Diagnosis and Treatment of Chronic Lymphocytic Leukemia: Recommendations of the French CLL Study Group (FILO)

Anne Quinquenel1,2, Thérèse Aurran-Schleinitz3, Aline Clavert4, Florence Cymbalista5,6,7, Caroline Dartgea8, Frédéric Davi9, Sophie de Guibert10, Alain Delmer1,2, Marie-Sarah Dilhuydy11, Pierre Feugier12, Luc-Matthieu Fornecker13,14, David Ghez15, Romain Guieze16, Kamel Laribi17, Véronique Leblond9, Stéphane Leprêtre18, Rémi Letestu5,6,7, Vincent Lévy5,7, Florence Nguyen-Khoa9, Anne-Sophie Michallet19, Cécile Tomowiak20, Olivier Tournilhac16, Loïc Ysebaert21, Xavier Troussard22, on the behalf of the FILO-LLC Group

Correspondence: Anne Quinquenel (e-mail: aquinquenel@chu-reims.fr).

Abstract
As a result of significant recent developments, the management of patients with chronic lymphocytic leukemia (CLL) is changing, and new therapeutic options will continue to emerge in the near future. The recommendations of the French Innovative Leukemia Organization (FILO-CLL) group presented here are intended to provide practical recommendations for physicians taking care of CLL patients, taking into account the availability of both biological tests and therapies in daily practice in France at the time of publication. This text details the documented information and guidelines on diagnosis, indications for treatment, infectious complications and therapeutic strategies in frontline and relapsed CLL as well as in particular conditions such as autoimmune cytopenia or Richter syndrome.

Definition
Chronic lymphocytic leukaemia (CLL), a recognized entity in the WHO/WHO 2016 classification of haematopoietic and lymphoid tissues and in ICDO-3 (9823/3), is defined by the accumulation of small lymphocytes with clumped chromatin in the blood, marrow and secondary lymphoid organs.1 The diagnosis of CLL relies on blood smear examination and the presence of more than 5 × 10^7/L clonal B lymphocytes with a characteristic immunophenotypic profile.2 The presence of less than 5 × 10^7/L clonal B lymphocytes defines monoclonal B lymphocytosis (MBL) (9823/1), a mandatory step that precedes the onset of CLL.1,3

1Centre Hospitalier Universitaire (CHU) de Reims, Hôpital Robert Debré, Reims, France
2Université Reims Champagne-Ardenne, unité de Formation et de recherche (UFR) Médecine, Reims, France
3Institut Pauli Calmettes, Marseille, France
4CHU d’Angers, Angers, France
5Groupe des Hôpitaux Universitaires Paris Seine Saint-Denis (GHUPSSD), Assistance Publique Hôpitaux de Paris (AP-HP), Bobigny, France
6Unité Mixte de recherche (UMR) U978 INSERM, Bobigny, France
7Université Paris 13, UFR Santé Médecine Biologie Humaine (SMBH), Bobigny, France
8CHU de Tours, Tours, France
9Sorbonne Université, Hôpital de la Pitié-Salpêtrière, AP-HP, Paris, France
10CHU de Rennes, France
11CHU de Bordeaux, Pessac, France
12CHU Nancy, Vandœuvre les Nancy, France
13Institut de Cancérologie de Strasbourg Europe, Strasbourg, France
14INSERM S-113, Strasbourg, France
15Institut Gustave Roussy, Villejuif, France
16CHU de Clermont Ferrand, Clermont-Ferrand, France
17Centre Hospitalier du Mans, Le Mans, France
18Inserm U1245 and Department of Hematology, Centre Henri Becquerel and Normandie Univ UNIROUEN, Rouen, France
19Centre Leon Bérard, Lyon, France
20CHU de Poitiers, Poitiers, France
21Institut Universitaire du Cancer de Toulouse (IUCT) – Oncopole, Toulouse, France
22CHU de Caen Normandie, Caen, France

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
HemaSphere (2020) 4:5(e473). http://dx.doi.org/10.1097/HS9.0000000000000473.
Received: 22 April 2020 / Accepted: 24 July 2020
Epidemiology

In 2018, the estimated number of new incident cases of CLL in France was 4674. The male predominance is marked, with 59.3% of CLL cases identified in men (2770 patients) and 40.7% of cases identified in women (1904 patients). The median age at diagnosis is 71 years in men and 73 years in women. The standardized incidence rate for the world population is 4.1/100,000 person-years (PY) for males and 2.1 for females. US studies show ethnic variations, with the highest incidence among non-Hispanic Caucasians and the lowest among Asians. The risk of developing CLL is significantly higher in the patients with a family history of CLL (the relative risk is 8.5 times higher in the offspring of patients with CLL). A national registry records all family cases. The risk of secondary cancers is increased in patients with CLL. This risk is mainly observed for cancers related to tobacco exposure (lung cancers), skin cancers, and Merkel cell carcinoma.

Diagnosis

Persistent lymphocytosis (higher than 4 × 10^9/L) for more than 3 months requires a blood smear and lymphocyte immunophenotyping. The presence on the blood smear of an excess of small mature lymphocytes and smudge cells is suggestive. The description of less than 10% of prolymphocytes and/or cleaved lymphocytes should not affect the diagnosis of CLL. A prolymphocyte level of greater than 55% (of lymphoid cells) suggests the diagnosis of prolymphocytic leukemia.

