophylaxis (entecavir, 0.5 mg/day; or tenofovir disoproxil fumarate 245 mg/day) is recommended for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B cell–depleting agents) (Reddy et al., 2015). According to the European Association for the Study of the Liver (EASL) guidelines (version 2017) (EASL, 2017), lamivudine prophylaxis (100 mg/day) is preferred in HBsAg negative/anti-HBc-positive patients.

CMV reactivation is a possible complication in patients receiving brentuximab-vedotin therapy, especially if combined with bendamustine. In a prospective clinical trial in relapsed HL, CMV reactivation rate was 0.2 % and was potentially clinically significant in only 1 patient (O'Connor et al., 2018).

Fatal cases of JC virus infection resulting in PML have been reported for brentuximab treatment (1.47 % of total adverse events), and for obinotuzumab (0.49 % of total adverse events) (Carson et al., 2014; Raisch et al., 2016).

As regards to CAR-T cell, Hill et al. found that viral infections were extremely common, with 13 infections in 133 patients (*Rhinovirus*: 4 cases; *Parainfluenza*: 3; *Influenza A*: 1; *Metapneumovirus*: 1; *Coronavirus:* 1; CMV viremia: 1; EBV viremia: 1; EBV in cerebrospinal fluid of unclear clinical significance: 1), although the rate was similar to that of patients with relapsed/refractory B-cell lymphoma undergoing immune-chemotherapy (Hill et al., 2018). Patients treated with nivolumab and pembrolizumab for relapsed/refractory HL and NHL do not have an increased risk of viral infection (Redelman-Sidi et al., 2018).

Prophylaxis against VZV might be considered in patients receiving conventional chemotherapy (Expert opinion). We recommend for CMV seropositive patients in treatment with idelalisib to perform regular PCR monitoring of DNA (Expert opinion). Idelalisib should be discontinued and ganciclovir/valganciclovir preemptively initiated in patients with positive CMV PCR and symptoms consistent with CMV infection.

Any patient receiving brentuximab presenting new-onset signs and symptoms of CNS abnormalities should hold treatment for any suspected case of PML and discontinue if a diagnosis of PML is confirmed (neurologist consultation, brain MRI, and lumbar puncture recommended).

6. Multiple Myeloma (MM)

Over the last ten years, therapeutic options for patients with MM have largely increased. Nowadays, the use of new generation immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) in induction and maintenance of transplant eligible and ineligible patients have modified the natural history of the disease, as well as the introduction of monoclonal antibodies (MoAb) alone or in combination with IMiDs/PIs in patients with relapse/refractory (R/R) MM. Due to the humoral and cellular immune deficit, infections are among the leading causes of death in MM.

In 2015, a population-based study (Blimark et al., 2015) compared the risk of infection between patients with MM and sex-, age-, country residence-matched controls from total population registry; the authors reported an overall risk of infection 7 times higher in patients with MM, with a risk 11 times higher during the first year after diagnosis. Moreover, the risk of infection has increased 2.9-fold from 1988 to 1993 to 2000–2004, with a cumulative risk at 5 years growing from 14.4%–46%.

Two meta-analyses have been recently published, evaluating the impact of IMiDs or PIs on the development of infections in patients with MM at different phases of treatment (Chen et al., 2018; Teh et al., 2016). In newly diagnosed MM patients who were eligible for autologous stem cell transplantation (ASCT), the risk of severe infections during first line therapy with thalidomide was up to 14.8 %. Comparing patients treated with thalidomide versus lenalidomide, the incidence of severe infections was 11.7 % and 12.3 %, respectively, in transplant ineligible patients, and 10.7 % and 8.2 %, respectively, during maintenance. Among R/R patients, the highest incidence of severe infections was reported with pomalidomide (23 %). (Chen et al., 2018). Among patients treated with PI-based induction, the incidence of severe infection was 9.7 % and 19.7 % in transplant ineligible and eligible patients, respectively, and up to 23 % for all grade infections (Teh et al., 2016).

Two clinical trials investigated the role of ASCT in the setting of lenalidomide-based treatment. (Palumbo et al. (2014)), compared ASCT with melphalan-prednisone-lenalidomide (MPR) consolidation, showing a significant higher incidence of grade 3–4 infection in the ASCT arm compared with MPR arm (16.3 % *vs*0.8 %, p = 0.001). Similarly, (Attal et al. (2017)) reported a significant higher incidence of severe infections among transplant recipients compared to patients receiving lenalidomide, bortezomib and dexamethasone (VRD) as consolidation (20 % *vs* 9%). A recent retrospective study evaluated the incidence of infections in patients treated with daratumumab-containing regimens: the rate of infections ranged from 26 % to 56 % when daratumumab was used as single agent or combined with other agents (Johnsrud et al., 2020 e). Fig. 1 shows a schematic representation of anti-infective prophylaxis in patients with MM.

