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Infection control in patients treated for chronic lymphocytic leukemia with ibrutinib or idelalisib: recommendations from Italian society of hematology

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ABSTRACT

The introduction of new therapeutic agents in chronic lymphocytic leukemia (CLL), including the new kinase inhibitors (KIs) ibrutinib and idelalisib, has changed the therapeutic landscape of the disease. The new KIs have also changed frequency and epidemiology of infections, that represent a major cause of morbidity and mortality of the disease. Hence, the great strides in the indications and use of new KIs need parallel amelioration of prophylaxis and supportive treatment for infections. Moving from the recognition that infection control represents an unmet need, the Italian Society of Hematology (SIE) convened a panel of experts who had published and/or expressed an interest in infection complications in CLL. The goal of the project was to provide practice recommendations for the management of the infectious complications of CLL during ibrutinib or idelalisib therapy. The present publication represents the results of a series of email correspondences and meetings held during 2017 and 2018. Three domains of infectious complications during KIs therapy for CLL were explored: risk assessment, risk management and risk monitoring. We hope these recommendations will help to minimize infectious adverse events, and we believe that an optimal management of them will be rewarded by better outcomes, and better quality of life.

1. Introduction

Advances in the understanding of B cell receptor (BCR) signaling and its role in promoting B cell survival and proliferation have highlighted new targets for the treatment of chronic lymphocytic leukemia (CLL). Ibrutinib is a first in class Bruton's tyrosine kinase inhibitor (KI) that was approved by US Food and Drug Administration (FDA) for relapsed CLL in February 2014, for high-risk CLL with 17p deletion in July 2014, and for first-line treatment in March 2016. Ibrutinib is indicated in Europe for the treatment of adult patients with previously untreated CLL as a single agent; who have received at least one prior therapy as a single agent or in combination with bendamustine and rituximab; relapsed or refractory mantle cell lymphoma and patients with Waldenstrom macroglobulinemia (WM) who have received at least one prior therapy, or in first-line treatment for WM patients unsuitable for chemo-immunotherapy. Idelalisib is a first in class inhibitor of PIK3-delta, another component of the BCR signaling pathway: it was approved by FDA in 2014 for the treatment of relapsed CLL in combination with rituximab (IR). European Medicines Agency (EMA) granted IR marketing authorization also for the upfront treatment CLL patients in the presence of 17p deletion or TP53 mutation, provided that they are unsuitable to chemoimmunotherapy.

Infections are a major cause of morbidity and mortality in patients with CLL. In a cohort of patients with newly diagnosed CLL, major infections occurred at a 20.3/100 person-year rate and opportunistic micro-organism caused 15% of the reported infections [1].In a registry-based study, severe infections prior to treatment of CLL had a five-year cumulative incidence of 31% among 2905 CLL patients [2].

Both ibrutinib and idelalisib affect critical components of the immune system, as proved by the increased infection burden reported in

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Table 1
Rate of grade 3 or higher infections from phase 3 randomised clinical trials in CLL patients treated with ibrutinib.

Author, year (n. reference)	Characteristics of the study	N. of patients	Rate of most common infections, %	Comments
Byrd, 2014 [13]	ibrutinib vs ofatumomab in previously treated patients; RESONATE Study. 70 years of age or older, median age, 67 years.	Ibrutinib, 195 patients Ofatumumab, 191 patients	Pneumonia, 7% Upper respiratory infections, 1% Urinary tract infection, 4% Sinusitis 1% Pneumonia, 5% Upper respiratory infections, 2% Urinary tract infection, 1%	Infections of any grade were more common in the ibrutinib group (70% vs. 54%), whereas the frequency of infections of grade 3 or higher was similar in the two study groups (24% vs. 22%).However, treatment exposure was longer among patients receiving ibrutinib than among those receiving ofatumumab
Chanan-Khan, 2016 [14] Fraser, 2018 [15]	Ibrutinib-bendamustine-rituximab vs placebo-bendamustine-rituximab in previously treated patients; HELIOS Study. 18 years of age or older, median age, 64 years.	Ibrutinib-bendamustine-rituximab, 287 patients Placebo-bendamustine-rituximab, 287 patients	Pneumonia, 8% Upper respiratory infections, 2 %Febrile neutropenia, 12% Pneumonia, 7% Febrile neutropenia, 9%	The frequency of infections was similar between the ibrutinib and placebo groups (all-grade 70% vs 70%; grade ≥3: 29% vs 25%). The exposure adjusted incidence of infections was lower in the ibrutinib group than in the placebo group (10.3 vs 11.2 per 100 patient-months), with similar incidence of grade 3 or worse infections (2.4 per 100 patient-months in each group).
Huang, 2018 [16]	ibrutinib vs rituximab in previously treated patients. 21 years of age or older, median age, 66 years.	Ibrutinib, 104 patients Rituximab, 52 patients	Pneumonia, 16.3% Upper respiratory infections, 6.7 % Pneumonia, 9.6% Upper respiratory infections, 1.9 %	Any grade Infections were reported in 68.3% of patients in the ibrutinib arm and 40.4% of patients in the rituximab arm. Unspecified lung infections (20.2% in the ibrutinib arm and 11.5% in the rituximab arm) were the most frequently reported in both treatment arms.
Burger, 2015 [17]	First line therapy, ibrutinib vs chlorambucil; RESONATE 2 Study. 65 years of age or older, median age, 73 years.	Ibrutinib, 135 patients Chlorambucil, 132 patients	Pneumonia, 4% Febrile neutropenia, 2% Cellulitis, 2% Upper respiratory infections, 2% Pneumonia, 2% Febrile neutropenia, 2% Upper respiratory infection, 2%	Although early discontinuation of treatment due to adverse events was more than twice as frequent with chlorambucil as with ibrutinib, no significant difference in the rate and severity of infections was observed in the two groups. However, treatment exposure was longer among patients receiving ibrutinib than among those receivingchlorambucil