Immunophenotyping of blood lymphocytes is mandatory to assess clonality and to determine the number of CD19(+), CD5(+), CD23(+) B lymphocytes. The Royal Marsden Hospital (RMH) or Matutes score is still commonly used in France, but some other markers such as CD200 have an increasing importance (Table 1). If the RMH score is ≥ 4, the diagnosis of CLL is supported. If the score is lower than 3, the diagnosis of CLL is not supported. For patients presenting with a CD5 and CD23 positive RMH score 3; the positivity of additional markers such as CD200 (low), CD43(+) and CD200 (bright) supports the diagnosis of CLL in the absence of t(11;14) or (q13;q32) translocation (or the expression of cyclin D1). The diagnosis of CLL requires neither a bone marrow infiltration nor a lymph node biopsy, and these tests must be avoided in typical CLL cases (RMH score of 4 or 5). Lymph node infiltration by small lymphocytes with a CLL phenotype in the absence of hyperlymphocytosis higher than 5 × 10^9/L leads to the diagnosis of small lymphocytic lymphoma (SLL). Blood lymphocyte immunophenotyping often reveals the presence of a small CLL circulating clone.

In the presence of a clone at a level lower than 5 × 10^9/L with an immunophenotypic profile identical to that observed in CLL and the absence of bone marrow failure or peripheral lymphadenopathy, the diagnosis of MBL should be made.

Evaluation at diagnosis

A prior history of infection, autoimmune disease or familial hematological malignancy must be determined. A physical examination to identify the general signs; presence, number and size of superficial lymphadenopathies; hepatomegaly; splenomegaly; and tonsil hypertrophy is mandatory.

The following are the required blood tests:
- Complete blood count with reticulocyte count;
- Serum protein electrophoresis;
- Direct Coombs test (or direct antiglobulin test); and
- LDH and beta-2 microglobulin levels.

In the absence of criteria for treatment initiation, initial staging does not require imaging.

The CLL should then be classified according to Binet classification system. In this classification system, deep lymphoid areas and the mechanism of cytopenia (central or peripheral) are not taken into account. The Rai classification is less commonly used in Europe.

For patients not needing treatment, the analysis of biological prognostic factors is not recommended at this stage. However, the following easily available markers reflecting proliferation are useful when assessing the risk of evolution: lymphocyte doubling time (LDT), beta-2-microglobulin, LDH levels and CD38 expression.

Indications for treatment

Patients with progressive Binet stage A or B and patients with Binet stage C should receive a specific treatment. The appearance of anemia in a stable stage A patient requires questioning the aetiology of the anemia (either bone marrow failure, autoimmune hemolytic anemia or non-CLL-related anaemia such as iron deficiency) before attributing it to CLL progression.

The progression criteria have been defined by the IWCLL and are represented by:
- Progressive bone marrow failure with the development or aggravation of anemia and/or thrombocytopenia. The thresholds usually considered for the initiation of specific therapy are a hemoglobin level lower than 100 g/L or a platelet level lower than 100 × 10^9/L. Nevertheless, some patients considered to be in Binet stage C due to moderate thrombocytopenia may remain stable and asymptomatic for a long period of time without treatment. In this case, the evolution of cytopenia over time should be taken into account before deciding to start treatment.
- Massive or progressive or symptomatic splenomegaly.
- Significantly enlarged or symptomatic or progressive lymphadenopathies.
- Progressive lymphocytosis, with an increase of more than 50% over a period of 2 months or a LDT of less than 6 months. In patients with an initial lymphocyte count < 30 × 10^9/L, LDT alone should not be used as a single parameter to decide treatment initiation and should be interpreted in the overall clinical context.

### Table 1

**Recommended Markers for the Diagnosis of CLL.**

| Minimally Recommended (ERIC Recommendations and RMH Scoring) | Other Important Markers |
|-------------------------------------------------------------|-------------------------|
| CD19, CD5, Ig light chains kappa & lambda (membrane staining) | CD200, CD23, CD20, CD79b, and/or CD22 (for RMH scoring) |
| CD79b and/or CD22 (for RMH scoring) | CD20, CD56, CD10 |
| FMC7 (for RMH scoring) | |
Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapies.

- The presence of constitutive symptoms as defined by one or more of the following signs or symptoms related to the disease:
  - Unintentional weight loss of 10% or more in the previous 6 months,
  - Significant fatigue (ECOG PS 2 or worse; inability to perform usual activities),
  - Fever over 38.0°C for 2 weeks or more without signs of infection, and
  - Night sweats lasting more than a month with no sign of infection.

In patients for whom abstention is recommended, clinical and biological evaluations should be performed at least every 6 to 12 months. No imaging workup should be performed routinely.

**Chronic lymphocytic leukemia and the risk of infection**

The prevention of infectious complications remains a major challenge in the management of CLL patients. The risk of infection affects all stages of CLL, and it is estimated that at least one-third of CLL patient deaths are related to infection.

**Vaccination**

The vaccination strategy applies to all patients with CLL. The vaccination program must be initiated as early as possible in the course of the disease, ideally before starting specific treatment, to increase the effectiveness of the vaccine response.

The recommended vaccines are as follows:

- Annual influenza vaccination.
- Pneumococcal vaccine: 13-valent pneumococcal conjugate vaccine (PREVENAR 13®) followed at least 8 weeks later by a 23-valent polysaccharide vaccine (PNEUMOVAX®). A further injection with PNEUMOVAX® is proposed 5 years after the initial vaccination.
- *Haemophilus influenzae* vaccination: ACT-HIB (R) 1 injection.

Live attenuated vaccines are contraindicated. However, such vaccines may be considered in certain situations on a case-by-case basis after having considered the risk of vaccination and the risk of the infectious disease.

**Antibiotic prophylaxis**

CLL patients have a higher risk of community-acquired infections that are mainly bacterial infections of the respiratory tract, urinary tract and skin. The primary responsible pathogens are *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes*, and *Escherichia coli*. Primary prophylaxis with antibiotics is a widely used strategy in some countries, even if evidence is lacking. Azithromycin (250mg × 3/week) appears to be relatively commonly prescribed to patients with bronchiectasis. To limit drug interactions, azithromycin may be substituted for spiramycin in patients on ibrutinib.