6.1. Bacterial infections

Bacteria were found to be the main agent responsible for infectious complications in several studies including patients with MM (Blimark et al., 2015; Teh et al., 2015). In a population-based study including 1154 patients diagnosed from 2010 to 2013 and treated with novel agents, the peak of incidence of bloodstream infections (BSI) was within the first 6 months from MM diagnosis and risk factors of BSI were markers for aggressive disease, namely ISS-III and high LDH (Sørrig et al., 2018). The early occurrence of BSI have been confirmed by other studies, showing an incidence of BSI of 11.7 % within 3 months from diagnosis of MM with the highest rate at 4–6 months from the diagnosis (Teh et al., 2015; Huang et al., 2017). In the FIRST trial comparing lenalidomide plus dexamethasone (Rd) continuous *vs* MPT or Rd18 in 1623 transplant-ineligible patients, the number of grade ≥ 3 infections/month was highest during the first 4 months of treatment. Moreover, 75 % of all grade ≥ 3 infections occurred in the absence of neutropenia and the development of early severe infections was an independent risk factor for death (Dumontet et al., 2018). Moreover, in patients with MM a near 8-fold increased risk (HR = 7.7) of developing bacterial pneumonia compared to matched controls (Redelman-Sidi et al., 2018) was reported.

The role of antibiotic prophylaxis in preventing the incidence of bacterial infections during MM treatment has been investigated in several studies (Oken et al., 1996; Vesole et al., 2012; Jung et al., 2014).

Oken et al. ((Oken et al., 1996)) compared a group of 28 patients randomly assigned to PJP prophylaxis with TMP-SMX for 2 months after the start of chemotherapy with a control group of 26 patients who did not receive any prophylaxis, documenting a significant lower rate of bacterial infection during the 3-month study period (2.43 per patient-year for controls *vs* 0.29 per patient-year for the TMP-SMX group). However, a further study of the same group comparing three groups of MM patients receiving initial chemotherapy randomized on a 1:1:1 basis to daily ciprofloxacin, TMP-SMX or no prophylaxis, failed to demonstrate any difference in incidence of serious bacterial infections during the first 2 months from induction chemotherapy (Vesole et al., 2012). More recently, (Jung et al. (2014)) analyzed the incidence of severe infections in a cohort of 80 MM patients receiving prophylaxis with levofloxacin after bortezomib-based regimens compared to an historical control group (n = 139) of patients who did not receive prophylaxis: the results of the study showed a significant decrease in the rate of severe infections in the prophylactic group (17.5 %) compared to the control group (30.9 %) (Ribera et al., 2016). Interestingly, a

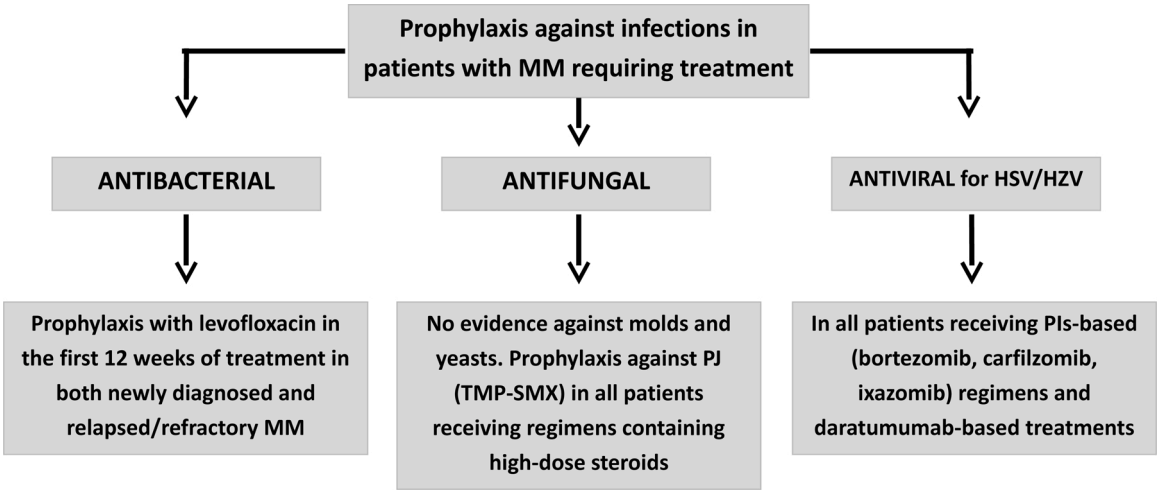

Fig. 1. Proposal of anti-infective prophylaxis in patients receiving treatment for Multiple Myeloma (MM).