patients with hereditary mutations of both Bruton's tyrosine kinase and PIK3-delta [3–5]. For these reasons, the risk of infection in patients treated with the new KIs is higher than the overall risk reported in CLL population. Hence, the great strides in the indications and use of new treatments for CLL need parallel progress in the best approach to prophylaxis and supportive treatment for infections.

In view of these considerations, the Italian Society of Hematology (SIE) convened a panel of experts to exploit a project aimed to provide guidelines for the management of the infectious complications during treatment with new KIs in CLL. The present publication represents a consensus document from a series of meetings and email correspondence held during 2017 and 2018.

2. Design and methods

Two chairmen (ST and GB) appointed a Panel of 7 experts (hereafter called the Panel), selected for their expertise in research and clinical practice of CLL. A clinician with expertise in clinical epidemiology (GB) assured the methodological consistency of the project. During an initial meeting, the Panel agreed on the areas of major concern in the risk of infections in CLL by generating and rank-ordering clinical key-questions using the criterion of clinical relevance, i.e. impact on the management of patients and risk of inappropriateness, through a Delphi process [6]. The five candidate key-questions that ranked highest formed the set of questions of the present document. During a second meeting, the Panel examined the current state of knowledge regarding infections and CLL. Then, each panelist drafted statements that addressed one or more of the preliminarily identified key questions. Subsequently, each panelist scored his agreement with the statements made by other panelists and provided suggestions for rephrasing. For exploiting this phase of the process, the Panel was convened and two consensus conferences were held in Bologna, Italy. The overall goals of the meetings were to reach a definite consensus over question-specific statement. The nominal group technique was used by which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote [7]. If an at least 80% consensus on the statement was not achieved, the choices were discussed and a second vote taken. If an 80% consensus was still not attained, the issue was declared undecidable, and no further attempt was made.

3. Results

3.1. Infections in patients receiving ibrutinib for CLL

Evidence supporting a potential for infectious complications by ibrutinib and idelalisib has been provided mostly by clinical trials.

In a phase-2, open label, multicenter study, ibrutinib was administered to 144 patients with relapsed or refractory CLL with 17p deletion (RESONATE-17) [8]. Overall, the most frequent grade > 3 infections were pneumonia (14.5%) and urinary tract infection (5%). Out of 22 patients who discontinued treatment owing to adverse events (excluding clinical progression) in 7 cases it was caused by an infection.

In a recent analysis of a three-year follow-up of 132 patients with CLL and small lymphocytic lymphoma (SLL) treated with ibrutinib, the rate of overall infectious side effects and rate of ≥grade 3 infections was up to 51% in relapsed/refractory patients as compared to 13% in treatment naïve patients [9]. The difference in the two groups was observed for pneumonia (25% vs 6%), sepsis (7% vs 0%), cellulitis (5% vs 0%), sinusitis (5% vs 0%), and bacteremia (4% vs 0%).

In the extended follow-up of the RESONATE study, the longer-term safety profile of ibrutinib was consistent with the 3-year follow-up from the phase 2 study [10]. The most common (> 10%) infections included upper respiratory tract infections (25% any grade, 0.5% grade ⩾3), sinusitis (19% any grade, 0.5% grade ⩾3), pneumonia (17% any grade, 12% grade ⩾3), and urinary tract infections (14% any grade, 4% grade ⩾3). Nineteen patients (10%) in the ibrutinib arm had received

prophylactic growth factor support, and 131 patients (67%) had received some form of anti-infective prophylaxis. In this relapsed CLL population, the rate of new infection, appeared lower later in follow-up when compared with the first 6 months, consistent with a recent report of long-term follow-up with ibrutinib at the Ohio State University, in which patients who discontinued for reasons other than progression did so relatively early, followed by a plateau [11].

Evidence that the frequency of infections decreases on continuous therapy was also provided by long-term therapy with ibrutinib in patients with TP53 aberration or age 65 years or older enrolled in an investigator-initiated phase 2 study [12]. Infection of any grade occurred in 24 (27.9%) patients and infection grade 3 or higher in 9.3%. Notably, the overall frequency of infections decreased with time receiving therapy, suggesting improvements in immune function.

Epidemiological data on grade $\geq$3 infections from large phase 3 clinical trials in CLL patients treated with ibrutinib are detailed in Table 1 [13–17].

Some real life clinical series of CLL patients who received ibrutinib as first- line or salvage therapy and with detailed data on infectious complications have been recently published. Grade $\geq$3 infections reported in the real life occurred at rates similar to those reported in the RESONATE trials, i.e. 22% out of 110 patients enrolled in a Named Patient Program [18]. In a well-defined regional cohort of CLL patients, forty-two (63.6%) of the 66 patients treated with ibrutinib experienced at least one infection during or after ibrutinib treatment [19]. An intra-patient comparison of infection risk conducted for the 47 patients receiving salvage ibrutinib after chemoimmunotherapy showed a significant 135% increased risk of a major infection during their time on ibrutinib versus previous chemoimmunotherapy. The risk of infection in CLL patients remains high even with use of less immunosuppressive therapies.