Moreover, specific CLL treatment may favor the onset of opportunistic infections. The risk of infection depends on the type of treatment and increases with the number of therapeutic lines. Table 2 summarizes the prophylactic measures stratified by CLL treatment.

**Supplementation with polyvalent immunoglobulins**

In CLL, the use of polyvalent immunoglobulins (Ig) has been common practice for several decades and is based on a trial published in 1988 (Ig vs placebo) showing a lower frequency of bacterial infections in treated patients but no effect on viral or fungal infections. Because of the recurrent shortage of polyvalent Ig, the French Health Agency edited their recommendations. The prescription of polyvalent Ig should be restricted to patients with recurrent infections leading to hospitalization and IgG levels lower than 4g/L. IVIG should be administered every 3 to 4 weeks (every week or twice a month if subcutaneous). IgG level may help dose adjustment, with a goal of 6g/L which may not supplant clinical evaluation.

**Pre-treatment assessment**

In addition to complete a clinical evaluation and the standard blood tests, which are detailed in Table 3, performing a CT scan to evaluate the presence of lymphadenopathies is recommended by the FILO-CLL, contrary to the IWCLL guidelines, where it is reserved to patients included in clinical trials. Indeed, some patients may present with small peripheral lymphadenopathies but massive abdominal mass and being aware of bulky disease is important, especially for patients receiving venetoclax.

Specific tests are also essential to stratify patients, which is necessary to define the best strategy for each patient. Specific assessments that are required prior to the initiation of targeted therapies are presented in Table 4.

**Cytogenetics**

Assessing for 17p deletion by FISH is mandatory for defining the therapeutic strategy. The other cytogenetic tests can be...
### French Recommendations for CLL Management

**Pre-treatment Evaluation.**

| Clinical evaluation                                   | Mandatory | Recommended |
|-------------------------------------------------------|-----------|-------------|
| ECOG PS                                               | X         |             |
| Constitutive symptoms                                 | X         |             |
| Number and size of lymphadenopathies                  | X         |             |
| Hepatomegaly and/or splenomegaly                      | X         |             |
| Tonsil hypertrophy                                    | X         |             |
| Skin evaluation and biopsy if suspicious skin lesion   | X         |             |
| Oncoangiogenic examination for frail elderly patients  | X         |             |

**Biological standard tests**

- Complete blood count and reticulocyte count X
- LDH, haptoglobin and direct antiglobulin test X
- Blood group (if not known) X
- Serum creatinine level and glomerular filtration rate X
- Transaminases, bilirubin, gamma-GT X
- LDH and beta-2 microglobulin X
- Serum protein electrophoresis X
- HIV, B and C hepatitis serology X
- Cryopreservation of blood cells (tumour library) X

**Cytogenetics**

- Karyotype X
- FISH X
- 17p deletion X
- 11q deletion X
- 13q deletion X
- Trisomy 12 X

**Molecular biology**

- IGHV mutational status X
- TP53 mutations by NGS X

**Imaging**

- CT scan of chest, abdomen and pelvis X

### Table 3

| Clinical evaluation | Mandatory | Recommended |
|---------------------|-----------|-------------|
| ECOG PS             | X         |             |
| Constitutive symptoms | X       |             |
| Number and size of lymphadenopathies                  | X         |             |
| Hepatomegaly and/or splenomegaly                      | X         |             |
| Tonsil hypertrophy                                    | X         |             |
| Skin evaluation and biopsy if suspicious skin lesion   | X         |             |
| Oncoangiogenic examination for frail elderly patients  | X         |             |

### Somatic mutations of the immunoglobulin heavy chain gene (IGHV)

Until recently, this test was only indicated in clinical trials but is now being performed to facilitate patient stratification and have prognostic implications.

- **Karyotyping (blood):** Karyotyping is recommended but not mandatory for management. Stimulation protocols for metaphase induction based on immunostimulatory cytosine guanine dinucleotide (CpG)-oligonucleotide DSP30 and interleukin 2 must be performed. Evidences suggested that complex karyotype (CK) defined by the presence of ≥ 3 chromosomal aberrations may be considered as a predictive factor, even in patients receiving targeted therapies. More recently, high-CK has been defined by the presence of ≥ 5 chromosomal aberrations, and high CK emerges as a stronger predictive factor, independently of the presence of TP53 alterations.\(^{15}\)

- **FISH (blood):** Identify the following aberrations: 11q deletion (del11q), 13q deletion (del13q) and trisomy 12 (tri12).\(^{16}\)

Testing for the 11q (ATM) deletion is highly recommended because it has prognostic implications.

**TP53 mutations**

This test is mandatory before any treatment. At least half of patients with a TP53 mutation do not have a 17p deletion and for these patients, abnormality of TP53 cannot be identified by FISH.\(^{24,25}\) The presence of a significant TP53 alteration is a contraindication to CIT and an indication for the use of targeted therapy. In the ERIC (European Research Initiative on CLL) guidelines published in 2018, a threshold of 10% is recommended, which is the detection limit of Sanger sequencing.\(^{26}\) Next-generation sequencing (NGS) rapidly spreading use is currently leading to reconsider this threshold. NGS is widely available in France in certified laboratories and is now considered as the technique of choice, and allows the reliable detection of smaller clones. Recent data have strongly suggested that minor TP53-mutated clones are clinically relevant and therefore, the FILO-CLL advises that any confirmed clone should be reported to the clinician.

**Other recurrent mutations**

Other recurrent mutations in CLL have prognostic and even theragnostic impacts. For example, the presence of a NOTCH1 mutation implies rituximab resistance.\(^{27}\) Nevertheless, the detection of these mutations is not recommended at this time outside the context of clinical trials.