randomized, double-blind, placebo-controlled multi-center phase III clinical trial assessing the benefits of prophylaxis with levofloxacin in 977 newly diagnosed MM patients (Tackling EArly Morbidity and Mortality in Myeloma, TEAMM), demonstrated that levofloxacin prophylaxis significantly reduced the rate of febrile episodes and deaths within the first 12 weeks of treatment, without significant difference between the 2 arms for carriage or infection with *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* and ESBL-producing Gram--negative bacteria (Drayson et al., 2017).

The role of intravenous immunoglobulin supplementation (IVIG) during induction or transplantation is not fully elucidated. Two randomized trials reported a significant benefit from infusion of IVIG on severe and life-threatening infections during chemotherapy (Chapel et al., 1994; Musto et al., 1995). A meta-analysis published in 2009 confirmed the protective role of IVIG in preventing severe infections (Raanani et al., 2009). On the other hand, two recent studies investigating the use of IVIG in the peri-transplant period failed to show a significant reduction of overall rate of infection in patients treated with IVIG compared to placebo (Blombery et al., 2011; Park et al., 2015).

The risk of infection in patients with MM is high regardless of neutropenia, especially in the first 3–4 months of induction therapy, and infection is still the number one cause of death for these patients particularly in older patients. Community acquired pneumonia are the most frequent clinically documented infections. FQ-based prophylaxis during the first 12 weeks of induction, particularly in older patients and in those with high burden of disease, is recommended, although definitive data are still lacking.

6.2. Fungal infections

Few studies evaluated the epidemiology of fungal infections in patients with MM. Kurosawa et al. reported an incidence of proven/probable IFI of 0.8 %, similar to the rate reported by Pagano et al. (0.5 %), while Huang et al. observed a remarkable higher incidence around 12 % (Kurosawa et al., 2012; Pagano et al., 2006b; Huang et al., 2009). The study by Teh et al. suggested a direct correlation between the number of therapy lines and the risk of IFI, which increases up to 15 % after three or more lines of treatment: the study did not show an increased incidence of IFI with the administration of pomalidomide, carfilzomib or monoclonal antibodies as elotuzumab and daratumumab (Johnsrud et al., 2020 e). MM patients, particularly those receiving high-dose corticosteroids, are at high risk of *P.jirovecii* pneumonia (PJP) (Mellinghoff et al., 2018). The literature reported some cases of PJP in patients receiving bortezomib suggesting that failure of host cell apoptosis caused by the PI may facilitate the infection (Swan and Reid, 2014).

The use of TMP-SMZ prophylaxis against P. jirovecii is mostly recommended among MM patients who receive high dose corticosteroids. There is currently no strong evidence to support PJP prophylaxis in patients with MM receiving PIs as single agent. Due to the low rate of invasive fungal infection in patients with MM, routinely antifungal prophylaxis is not recommended.

6.3. Viral infections

The introduction of bortezomib to standard therapies was associated to an increased risk of VZV infections from 4 to 22 % in randomized and retrospective clinical trials (RCT) (San Miguel et al., 2008; Chanan-Khan et al., 2008; Kim et al., 2008a). However, the introduction of antiviral prophylaxis reduced the incidence of VZV infections to less than 1% (Palumbo et al., 2010). In patients receiving lenalidomide-based regimens, particularly Rd, the incidence of VZV infection ranges from less than 1%–4% (Dumontet et al., 2018; Caravita et al., 2012) (Table 5). A recent observational prospective study described a VZV reactivation in 8.5 % of patients during induction therapy and 21.5 % after ASCT, peaking at 8 months from chemotherapy (Kamber et al., 2015). Patients receiving MoAb as elotuzumab and daratumumab in combination with IMIDs or PIs have a rate of VZV reactivation ranging from 2% to 5% even during antiviral prophylaxis.

Table 5
Summary of Key Points for antimicrobial prophylaxis in patients with lymphoproliferative diseases.