The spectrum of serious infections in 378 patients with lymphoid malignancies who received ibrutinib from 2012 to 2016 at the Memorial Sloan Kettering Cancer Center was retrospectively reviewed [20]. Out of 165 patients affected by CLL, ibrutinib was administered as single drug in 96% of cases and as second-line therapy in 67% of cases (after fludarabine, rituximab or alemtuzumab). Only a minority of patients received antimicrobial prophylaxis during ibrutinib treatment. Overall 20 of 165 (12.1%) patients developed a severe infection generally during the first year of treatment (fungal, bacterial and viral infection in 10, 9 and 1 cases, respectively). Receipt of at least three prior anti-tumor regimens, and the presence of neutropenia at any time point during the course of ibrutinib were significantly associated with increased risk of severe infection. The use of corticosteroids at any time of ibrutinib treatment was a risk factor associated with the development of an invasive fungal disease (IFD).

A single-institution retrospective study was conducted to determine the incidence and type of opportunistic infections (OI) during ibrutinib treatment as well as outcomes and characteristics associated with risk [21]. In 566 patients treated with ibrutinib from June 2010 to March 2016 (being 74% of patients affected by CLL) the cumulative incidence of OI was 2.3% at 0.5 years and increased to 4.7% at 5 years. IFDs (mainly invasive aspergillosis) accounted for 74% of OI. In a multivariable analysis $\geq$3 prior treatments (HR 2.87, 95% CI: 1.12–7.35), diabetes (HR 3.63, 95% CI: 1.50–8.77), and liver disease (HR 7.53, 95% CI: 2.14–26.49) retained independent association with OI development.

A multicenter survey aimed at identifying cases of IFD in ibrutinib treated CLL patients was conducted in France [22]. Out of 33 IFDs, 27 were proven, probable or possible invasive aspergillosis with cerebral localization in 40% of cases. The remaining infections were cryptococcosis (4 cases), mucormycosis (one case) and *Pneumocystis jirovecii* pneumonia (PJP) (one case). Remarkably, 85% of IFD occurred in the first six months after starting ibrutinib and 61% occurred in the first 3 months. This suggests that risk for IFD may decrease with longer exposure to ibrutinib. In most cases, other conditions that could have contributed to decreased antifungal responses, such as corticosteroids, neutropenia, or combined immune-chemotherapy, were present.

3.2. Infections in patients receiving idelalisib for CLL

For idelalisib, the initial phase 1 study for CLL patients reported serious adverse events with $\geqslant$ grade 3 pneumonia occurring in 20% and additionally febrile neutropenia and bacteremia occurring in 5.6% and 9.3% of patients, respectively, with even fatal clinical course [23]. Yet, it has to be kept in mind that patients had previously received intensive treatment regimens such as purine analogues or alemtuzumab prior to idelalisib.

In an analysis which sought to explore the contribution of changes in immunoglobulins and normal B cells on the risk of infection from a phase 2 trial [24], at a median follow-up of 27.8 months, infections were more frequent during the first 6 months with an average rate of 16.3 infections per 100 patient-months compared with 6.9 thereafter. Respiratory tract infections were the most common (65%), followed by gastrointestinal or genitourinary (16%) and skin (13%) infections. Patients with relapsed/refractory CLL had more infections of any grade than previously untreated patients (risk ratio, 1.58). Prior treatment was also associated with a higher rate of grade $\geq$3 infections (risk ratio, 2.23) [25].

The combination of idelalisib and rituximab in newly diagnosed CLL patients reported pneumonia in 28% of patients, with 19% classified as serious adverse events and also infection-related fatalities [26].

Epidemiological data on grade $\geq$3 infections from large phase 3 clinical trials in CLL patients treated with idelalisib are detailed in Table 2 [27–29].

Since the completion of these studies, new safety data have emerged showing an increased incidence of opportunistic infection and death in other randomised phase 3 studies (including a study of idelalisib in combination with bendamustine plus rituximab in frontline CLL, GILEAD 312-0123/NCT01980888). These findings have led by US Food and Drug Administration (FDA) to mandatory prophylaxis for *P. jirovecii* pneumonia and monitoring for cytomegalovirus infection during treatment with idelalisib.

3.3. Pre-therapy assessment of infectious risk

Information useful to be taken before the initiation of ibrutinib or idelalisib therapy in CLL patients are directed to those infective agents that usually persist lifelong in the host after primary infection and can be reactivated under certain conditions, like tuberculosis (TB), hepatitis B and C viruses, and herpes virus family.

Even though only few cases of TB infection/reactivation have been reported in patients undergoing ibrutinib or idelalisib therapy [30–32], targeted screening and treatment of latent tuberculosis infection (LTBI) is an important strategy for patients at high risk of developing active TB [33]. A recent meta-analysis showed that patients with hematologic cancer have a 9-fold higher rate of developing active TB compared to those without cancer and would benefit from targeted LTBI screening and therapy [34].