### First-line treatment

Therapeutic strategies in CLL are currently changing, with a significant reduction of the indications for CIT. The development of targeted therapies as led to the emergence of new sides effects, which had to be learned to manage. Specific recommendations for patients receiving these molecules are summarized in Table 4. Treatment options may differ among countries, depending on drug reimbursements and medical practice. Inclusion in a clinical trial should be proposed whenever possible. Assessment for TP53 alteration (17p deletion and TP53 mutation) is essential, as it contraindicates the prescription of CIT. The recommendations of the FILO group for frontline therapy are summarized in Figure 1.

### In the absence of TP53 inactivation

The first selection criterion is based on fludarabine eligibility, which is usually defined by an age below 65 to 70 years, the absence of significant comorbidities (CIRS score < 6) and adequate renal function (GFR > 60 mL/min).

Analysis of the IGHV mutation status is also required. Indeed, while several trials have demonstrated a superiority of the new
### Table 4
**Targeted Therapies – Recommendations for Use.**

#### Ibrutinib – recommendations for use

| Pre-treatment assessment | Medical history, medications, scheduled dental or surgical operations |
|--------------------------|---------------------------------------------------------------|
|                          | Medication reconciliation (CYP3A4 or PgP interactions)       |
|                          | Cardiac evaluation: mandatory electrocardiogram for all patients, echography and Holter ECG in elderly patients or in case of cardiac history |
|                          | HBV and HCV serologies                                       |
| Absolute contraindications<sup>a</sup> | Heart failure according to cardiological opinion |
| At-risk situations relative contraindications<sup>a</sup> | Atrial fibrillation |
|                         | Vitamin K antagonists (VKA) → prefer direct oral anticoagulants (DOA) |
|                         | Anti-platelet treatment AND VKA or DOA                      |
|                         | Platelets < 30 × 10⁹/L                                     |
|                         | Concomitant treatment with corticosteroids                  |
|                         | History of invasive fungal infection                        |
|                         | Cured or active hepatitis B                                 |

#### Prophylaxis

- Pneumocystis and zoster prophylaxis
- No international consensus on systematic prophylaxis<sup>59</sup>
  → to be considered based on previous treatment, history of infection and immune status of the patient
- B Hepatitis (even non replicative)
  - Viral load monitoring every 3 months
  - Hepatologic advice for antiviral therapy (entecavir or tenofovir)

#### Venetoclax – recommendations for use

| Pre-treatment assessment | Medical history, medications |
|--------------------------|------------------------------|
|                          | Medication reconciliation (CYP3A4 or PgP interactions) |
| Evaluation of the tumour lysis syndrome (TLS) risk: | |
| - Low: lymphadenopathy < 5 cm and lymphocytosis < 25 × 10⁹/L | |
| - Medium: any lymphadenopathy from 5 to 10 cm OR lymphocytosis ≥ 25 × 10⁹/L | |
| - High: any lymphadenopathy ≥ 10 cm OR any lymphadenopathy ≥ 5 cm AND lymphocytosis ≥ 25 × 10⁹/L | |
| TLS prevention | |
| Dose ramp-up phase: Hydration and urate lowering treatment: allopurinol for all patients, consider rasburicase in high-risk patients Hospitalization (at least for the two first doses) |

#### Prophylaxis

- Pneumocystis and zoster prophylaxis
  → to be considered based on previous treatment, history of infection and immune status of the patient

#### Management of neutropenia

- G-CSF in case of grade 4 neutropenia
- Consider dose reduction in case of persistent neutropenia

---

<sup>a</sup>Contraindications from the FILO group.

---

#### Figure 1. First-line treatment of CLL

BR = bendamustine and rituximab; CIT = chemoimmunotherapy; Clb = chlorambucil; FCR = fludarabine, cyclophosphamide and rituximab; G = obinutuzumab; R = rituximab; VEN = venetoclax; *no reimbursement in France for this indication.
targeted therapies in terms of progression-free survival (or even overall survival) compared to CIT, subgroup analyses showed no superiority of most of these new molecular therapies in patients with mutated IGHV status. In fludarabine-eligible patients with mutated IGHV status, the reference treatment is the fludarabine, cyclophosphamide and rituximab (FCR) combination. In patients under 65 years of age, the standard regimen consists of 6 monthly cycles. In older subjects, a strategy based on 4 cycles of FCR followed by 2 injections of rituximab may be proposed. Anti-infectious prophylaxis (anti-HSV and anti-pneumocystis jirovecii) and the use of G-CSF are essential. In the case of unmutated IGHV status, the FCR regimen remains an option, but the use of ibrutinib as a monotherapy will also be valuable once reimbursement is obtained. In the absence of direct comparison, the benefit of the addition of obinutuzumab to ibrutinib has not been demonstrated. This combination is therefore not recommended and will not be reimbursed in France. Currently, in FCR-ineligible patients with mutated IGHV status, CIT remains the gold standard. Two options can be proposed: the combination of bendamustine and rituximab (BR), or the combination of chlorambucil plus obinutuzumab (G-CLB). Ibrutinib may represent an option as soon as a reimbursement is obtained. In patients with unmutated IGHV status, due to the disappointing results of CIT, continuous ibrutinib treatment is the best option to date. It should also be noted that the combination of obinutuzumab and venetoclax (G-VEN) for a fixed duration of one year demonstrated superiority in terms of progression-free survival compared to G-CLB for both patients with mutated and unmutated IGHV, but this combination is not reimbursed yet.

In the presence of TP53 inactivation
CIT is not effective in patients with p53 pathway inactivation (8%–10% of patients requiring first-line treatment). Continuous ibrutinib treatment is therefore the standard of care as a first-line treatment for these patients. The toxicity of idelalisib restricts its use, and it is now reserved for patients with a contraindication to ibrutinib. Venetoclax may also be an option in case of TP53 disruption and ibrutinib contraindication, but it is not reimbursed in France for this specific indication.

Treatment of small lymphocytic lymphoma
Before initiating treatment, the assessment for TP53 alteration in the blood (if a CLL circulating clone has been evidenced) or the lymph node biopsy is recommended. The indications for treatment and therapeutic modalities are identical to those defined above for CLL.