Acute lymphoblastic leukemia	FQ prophylaxis should be considered during induction/reinduction phase of treatment, although monitoring of bacterial epidemiology should be done, in order to detect early emerging antibiotic resistant strains Antifungal prophylaxis should be considered at least in patients receiving intensive regimen protocols and particularly in older patients.
Chronic lymphocytic leukemia	Patients receiving idelalisib should receive PJP prophylaxis as well as patients receiving fludarabine based chemotherapy There is a strong recommendation to carefully monitor patients receiving idelalisib, with a prospective PCR-based diagnostic strategy for CMV reactivation
Non-Hodgkin Lymphoma	PJP prophylaxis is recommended in patients >60 years until 2−6 months after chemotherapy discontinuation, in particular in patients treated with brentuximab-vedotin as consolidation or salvage therapy following stem cell transplantation
Multiple myeloma	FQ-based prophylaxis is recommended during the first 12 weeks of induction, particularly in older patients and in those with high burden of disease

Abbreviations: FQ: fluoroquinolones; **PJP**: *Pneumocystis jirovecii* pneumonia **CMV:** Cytomegalovirus;

Patients with MM are at high risk of CMV reactivation during the post ASCT period and during disease progression. Respiratory viral infections are common with the use of combination therapies and may occur throughout the year (Chen et al., 2018), especially in patients with progressive disease and those receiving more than 3 lines of therapy (The et al., 2015). MM patients should be screened for HBV serology and categorized into the high- or moderate- or low-risk score based on the type of serum positivity (Reddy et al., 2015). Patients HBsAg-positive receiving anthracycline and/or steroids should be treated with an anti-nucleoside at high genetic barrier (entecavir or tenofovir) for at least 6 months following antineoplastic treatment as prophylaxis, while HBsAg negative/anti-HBc-positive patients should receive lamivudine for at least 6 months. HBsAg-positive patients treated with bortezomib have a HBVr risk of 1–10 % (moderate-risk group) and require prophylaxis with lamivudine for at least 6 months after discontinuation of immunosuppressive therapy (EASL, 2017).

Acyclovir or valacyclovir prophylaxis is recommended to reduce viral-related morbidity and should be used during the treatment with PIs and after ASCT for 6–12 months after the end of the therapy. In the setting of multiple lines of therapy with associated CD4 lymphopenia, monitoring for CMV viremia should be considered.

7. Conclusions

Large studies are needed to assess the epidemiology of infectious complications in patients with lymphoproliferative diseases receiving targeted therapies. Based on these studies, we will be able to select patients who may benefit from anti-infective prophylaxis.

The role of FQ prophylaxis in patients with lymphoproliferative diseases receiving high-dose immuno-chemotherapy is still a matter of debate and prospective randomized trials seem to be necessary to assess whether the potential beneficial effect of prophylaxis is offset by the emergence of MDR bacteria.

Mold active antifungal prophylaxis is not routinely indicated in patients with lymphoproliferative disorders except for patients receiving intensive chemotherapy regimens for the treatment of ALL. PJP prophylaxis is indicated in patients with lymphoproliferative disorders.

Table 6 summarizes the closing remarks.

Declaration of Competing Interest

A.B. has received honoraria from Gilead Sciences, MSD, Pfizer Pharmaceuticals and Jazz Pharmaceuticals; he has been speaker for Gilead Sciences, Merck, Pfizer Pharmaceuticals and Novartis; he is part of an Advisory Board of GILEAD and Pfizer; M.O. Has received honoraria from Celgene, Janssen, Amgen, BMS, Takeda; A.C. Has received honoraria from Celgene, Janssen, Gilead, Pfizer and MSD; M.D. Has received honoraria from Gilead, Pfizer and MSD; N. F. Has received honoraria from Gilead, Pfizer, MSD and Amgen; M. M. is part of an Advisory Board of Biotest; F. M. Has received honoraria from MSD; he is part of an Advisory Board of Sandoz and Pfizer; L.P. was Board member of Gilead Science, MSD, Pfizer, Basilea, Janssen, Novartis,Cidara and has been speaker for Gilead Sciences, MSD, Pfizer Pharmaceuticals, Astellas Pharma. C.C., E.D.C., G.N., M.P., E.C., M.C., R.D.P., I.D.P.,R.F., F.F., C. G., M.P., L.P., A.M.Q., A.S., M.C.T., F.T., E.M. T., P.Z., declared nothing to disclose.

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