There is few information pertaining to the incidence of hepatitis B virus (HBV) infection and the risk of HBV reactivation in CLL patients receiving new KIs. To our knowledge, published studies do not reveal the possible role of ibrutinib as a trigger of HBV reactivation and there is only one case reporting an occult HBV flare during KIs treatment [35]. In a single center experience, seven CLL patients with a hepatitis B positive serology (HBsAg neg/HBcAb positive) treated with ibrutinib did not receive any antiviral prophylaxis and were closely monitored for HBsAg and HBV DNA. After a median follow-up of 25 months, none of the patients showed a HBV reactivation [36]. In most idelalisib clinical trials, patients with active HBV infections were excluded while patients with serologic evidence of prior exposure but with negative DNA testing were eligible. In these studies, no HBV reactivation was mentioned, even though no information on the use of antiviral

Table 2
Rate of grade 3 or higher infections from phase 3 randomised clinical trials in CLL patients treated with idelalisib.

Author, year (n. reference)	Characteristics of the study	N. of patients	Rate of most common infections, %	Comments
Furman, 2014 [27]	Idelalisib plus rituximab vs. rituximab plus placebo. Patients with relapsed CLL, with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses.	Idelalisib plus rituximab, 110 patients Rituximab plus placebo, 110 patients	Pneumonia, 6% Sepsis, 4% Pneumocystis jiroveci pneumonia, 3% Pneumonia, 8% Sepsis, 3% Pneumocystis jiroveci pneumonia, 1%	The follow-up of this study was a median of 3.8 months in the idelalisib group, and 2.9 months in the placebo group.
Zelenetz, 2017 [28]	Bendamustine plus rituximab plus idelalisib vs. bendamustine plus rituximab plus placebo. Patients with relapsed or refractory CLL	Bendamustine, rituximab, idelalisib, 207 patients Bendamustine, rituximab, placebo, 209 patients	All grade infections and infestations, 39% All grade infections and infestations, 25%	The duration of exposure to therapy was longer in the idelalisib group. Infection related deaths occurred in 6 patients in the chemo-immunotherapy-idelalisib group, versus 3 patients in the chemoimmunotherapy group.
Jones, 2017 [29]	Idelalisib plus ofatumumab vs. ofatumumab alone in patients with relapsed CLL progressing less than 24 months from last therapy	Idelalisib plus ofatumumab, 174 patients Ofatumumab alone, 87 patients	Pneumonia, 13% Sepsis, 7% Pneumonia, 10%	Treatment related deaths occurred in 22 versus 6 patients and were almost infection-related.

prophylaxis was available.

Reactivation of chronic hepatitis B in hematologic patients undergoing immunosuppressive or antineoplastic treatment approximately occurs in 20–50% of HBsAg-positive patients and 1–10% in HBsAg-negative/HBcAb-positive patients. In all patients about to receive treatment for malignant disease, HBV screening is recommended in order to plan a prophylaxis strategy or a laboratory monitoring of sero-reversion and/or viremic rebound, and the subsequent introduction of pre-emptive therapy [37].

Three cases of disseminated zoster in patients on ibrutinib and idelalisib were reported [38]. Two cases included visceral involvement, manifesting as pancreatitis, gastritis, and hepatitis. In the phase 3 trial that led to FDA approval of idelalisib with rituximab in relapsed CLL, no cases of herpes zoster were reported [39].

Recommendations

The history of previous infectious complications and treatments should be carefully collected in patients with CLL candidate to ibrutinib or idelalisib treatment.

The Panel agreed on recommending screening with IFN-γ-release assays (IGRAs) or tuberculin skin testing (TST) or a combined TST-IGRA testing to detect LTBI in all CLL patients prior to ibrutinib or idelalisib treatment in high tuberculosis (TB) prevalence regions.

In low TB prevalence regions screening is recommended in persons with a suspected history of TB infection, in those who come from high TB prevalence regions, and in those who have other conditions that are associated with an increased risk for TB infection.

All patients with a new diagnosis of CLL and candidate to ibrutinib or idelalisib therapy should undergo HBV screening with the following exams: HBsAg, anti-HBc, anti-HBs; HBV DNA if HBsAg or anti-HBc detected. All patients with a new diagnosis of CLL should undergo HCV screening with the following exams: anti-HCV and HCV RNA if anti-HCV positive.

3.4. Infection control before treatment with ibrutinib or idelalisib

In clinical trials of CLL patients receiving ibrutinib or idelalisib treatment, ongoing active, serious infection requiring systemic therapy, and active B or C hepatitis were generally considered exclusion criteria. Consequently, few information is specifically available on the infectious conditions which may contraindicate treatment with KIs. While waiting for the results of real life experience, precautions already used in other patients with comparable immune system impairment were considered.

Recommendations

In patients candidate to ibrutinib or idelalisib therapy and evidence of ongoing bacterial, fungal or viral disease, the treatment should be delayed and started after an appropriate control of the infectious disease. All HBV-DNA positive patients should be referred to an infectious or hepatic disease expert.

Active HBV infection (HBV-DNA positive and HBsAg positive) is not a contraindication to ibrutinib or idelalisib therapy provided that appropriate antiviral treatment, in association to strict viral monitoring, is administered under the supervision of an infectious or hepatic disease expert.

In patients with a positive screening for TB, CLL treatment delay and anti-TB treatment should be considered under the supervision of an infectious disease expert.