Treatment of relapse disease
The criteria for initiating a new therapeutic line remain the same as those for initiating a first-line therapy and are based on the IWCLL criteria. A systematic attempt to identify whether a p53 pathway inactivation is present (del17p and TP53 mutation) must be made before each new therapeutic line is initiated. Moreover, a PET scan and a lymph node biopsy must be systematically performed if Richter transformation is suspected.

Two situations need to be distinguished between: post-CIT and post-ibrutinib relapses (Fig. 2).

Relapse after chemoimmunotherapy
Because of the spectacular results of targeted therapies, CIT is no longer recommended for relapsed CLL, even in the case of a very prolonged response after first-line CIT. Since the RESONATE study, ibrutinib has become the standard of care in the event of relapse after CIT, irrespective of TP53 status. More recently, the MURANO phase 3 trial demonstrated the superiority of a 2-year fixed duration combination of rituximab and venetoclax (R-VEN) over a standard CIT regimen with BR.
In addition, this association is able to induce high rates of undetectable minimal residual disease (MRD). These 2 therapeutic options are now available in France but, as they have never been directly compared in clinical trials, there is no recommendation assisting the clinician’s choice. However, their different toxicity profiles should be taken into account.

**Treatment after ibrutinib failure**

The reason for ibrutinib withdrawal is important, as therapeutic options may differ between patients who discontinued ibrutinib because of intolerance and those who discontinued ibrutinib because of disease progression.

For patients progressing on ibrutinib therapy, testing for mutations of BTK and PLCG2 is desirable, especially if subsequent treatment with an alternate BTK inhibitor is considered. Venetoclax is the treatment of choice after progression on ibrutinib either as continuous monotherapy or in combination with rituximab for a total of 2 years. The use of idelalisib after progression on ibrutinib is not recommended because, in addition to its toxicity, idelalisib is unlikely to induce a prolonged response and it has an unfavourable safety profile. In relapsed patients with TP53 abnormalities, the indication for allogeneic stem-cell transplantation (AlloHCT) should be discussed.

In situations where ibrutinib has been discontinued due to toxicity, the resumption of ibrutinib may be considered if a transient discontinuation has resulted in a complete resolution of the side effects. If resuming ibrutinib is not possible, treatment with venetoclax (or R-VEN) is the therapeutic alternative of choice. The combination of rituximab and idelalisib may be an alternative in cases of contraindication to venetoclax.

**Treatment after failure of both kinase inhibitors and venetoclax**

In this situation, there is no consensus on treatment, and patients should be included in therapeutic trials whenever possible. If the patient is eligible, alloHCT is indicated once the control of CLL is achieved. There are only very few data concerning the efficacy of CIT after the failure of kinase inhibitors and venetoclax.

**Allogeneic transplantation**

The indications for alloHCT changed with a new EBMT-ERIC algorithm through 2 levels. Level 1 includes patients with impaired p53 pathway who have relapsed or are refractory to CIT but respond to treatment with ibrutinib or venetoclax. Here alloHCT is only suggested as an option for patients with a 10/10 HLA donor and no comorbidities. The del(11q) is no longer retained as a level 1 defining element. Level 2 includes patients who have relapsed or are refractory to both ibrutinib or venetoclax. They have a higher risk, justifying alloHCT even with a non-HLA 10/10 donor and even if comorbidities are present.

Beyond eligibility and donor availability, using these levels requires objective assessment of therapeutic history and comprehensive biologic evaluation of p53 pathway inactivation and if possible, karyotype. It must be established whether a patient has been intolerant or resistant to BCR inhibitor or venetoclax and whether the progression is to CLL or Richter syndrome for which allografting should also be discussed (see below).

We propose to apply the algorithm to the current practice including of the majority of patients either treated with CIT followed by ibrutinib and then venetoclax or treated 1st line with ibrutinib due p53 pathway inactivation and who will receive 2nd line venetoclax. In this typical level 2 we consider alloHCT, all the more so (1) it was a true resistance to ibrutinib before venetoclax, (2) there were unfavourable features including bulky adenopathies >5-10 cm, TP53 pathway inactivation and specially complex karyotype, (3) there is a poor response to venetoclax (ie, is no CR/CRI) at 9 months or if blood MRD remains or returns to positive.

If this therapeutic sequence is maintained and the patient becomes double refractory to both ibrutinib and venetoclax the indication for alloHCT will be all the more obvious, but then less feasible. This algorithm will need to be rethought with the move to targeted therapies as first-line therapy for many patients and with the potential development of CAR-T cell therapy. Finally, if alloHCT is decided serial MRD assessment should performed to guide pre-emptive post alloHCT management to reduce the risk of relapse.

**Autoimmune cytopenia**

Autoimmune cytopenia (AIC) is a frequent complication of CLL, occurring in 4% to 14% of patients. This complication can occur during treatment, whatever treatment is being used. Furthermore, CLL therapeutic regimens have never clearly been demonstrated to cause AIC, and therefore the occurrence of “on-therapy” AIC should be considered as CLL progression.

**Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP)**

Corticosteroid therapy with prednisolone at an initial dosage of 1 to 2 mg/kg/day is the first-line treatment. More than 70% of patients will respond, but the response is durable in only a minority of patients. The response to polyclonal immunoglobulins is not as good as that for idiopathic AIC, and this treatment should be reserved for emergency situations. Thrombopoietin agonists (romiplostim and eltrombopag), although inconsistently effective, may be useful in this context. In the absence of concomitant CLL progression, rituximab monotherapy is a second-line option. Immunosuppressive therapies (eg, ciclosporin) may also be used.