3.5. Antibacterial, antiviral and anti-fungal prophylaxis

Several issues should be considered in the definition of an antimicrobial prophylaxis strategy in patients candidate to treatment with ibrutinib or idelalisib. Both ibrutinib and idelalisib are substrates of the CYP3A4 enzyme and, due to important drug-drug interactions, co-administration of CYP3A4 inhibitors may be contraindicated. In particular co-administration of fluoroquinolones, macrolids and certain antifungal triazoles may significantly increase ibrutinib levels with possible

increase of toxicity [40]. Co-administration of CYP3A4 inducers (i.e. rifampin) is contraindicated. Both drugs are generally administered for a prolonged period until time of progression, therefore the risk of infection should be calculated over time and the cost-effectiveness of a prolonged antimicrobial prophylaxis considered accordingly.

Although lower respiratory tract was the most common site of infection in patients treated with ibrutinib or idelalisib, only few data are available on the etiology of such infections and there is very few information on the indication and efficacy of antibacterial and antifungal prophylaxis [41]. EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the committee that is responsible for assessing all aspects of the risk management of medicines for human use, recommends that all patients treated with idelalisib should receive antibiotics to prevent *P.jirovecii* pneumonia (PJP). This is a provisional recommendation which the PRAC has issued, as a precaution, to protect patients while the medicine is being reviewed.

PJP was usually reported in less than 1% of patients receiving ibrutinib [42]. Only one report documented 5 cases out of 96 treated patients [43]. It was highlighted that four of the five cases had previously untreated CLL. This seems to indicate that the infectious risk was not related to prior therapies. Moreover, there is documentation that the reported rate of PJP is much lower in patients receiving ibrutinib to treat other hematological malignancies [44,45]. This was interpreted as indicating that the risk of infection is related to immunosuppression from the underlying disease or the concomitant treatment as opposed to the drug itself. However, three phase 3 clinical trials assessing the addition of idelalisib to standard therapies in first-line treatment of relapsed indolent non-Hodgkin lymphoma or CLL, reported an unexpected high rate of serious adverse events and increased mortality. In these studies the combined percentage of deaths in the idelalisib arm was 7.4% compared to 3.5% in the placebo arm. The excess of deaths were mainly associated to infections, namely PJP and human cytomegalovirus (HCMV) related disease [45]. Moreover, 31 cases of PJP were reported in 5 randomised trials in frontline CLL and early-line indolent non-Hodgkin lymphoma [46]. Such data were confirmed by a systematic review of 2,198 patients (including CLL patients) treated with idelalisib (and rituximab in CLL cases) in 8 comparative and non-comparative clinical trials recently reported PJP infection in 2.5% of patients on idelalisib +/- co-therapy versus 0.2% of patients receiving anti-CD20 mAb or brentuximab (relative risk 12.5). The median time to a PJP event was 141 days since initiation of idelalisib [47]. Prophylaxis of PJP reduced the incidence of infection to 1.3% (versus 3.4% not receiving prophylaxis).

Recommendations

Neither antibacterial prophylaxis nor prophylaxis against molds and yeasts is recommended during treatment with ibrutinib or idelalisib.

Co-trimoxazole prophylaxis against P.jirovecii is recommended during treatment with idelalisib; prophylactic treatment should be continued for up to 2–6 months after therapy discontinuation.

P.jirovecii prophylaxis is not generally recommended during treatment with ibrutinib. However, the Panel argued that patients receiving immunosuppressive drugs are at high risk of P.jirovecii infection: thus, anti P.jirovecii prophylaxis should be considered during treatment with ibrutinib when the drug is associated with anti-CD20 and/or steroid therapy.

These are provisional recommendations until more detailed epidemiological data will be available.

Anti varicella zoster virus (VZV) or herpes simplex virus (HSV) prophylaxis is not recommended during ibrutinib or idelalisib treatment; however, a suppressive therapy with acyclovir or valacyclovir should be considered in patients with a history of recurrent VZV or HSV disease in the last 12 months.

HBsAg-positive or HBV-DNA positive CLL patients receiving ibrutinib or idelalisib, should be always considered at high-risk of HBV reactivation and should be treated with tenofovir or entecavir under the supervision of an infectious or hepatic disease expert.

HBsAg-negative/HBcAb-positive CLL patients receiving ibrutinib or idelalisib alone are at low risk of HBV reactivation and antiviral prophylaxis is not recommended but monitoring of sero-reversion and/or viremic rebound should be considered.

HBsAg-negative/HBcAb-positive CLL patients receiving ibrutinib or idelalisib in association with anti CD-20 immunotherapy or chemotherapy should be considered at risk of HBV reactivation and lamivudine prophylaxis is recommended.

Antiviral prophylaxis should be initiated prior (at least 1 week) or in concomitance with starting immunosuppressive treatment and should be continued for the duration and up to 6 months after discontinuation of treatment.

Antiviral treatment should be considered for HCV RNA positive patients as soon as possible after the successful treatment of the hematological malignancy under the supervision of an infectious disease expert.

3.6. Intravenous immunoglobulin replacement therapy

The effects on immunoglobulin levels of ibrutinib and idelalisib is still unclear. In a phase 2 study with 40 patients with symptomatic high-risk CLL who received 420 mg of ibrutinib associated with rituximab once daily for 18 months, no significant changes in IgG or IgA levels were found, although a statistically insignificant decrease in IgM levels was noted [48]. Conversely, another phase 2 study followed 86 patients with CLL who received ibrutinib for at least 1 year and found that IgG levels decreased significantly with prolonged treatment (23% median decrease at 2 years) but that IgA levels generally increased (64% median increase) [25].

Although routine intravenous immunoglobulin replacement therapy (IRT) is not recommended for CLL, a case report demonstrated that IRT can be a valuable treatment option to improve the quality of life and allow continued treatment for patients with CLL on ibrutinib [49].

Recommendations

There is no strong evidence on benefit of intravenous immunoglobulin replacement therapy in CLL patients under treatment with either ibrutinib or idelalisib. However, by highlighting a report from literature and the experts' individual experience, the Panel argued that immunoglobulin therapy is indicated in CLL patients treated with ibrutinib or idealisib when hypogammaglobulinemia is severe (IgG < 400 mg/dL) and there is a history of serious bacterial infections.

Treatment should be started with 400 mg/kg IV every 3–4 months or 100 mg/kg SC weekly.

Monitoring serum Ig levels should be done every four weeks to adjust the immunoglobulin dosing.

3.7. Antiviral or antibacterial vaccination

One study of influenza vaccination in 19 patients on single agent ibrutinib found that 26% had seroconversion to at least one vaccine strain [50]. Another study looking at 13 relapsed CLL patients on ibrutinib for median 7.5 months found no responders to influenza vaccine [51]. A similar study of 13-valent pneumococcal conjugate vaccination (PCV-13) found that all four untreated patients responded, while none of the four ibrutinib patients did [52].

Recommendations

In patients having not received pneumococcal vaccination at the onset of the hematological disease and already on ibrutinib or idelalisib treatment the response to vaccination is expected to be low. Nevertheless, considering the safety and the low costs of the vaccination practice, the Panel agreed that the cost-benefit ratio is in favor of vaccination and suggests in any case to administer the vaccines even after the start of ibrutinib and idelalisib treatment. Patients should receive the 13-valent conjugate vaccine (PVC-13) followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) after 8 weeks.

Vaccination against seasonal influenza is broadly recommended in

CLL patients candidate to ibrutinib or idelalisib therapy given the severity of the H1N1 pandemia, and the highly severe influenza impact respect to general population, despite poor responses in CLL even with two doses regimen. The evidence of poor response during the therapy advices to refrain from vaccination during therapy.

A recombinant, adjuvated VZV vaccine (Shingrix) has been evaluated in patients submitted to autologous stem cell transplant and in HIV positive subjects with promising results. However, no data are available in subjects on immunosuppressive therapy, including CLL patients. Consequently, to date no recommendation could be made regarding the use of this vaccine in patients treated with idelalisib or ibrutinib.

3.8. Monitoring the risk of infection

In the phase 3 clinical trials assessing the addition of idelalisib to standard therapies in first-line treatment of CLL and relapsed indolent non-Hodgkin lymphoma, an unexpected high-rate of serious adverse events and increased mortality was reported. The excess of deaths were mainly associated to infections, namely PJP and CMV-related disease. However, more epidemiological and clinical data from real-life experiences are required to better define the clinical implications of CMV DNAemia detection in this population.

Recommendations

In patients under treatment with idelalisib, a monthly molecular monitoring of cytomegalovirus (CMV) DNAemia should be performed when CD4 + T cells are less than 50, and when there is a previous of CMV infection.

In patients with evidence of CMV reactivation (positive CMV DNAemia without signs of end organ disease) idelalisib treatment should be halted and antiviral preemptive treatment (ganciclovir or foscarnet) considered.

It is not possible to define the cut-off of DNAemia to indicate the start of antiviral therapy.

Monitoring of liver function tests and HCV RNA or HBV DNA is recommended in HCV-of HBV-infected patients receiving ibrutinib or idelalisib treatment.

4. Discussion

In this article, experts in CLL judged whether the body of evidence was sufficient to provide recommendations regarding the infection control in patients candidate to new KIs therapy. The lack of randomised clinical trials testing infection screening and prophylaxis, that now represent uncertainties in the infectious disease management, has forced the Panel to use the methods of consensus for shaping the recommendations of this work.

Other recently issued reports providing guidance on how to optimize outcome with novel mechanism-based treatment [53,54], highlighted that a number of issues with treatment-emergent adverse events require further investigation. As a matter of fact, the incidence, timing, and prognosis of infectious complications with these drugs should be prospectively explored. Nevertheless, it is unlikely that ad hoc prospective trials will be designed and performed to specifically address the risk of infections and to define the most appropriate prophylaxis for treating them. Therefore, epidemiologic investigation are most advisable and successful examples of such an approach have been provided by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) in the setting of patients undergoing allogeneic and autologous stem cell transplantation [55,56].

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Disclosure

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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References