In the case of refractory AIC, or if AIC onset is associated with other features of CLL progression (lymphadenopathies or bone marrow failure), initiation of a specific CLL treatment with strong activity with regard to the CLL clone is required. The treatment strategy is therefore close to that for patients with progressive CLL without AIC, which implies taking into account prognostic factors as well as the previous lines received by the patient. There are limited data on the use of FCR therapy, but the combination is not contraindicated if hemolysis is controlled by corticosteroid therapy. Several retrospective studies have reported the efficacy of the rituximab, cyclophosphamide, and dexamethasone (R(2)CD) association, but this combination might not provide long-lasting control of the tumor clone. The efficacy of the BR combination has also been demonstrated. Kinase inhibitors (ibrutinib and idelalisib) can be used, but the risk of CAI relapse is high after treatment discontinuation. The risk of bleeding observed with ibrutinib treatment must be taken into account for patients with ITP. In addition, the use of corticosteroids must be avoided or their duration shortened as much as possible when ibrutinib is used concomitantly because of the risk.
Autoimmune pure red cell anemia (PRCA)

When PRCA occurs, the possibility of a concomitant infection with parvovirus B19 must be considered. The response to steroid therapy is usually poor, and the first-line treatment is based on cyclosporin. Responses to rituximab, RCD or ibrutinib have also been reported. Treatment with polyvalent Ig may also be pondered, if a parvovirus B19 infection is proven.

Richter syndrome

Richter syndrome (RS) is the development of aggressive lymphoma in the context of chronic lymphocytic leukemia.

Diagnosis of Richter syndrome

RS should be suspected in the presence of constitutive symptoms (fatigue, night sweats, weight loss, fever); rapid, asymmetrical lymph node growth; extranodal localizations; hypercalcemia or increased LDH level.

The diagnosis of RS necessarily requires an histopathologic proof of transformation, and biopsy may be repeated in case of negativity if RS is clinically suspected. A PET scan is needed to guide the biopsy. For untreated patients or for patients having received CIT, the description of a lesion with a SUVmax greater than 10 is highly suggestive of RS. Nevertheless, this does not exempt from performing a biopsy. For patients receiving targeted therapies, the PET scan may not be as discriminating and both sensitivity and specificity are lower to distinguish CLL from RS. Therefore, performing a biopsy is indispensable in case of RS suspicion even if the PET-scan is not informative.

Biological and pathological characteristics of Richter syndrome

Diffuse large B-cell diffuse lymphomas account for 90% of the cases of RS and are classified as the non-germinal center type in 90% to 95% of cases. In some cases, it is difficult to differentiate an “accelerated” CLL with many proliferative centres from true RS, and the biopsy must be reviewed by an expert hematopathologist. Hodgkin’s lymphoma, which is often described as the “mixed cellularity” type, accounts for 10% of the cases of RS.

In approximately 80% of cases, RS derives from the underlying CLL clone, while 20% of cases are described as unrelated clones. If technically feasible, the search for a clonal relationship between RS and CLL should be carried out as it may change the therapeutic management.

Richter syndrome prognosis

The prognosis for Richter syndrome is usually very poor, especially if the RS clonally related to CLL. In this situation, in the absence of intensive therapy, the median overall survival is short. The prognosis is better for non-clonally related RS or Hodgkin’s lymphoma type RS.

Treatment of Richter syndrome

In the absence of a randomized prospective study, it is difficult to define a consensus treatment. R-CHOP remains the reference option despite a very low complete response rate and an overall survival of 15 months. Combinations of aracytin and platinum, such as R-DHAP or R-ESHAP, represent an alternative, with a 25% complete response rate and a median survival of 15 months. Inclusion in a clinical trial should be preferred whenever possible. If feasible, allo-HCT should be offered to all eligible chemo-sensitive patients. Otherwise, autologous stem cell transplantation may be discussed. This intensive strategy does not apply to non-clonally related RS with a complete response to CIT, which can simply be monitored. Finally, Hodgkin’s type variants should be treated as recommended for de novo Hodgkin’s lymphoma.

Acknowledgments

The authors thank all other members of the CLL FILO group: Fanny Baran-Marszak (Bobigny, France), Marie-Christine Béné (Nantes, France), Fontanet Bijou (Bordeaux, France), Annie Brion (Besançon, France), Guillaume Cartron (Montpellier, France), Bernard Drenou (Mulhouse, France), Jehan Dupuis (Creteil, France), Emmanuelle Ferrant, Charles Herbaut (Lille, France), Katell Le Du (Lyon, France), Magali Le Garff Tavernier (Paris, France), Béatrice Mahé (Nantes, France), Karim Maloum (Paris, France), Marc Maynadie (Dijon, France), Fatih Merabet (Versailles, France), Pierre Morel (Amiens, France), Delphine Nollet (Tours, France), Brigitte Pégourie (Grenoble, France), Bertrand Pollet (Boulogne sur Mer, France), Stéphanie Poulin (Valenciennes, France), Sophie Raynaud (Nice, France), Daniel Ré (Antibes, France), Philippe Rodon (Périgueux, France), Damien Roos-Weil (Paris, France), Valérie Rouille (Montpellier, France), Laurence Sanhes (Perpignan, France), Laurence Simon (Corbeil-Essonnes, France), Małgorzata Truchan-Graczyk (Angers, France), Eric Van Den Neste (Bruxelles, France), Sandrine Vaudaux (Rouen, France), Marguerite Vignon (Paris, France), Jean-Pierre Viquet (Caen, France), Maud Voldoire (La Roche sur Yon, France), Lise Willems (Paris, France), and Jean-Marc Zini (Paris, France).