[1] J. Moreira, K.G. Rabe, J.R. Cerhan, et al., Infectious complications among individuals with clinical monoclonal B-cell lymphocytosis (MBL): a cohort study of newly diagnosed cases compared to controls, Leukemia 27 (1) (2013) 136–141.
[2] M.A. Andersen, C.T. Eriksen, C. Brieghel, et al., Incidence and predictors of infection among patients prior to treatment of chronic lymphocytic leukemia: a Danish nationwide cohort study, Haematologica 103 (7) (2018) e300–e303.
[3] J.A. Winkelstein, M.C. Marino, H.M. Lederman, et al., X-linked agammaglobulinemia: report on a United States registry of 201 patients, Medicine (Baltimore) 85 (4) (2006) 193–202.
[4] S. Xie, M. Chen, B. Yan, X. He, X. Chen, D. Li, Identification of a role for the PI3K/AKT/mTOR signaling pathway in innate immune cells, PLoS One 9 (4) (2014) e94496.
[5] A. Charalambous, M.A. Schwarzbich, M. Witzens-Harig, A. Charalambous, M.A. Schwarzbich, M. Witzens-Harig, Recent Results Cancer Res 212 (2018) 133–168.
[6] P.L. Williams, C. Webb, The delphi technique: a methodological discussion, J. Adv. Nurs. 19 (1) (1994) 180–186.
[7] S.S. McMillan, F. Kelly, A. Sav, et al., Using the nominal group technique: how to analyse across multiple groups, Health Serv. Outcomes Res. Methodol. 14 (3) (2014) 92–108.
[8] S. O'Brien, J.A. Jones, S.E. Coutre, et al., Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study, Lancet Oncol. 17 (10) (2016) 1409–1418.
[9] J.C. Byrd, R.R. Furman, S.E. Coutre, et al., Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib, Blood 125 (16) (2015) 2497–2506.
[10] J.R. Brown, P. Hillmen, S. O'Brien, et al., Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL, Leukemia 32 (1) (2018) 83–91.
[11] K.J. Maddocks, A.S. Ruppert, G. Lozanski, et al., Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia, JAMA Oncol. 1 (1) (2015) 80–87.

[12] I.E. Ahn, M.Z.H. Farooqui, X. Tian, et al., Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study, Blood 131 (21) (2018) 2357–2366.
[13] J.C. Byrd, J.R. Brown, S. O'Brien, et al., Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia, N. Engl. J. Med. 371 (3) (2014) 213–223.
[14] A. Chanan-Khan, P. Cramer, F. Demirkan, et al., Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): arandomised, double-blind, phase 3 study, Lancet Oncol. 17 (2) (2016) 200–211.
[15] G. Fraser, P. Cramer, F. Demirkan, et al., Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma, Leukemia 33 (4) (2019) 969–980.
[16] X. Huang, L. Qiu, J. Jin, et al., Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study, Cancer Med. 7 (4) (2018) 1043–1055.
[17] J.A. Burger, A. Tedeschi, P.M. Barr, et al., Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia, N. Engl. J. Med. 373 (25) (2015) 2425–2437.
[18] F.R. Mauro, A. Tedeschi, A. Piciocchi, et al., Outcome of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and/or 17p Deletion/TP53 mutations treated with ibrutinib according to a Named Patient Program (NPP) in Italy: preliminary analysis of a real life retrospective study, Blood 128 (2016) 2038.
[19] A.M. Williams, A.M. Baran, P.J. Meacham, et al., Analysis of the risk of infection in patients with chronic lymphocytic leukemia in the era of novel therapies, Leuk. Lymphoma 59 (3) (2018) 625–632.
[20] T. Varughese, Y. Taur, N. Cohen, et al., Serious infections in patients receiving ibrutinib for treatment of lymphoid malignancies, Clin. Infect. Dis. 67 (5) (2018) 687–692.
[21] K.A. Rogers, M. Luay, Q. Zhao, et al., Incidence and type of opportunistic infections during ibrutinib treatment at a single academic center, Blood 130 (2017) 830.
[22] D. Ghez, A. Calleja, C. Protin, et al., Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib, Blood 131 (17) (2018) 1955–1959.
[23] J.R. Brown, J.C. Byrd, S.E. Coutre, et al., Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia, Blood 123 (22) (2014) 3390–3397.
[24] M.Z. Farooqui, J. Valdez, S. Martyr, et al., Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial, Lancet Oncol. 16 (2) (2015) 169–176.
[25] C. Sun, X. Tian, Y.S. Lee, et al., Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib, Blood 126 (19) (2015) 2213–2219.
[26] S.M. O'Brien, N. Lamanna, T.J. Kipps, et al., A phase 2 study of idelalisib plus rituximab in treatment-naïve older patients with chronic lymphocytic leukemia, Blood 126 (25) (2015) 2686–2694.
[27] R.R. Furman, J.P. Sharman, S.E. Coutre, et al., Idelalisib and rituximab in relapsed chronic lymphocytic leukemia, N. Engl. J. Med. 370 (11) (2014) 997–1007.
[28] A.D. Zelenetz, J.C. Barrientos, J.R. Brown, et al., Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial, Lancet Oncol. 18 (3) (2017) 297–311.
[29] J.A. Jones, T. Robak, J.R. Brown, et al., Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial, Lancet Haematol. 4 (3) (2017) e114–e126.
[30] J.A. Hammel, G.M. Roth, N. Ferguson, J.A. Fairley, Lower extremity ecchymotic nodules in a patient being treated with ibrutinib for chronic lymphocytic leukemia, JAAD Case Rep. 3 (3) (2017) 178–179.
[31] S.Y. Wang, T. Ebert, N. Jaekel, S. Schubert, D. Niederwieser, H.K. Al-Ali, Miliary tuberculosis after initiation of ibrutinib in chronic lymphocytic leukemia, Ann Hematol 94 (8) (2015) 1419–1420.
[32] B. Lafon-Desmurs, G. Monsel, V. Leblond, et al., Sequential disseminated aspergillosis and pulmonary tuberculosis in a patient treated by idelalisib for chronic lymphocytic leukemia, Med. Mal. Infect. 47 (4) (2017) 293–296.
[33] G.H. Mazurek, J. Jereb, A. Vernon, P. LoBue, S. Goldberg, K. Castro, IGRA expert committee; centers for disease control and prevention (CDC). Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection - United States, 2010, MMWR Recomm. Rep. 59 (RR-5) (2010) 1–25.
[34] M.P. Cheng, C.N. Abou Chakra, C.P. Yansouni, et al., Risk of active tuberculosis in patients with cancer: a systematic review and meta-analysis, Clin. Infect. Dis. 64 (5) (2017) 635–644.
[35] P. De Jesus Ngoma, B. Kabamba, G. Dahlqvist, et al., Occult HBV reactivation induced by ibrutinib treatment: a case report, Acta Gastroenterol. Belg. 78 (4) (2015) 424–426.
[36] A. Tedeschi, A.M. Frustaci, M. Mazzucchelli, R. Cairoli, M. Montillo, Is HBV prophylaxis required during CLL treatment with ibrutinib? Leuk. Lymphoma. 58 (12) (2017) 2966–2968.
[37] V. Mallet, F. van Bömmel, C. Doerig, et al., Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation: recommendations of the 5th European conference on infections in leukaemia (ECIL-5), Lancet Infect. Dis. 16 (5) (2016) 606–617.
[38] K.V. Giridhar, T. Shanafelt, P.K. Tosh, S.A. Parikh, T.G. Call, Disseminated herpes zoster in chronic lymphocytic leukemia (CLL) patients treated with B-cell receptor pathway inhibitors, Leuk. Lymphoma 58 (8) (2017) 1973–1976.
[39] R.R. Furman, J.P. Sharman, S.E. Coutre, et al., Idelalisib and rituximab in relapsed chronic lymphocytic leukemia, N. Engl. J. Med. 370 (11) (2014) 997–1007.
[40] L. de Zwart, J. Snoeys, J. De Jong, J. Sukbuntherng, E. Mannaert, M. Monshouwer, Ibrutinib dosing strategies based on interaction potential of CYP3A4 perpetrators using physiologically based pharmacokinetic modeling, Clin. Pharmacol. Ther. 100 (5) (2016) 548–557.
[41] G. Chamilos, M.S. Lionakis, D.P. Kontoyiannis, Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways, Clin. Infect. Dis. 66 (1) (2018) 140–148.
[42] R. Lee, A. Nayernama, S.C. Jones, T. Wroblewski, P.E. Waldron, Ibrutinib-associated pneumocystis jirovecii pneumonia, Am J. Hematol. 92 (11) (2017) E646–48.
[43] I.E. Ahn, T. Jerussi, M. Farooqui, X. Tian, A. Wiestner, J. Gea-Banacloche, Atypical pneumocystis jirovecii pneumonia in previously untreated patients with CLL on single-agent ibrutinib, Blood 128 (15) (2016) 1940–1943.
[44] M.P. Cheng, A.E. Kusztos, J.N. Gustine, et al., Low risk of pneumocystis jirovecii pneumonia and invasive aspergillosis in patients with waldenström macroglobulinaemia on ibrutinib, Br. J. Haematol. (November (20)) (2018) [Epub ahead of print].
[45] C.Y. Cheah, N.H. Fowler, Idelalisib in the management of lymphoma, Blood 128 (3) (2016) 331–336.
[46] J.P. Sharman, G.A. Salles, W. Jurczak, et al., Temporal profiles of lymphocyte subsets and the correlation with infectious events in idelalisib-treated patients, Blood 128 (2016) 5583.
[47] L.H. Sehn, M. Hallek, W. Jurkzak, et al., A retrospective analysis of pneumocystis jirovecii pneumonia infection in patients receiving idelalisib in clinical trials, Blood 128 (2016) 3705.
[48] J.A. Burger, M.J. Keating, W.G. Wierda, et al., Ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study, Lancet Oncol. 15 (10) (2014) 1090–1099.
[49] F. Jiang, P. Verma, Management of hypogammaglobulinemia and recurrent infections in a chronic lymphocytic leukemia patient receiving ibrutinib, Ann Allergy Asthma Immunol. 120 (3) (2018) 324–325.
[50] C. Sun, J. Gao, L. Couzens, et al., Seasonal influenza vaccination in patients with chronic lymphocytic leukemia treated with ibrutinib, JAMA Oncol. 2 (12) (2016) 1656–1657.
[51] A.P. Douglas, J.A. Trubiano, I. Barr, V.K. Leung, M.A. Slavin, C.S. Tam, Ibrutinib may impair serological responses to influenza vaccination, Haematologica 102 (10) (2017) e397–e399.
[52] B. Andrick, A. Alwhaibi, D. deRemer, et al., Lack of adequate pneumococcal vaccination response in chronic lymphocytic leukaemia patients receiving ibrutinib, Br. J. Haematol. 182 (5) (2018) 712–714.
[53] M. Reinwald, J.T. Silva, N.J. Mueller, et al., ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (intracellular signaling pathways: tyrosine kinase and mTOR inhibitors), Clin. Microbiol. Infect. 24 (Suppl. 2) (2018) S53–S70.
[54] L.G. Rubin, M.J. Levin, P. Ljungman, et al., 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host, Clin. Infect. Dis. 58 (3) (2014) 309–318.
[55] C. Girmenia, A.M. Raiola, A. Piciocchi, et al., Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the gruppo italiano trapianto midollo osseo (GITMO), Biol Blood Marrow Transplant. 20 (6) (2014) 872–880.
[56] C. Girmenia, A. Bertaina, A. Piciocchi, et al., Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey, Clin. Infect. Dis. 65 (11) (2017) 1884–1896.