Disclosures

AQ declared consulting fees from Abbvie, honoraria from Abbvie, Janssen, Roche, Gilead and travel grants from Abbvie, Roche; AC declared consulting fees from Abbvie; FC declared honoraria and consulting fees from Janssen, Astra Zeneca, Abbvie, Sunesis and travel grants from Astra-Zeneca, Roche; FD declared consulting fees from Janssen and honoraria from Janssen, Gilead; AD declared consulting fees from Abbvie, Janssen, Roche, Astra Zeneca, honoraria from Abbvie, Janssen, Amgen and travel grants from Abbvie, Janssen, Roche, Gilead; MSD declared honoraria and travel grants from Abbvie, Janssen, PF declared consulting fees, honoraria or travel grants from Janssen, Roche, Gilead, Abbvie, Celgene, Astra Zeneca; LMF declared consulting fees, honoraria and travel grants from Roche, Janssen, Gilead, Abbvie, Takeda, Servier; DG declared research funding from Janssen and consulting fees from Janssen, Abbvie; RG declared consulting fees, honoraria or travel grants from Abbvie, Janssen, Amgen, Roche; KL declared research funding from AbbVie, Novartis, Takeda, Roche, Sandoz and honoraria from AbbVie, Novartis, Takeda, Roche, Sandoz, Celgene, Janssen, Amgen; VLeb declared consulting fees from Janssen, Abbvie, Roche, Astra Zeneca, honoraria from Janssen, Abbvie, Roche, Amgen, Astra Zeneca, Gilead and travel grants from Roche, Abbvie; SL declared consulting fees from Abbvie, Astra...
Zenea, Roche, Gilead, Janssen; RL declared consulting fees from Abbvie, Honoraria from Abbvie, Roche, Janssen and travel grant from Abbvie, Janssen; VLv declared consulting fees from Astra Zeneca, Gilead, Janssen, Octapharma and travel grants from Astra Zeneca, Janssen, Octapharma; FNK declared consulting fees, honoraria or travel grants from Gilead, Roche, Janssen, Incyte; ASM declared research funding from Novartis, Janssen and Abbvie; CT declared consulting fees from Janssen, research funding from Roche, Gilead and honoraria from Janssen, Abbvie, LY declared consulting fees, honoraria or travel grants from Abbvie, Astra Zeneca, Gilead, Janssen, Roche; XT declared research funding from Roche, Sysmex, consulting fees from Abbvie, Innate Pharma and travel grants or honoraria from Abbvie, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Gilead Sciences, Hospira, Janssen, Pfizer, Roche. For the remaining authors, no relevant conflicts of interest were declared.

References
1. Swerdlow SH, Campo E, Harris NL, et al (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised. 4th edition. Lyon, France: International Agency for Research on Cancer; 2017.
2. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, management of CLL, indications for treatment, response assessment, and supportive care. Blood. 2016;128:659–667.
3. Landgren O, Albitar M, Ma W, et al. B-cell clones as early markers for chronic lymphocytic leukemia. N Engl J Med. 2009;360:659–667.
4. Le Guyader-Peyrou S, Defossez G, Dantony E, et al. Estimations nationales de l’incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018 - Volume 2 - Hématopathies malignes: Étude à partir des registres des cancers du réseau Francim. Saint-Maurice (Fra): Santé publique France, 2019. https://www.santepubliquefrance.fr/content/download/190601/2335094. Accessed August 31, 2020.
5. Troussard X, Cornet E, Delafosse P, Monnerue A. Estimations nationales de l’incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018 - Volume 2: Hématopathies malignes: Leucémie lymphoïde chronique / lymphome lymphoïdique. 2019. https://www.santepubliquefrance.fr/content/download/190601/2335094. Accessed August 31, 2020.
6. Teras LR, DeSantis CE, Cronin KA, et al. Breast, colorectal, lung, ovary, and prostate cancer statistics, 2016. CA Cancer J Clin. 2016;66:443–459.
7. Saud A, Chattopadhyay S, Thomasen H, et al. Analysis of 153 115 patients with hematological malignancies refines the spectrum of familial risk. Blood. 2019;134:960–969.
8. Zheng G, Chattopadhyay S, Sud A, et al. Second primary cancers in patients with acute lymphoblastic, chronic lymphocytic and hairy cell leukemia. Br J Haematol. 2019;185:232–239.
9. Matutes E, Ouwts-Ankoom K, Morilla R, et al. The immunological profile of B-cell disorders and proposal of a scoring system for the diagnosis of CLL. Leukemia. 1994;8:1640–1645.
10. Zalcberg I, D’Andrea MG, Monteiro L, et al. Multidisciplinary diagnostics of chronic lymphocytic leukemia: European Research Initiative on CLL – ERIC recommendations. Hematol Transfus Cell Ther. 2020;42:269–271.
11. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48:198–206.
12. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;45:219–234.
13. Letestu R, Lévy V, Éclache V, et al. Prognosis of Binet stage A chronic lymphocytic leukemia patients: the strength of routine parameters. Blood. 2015;125:856–867.
14. Gale RP, Chapel HM, et al. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia/Immunovigilance immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med. 1988;319:902–907.
15. Binelis P, Jeromin S, Isaks M, et al. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. Blood. 2019;133:1205–1216.
16. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2003;349:1910–1916.
17. Danel RN, Wasil T, Fais E, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood. 1999;94:1840–1847.
18. Hamblin TJ, Davis Z, Gardner A, et al. Unmutated Ig (VH) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94:1848–1854.
19. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukemia (ILLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:43–56.
20. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoinmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379:2517–2528.
21. Shanafelt TD, Wang XJ, Kay NE, et al. Ibrutinib-Rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381:432–443.
22. Binelis P, Agathangeliadis A, Hadzidimitriou A, et al. Not all IGHV3-21 chronic lymphocytic leukemia are equal: prognostic considerations. Blood. 2015;125:856–859.
23. Jaramillo S, Agathangeliadis A, Schneider C, et al. Prognostic impact of prevalent chronic lymphocytic leukemia stereotyped subsets: analysis within prospective clinical trials of the German CLL Study Group (GCLLSG). Haematologica. 2019 December 26. [Epub ahead of print].
24. Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol. 2010;28:4473–4479.
25. Rossi D, Cerri M, Deambrogi C, et al. The prognostic value of TP53 mutations in chronic lymphocytic leukemia is independent of Del17p13: implications for overall survival and chemosensitivity. Clin Cancer Res. 2009;15:995–1004.
26. Malickova J, Tausch E, Rossi D, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia-update on methodological approaches and results interpretation. Leukemia. 2018;32:1070–1080.
27. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014;123:3247–3254.
28. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376:1164–1174.
29. Bartigas C, Van Den Neste E, Léger J, et al. Rituximab maintenance versus observation following abbreviated induction with chemoinmunotherapy in elderly patients with previously untreated chronic lymphocytic leukemia (CLL10): an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2018;5:e82–e94.
30. Michallet A-S, Aktan M, Hiddemann W, et al. Ibrutinib plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica. 2018;103:698–706.
31. Eichhorst B, Fink A-M, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17:928–942.
32. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370:1101–1110.
33. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line rituximab treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia 2020;34:787–798.
34. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019;380:2225–2236.
35. Fischer K, Ritgen M, Al-Sawaf O, et al. Quantitative analysis of minimal residual disease (MRD) shows high rates of undetectable MRD after fixed-duration chemotherapy-free treatment and serves as surrogate marker for progression-free survival: A Prospective analysis of the randomized CLL14 trial. Blood. 2019;134(Supplement 1):36–136.
36. Byrd JC, Hillmen P, O’Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib versus ofatumumab. Blood. 2019;133:2031–2042.
37. O’Brien S, Jones JA, Coutre SE, 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. 2016;17:1409–1418.
38. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukaemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. J Clin Oncol. 2019;37:269–277.
39. Quinquenel A, Fornecker L-M, Letestu R, et al. Prevalence of BTK and PLCG2 mutations in a real-life CLL cohort still on ibrutinib after 3 years: a FILO group study. Blood. 2019;134:641–644.
40. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol. 2018;19:65–75.
41. Godet S, Protin C, Dupuis J, et al. Outcome of chronic lymphocytic leukaemia patients who switched from either ibrutinib or idelalisib to alternate kinase inhibitor: A retrospective study of the French innovative leukemia organization (FILO). Am J Hematol. 2018;93:E52–E54.
42. Dreger P, Ghia P, Schettel J, et al. High-risk chronic lymphocytic leukaemia in the era of pathway inhibitors: integrating molecular and cellular therapies. Blood. 2018;132:892–902.
43. Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukaemia. J Clin Oncol. 2019;37:1391–1402.
44. Anderson MA, Tam C, Lew TE, et al. Clinico-pathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax. Blood. 2017;129:3362–3370.
45. Roberts AW, Ma S, Kipps TJ, et al. Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. Blood. 2019;134:111–122.
46. Tournilhac O, Le Garff-Tavernier M, Nguyen Quoc S, et al. Efficacy of minimal residual disease driven immune-intervention after allogeneic hematopoietic stem cell transplantation for high-risk chronic lymphocytic leukemia: results of a prospective multicentric trial. Haematologica. 2020 June 11. [Epub ahead of print].
47. Hodgson K, Ferrer G, Montserrat E, et al. Chronic lymphocytic leukaemia and autoimmunity: a systematic review. Haematologica. 2011;96:752–761.
48. Rossignol J, Michallet A-S, Oberic L, et al. Rituximab-cyclophosphamide-dexamethasone combination in the management of autoimmune cytopenias associated with chronic lymphocytic leukaemia. Leukemia. 2011;25:473–478.
49. Quinquenel A, Willekens C, Dupuis J, et al. Bendamustine and rituximab combination in the management of chronic lymphocytic leukemia-associated autoimmune hemolytic anemia: a multicentric retrospective study of the French CLL intergroup (GFLLC/MW and GOELAMS). Am J Hematol. 2015;90:204–207.
50. Quinquenel A, Godet S, Dartigues C, et al. Ibrutinib and idelalisib in the management of CLL-associated autoimmune cytopenias: a study from the FILO group. Am J Hematol. 2019;94:E183–E185.
51. Ghez D, Calleja A, Protin C, et al. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood. 2018;131:1955–1959.
52. Michallet A-S, Sesques P, Rabe KG, et al. An 18F-FDG-PET maximum standardized uptake value > 10 represents a novel valid marker for discerning Richter’s Syndrome. Leuk Lymphoma. 2016;57:1474–1477.
53. Mato AR, Wierda WG, Davids MS, et al. Utility of positron emission tomography-computed tomography in patients with chronic lymphocytic leukemia following B-cell receptor pathway inhibitor therapy. Haematologica. 2019;104:2258–2264.
54. Wang Y, Rabe KG, Bold MS, et al. The role of 18F-FDG-PET in detecting Richter’s transformation of chronic lymphocytic leukemia in patients receiving therapy with a B-cell receptor inhibitor. Haematologica. 2020 January 23. [Epub ahead of print].
55. Rossi D, Spina V, Gaidano G. Biology and treatment of Richter syndrome. Blood. 2018;131:2761–2772.
56. Tsimberidou A-M, O’Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter’s syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. J Clin Oncol. 2006;24:2343–2351.
57. Parkh SA, Kay NE, Shanafelt TD. How we treat Richter syndrome. Blood. 2014;123:1647–1657.
58. Durot E, Michallet A-S, Leprêtre S, et al. Platinum and high-dose cytarabine-based regimens are efficient in ultra high/high-risk chronic lymphocytic leukemia and Richter’s syndrome: results of a French retrospective multicenter study. Eur J Haematol. 2015;95:160–167.
59. Maschmeyer G, De Greef J, Mellinghoff SC, et al. Infections associated with immunotherapeutic and molecular targeted agents in hematology and oncology. A position paper by the European Conference on Infections in Leukemia (ECIL). Leukemia. 2019;33:844–862.