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

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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 5×10^9/L clonal B lymphocytes with a characteristic immunophenotypic profile.[2] The presence of less than 5×10^9/L clonal B lymphocytes defines monoclonal B lymphocytosis (MBL) (9823/1), a mandatory step that precedes the onset of CLL.[1,3]

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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).[4] The median age at diagnosis is 71 years in men and 73 years in women.[5] 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.[6] 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).[7] 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.[8]

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(+) B lymphocytes. The Royal Marsden Hospital (RMH) or Matutes score is still commonly used in France,[9] 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 rejected. For patients presenting with a CD5 and CD23 positive RMH score 3, the positivity of additional markers such as CD20(low), CD43(+) and CD200 (bright) supports the diagnosis of CLL in the absence of t(11;14) (q13;q32) translocation (or the expression of cyclin D1).[2,10] The diagnosis of CLL requires neither a bone marrow evaluation 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.[1]

Table 1

Recommended Markers for the Diagnosis of CLL.

Minimally Recommended (ERIC Recommendations and RMH Scoring)	Other Important Markers
CD19	CD200
CD5	CD43
Ig light chains kappa & lambda (membrane staining)	Intracellular Ig light chains kappa & lambda (if absence of membrane staining)
CD23	CD81
CD79b and/or CD22 (for RMH scoring)	CD38
CD20	CD10
FMC7 (for RMH scoring)	

ERIC = European Research Initiative on Chronic Lymphocytic leukemia; Ig = immunoglobulins; RMH = Royal Marsden Hospital.

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.[11] 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.[12]

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), beta2-microglobulin, LDH levels and CD38 expression.[13]

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[2] 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 $< 30 \times 10^9$/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 2

Anti-infectious Prophylaxis According to CLL Treatments.

Type of Treatment	Prophylaxis
Fludarabine-based or bendamustine	Pneumocystis prophylaxis (cotrimoxazole or atovaquone), Zoster prophylaxis (valaciclovir)
Anti-CD20 antibodies	Zoster prophylaxis (valaciclovir), B-hepatitis prophylaxis (tenofovir or entecavir) if anti-Hbc antibodies are present and/or the PCR is positive
Ibrutinib	Avoid concomitant corticosteroids or immunosuppressive therapy
	No recommendation for systematic pneumocystis and zoster prophylaxis
	No recommendation for systematic fungal prophylaxis
	Refer to hepatologist if anti-Hbc antibodies are present and/or the PCR is positive
Idelalisib	Pneumocystis prophylaxis (cotrimoxazole or atovaquone)
	CMV reactivation monitoring (antigenemia or monthly PCR)
Venetoclax	No recommendation for systematic pneumocystis and zoster prophylaxis

- 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 (250 mg × 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.[14] 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 4 g/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 6 g/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

Table 3

Pre-treatment Evaluation.

	Mandatory	Recommended
Clinical evaluation		
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	
Oncogeriatric 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	X	
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)		
Cytogenetics		
Karyotype		X
FISH	X	
17p deletion	X	X
11q deletion		X
13q deletion		
Trisomy 12		
Molecular biology		
IGHV mutational status	X	
TP53 mutations by NGS	X	
Imaging		X
CT scan of chest, abdomen and pelvis		

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.

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

Until recently, this test was only indicated in clinical trials but is now becoming an important decision-making element and must be performed before frontline therapy. Moreover, one third of the patient express stereotyped B cell receptor immunoglobulin and can be assigned to different subsets. Patients with an unmutated *IGHV* profile (homology percentage of at least 98% in comparison with a germline sequence) have a worse prognosis after treatment with chemoimmunotherapy (CIT).[17,18] Several recent clinical trials have shown the superiority of targeted therapies (BTK and BCL-2 inhibitors) in these patients. Conversely, no therapeutic trials have yet shown the superiority of ibrutinib in combination or not with anti-CD20 antibodies in frontline therapy in patients with mutated *IGHV* status and without adverse genetic abnormalities, but it is important to note that all these data arise from subgroup analysis.[19–21] However, there are some exceptions and patients with mutated *IGHV* expressing VH3-21 and assigned to subset 2 have a similar course to unmutated cases.[22,23]

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[a]	Heart failure according to cardiological opinion Double anti-platelet treatment
At-risk situations relative contraindications[a]	Atrial fibrillation Hypertension Vitamin K antagonists (VKA) → prefer direct oral anticoagulants (DOA) Anti-platelet treatment AND VKA or DOA Platelets $< 30 \times 10^9$/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 [59] → 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 $< 25 \times 10^9$/L - Medium: any lymphadenopathy from 5 to 10 cm OR lymphocytosis $\geq 25 \times 10^9$/L - High: any lymphadenopathy ≥ 10 cm OR any lymphadenopathy ≥ 5 cm AND lymphocytosis $\geq 25 \times 10^9$/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) Blood chemistry monitoring
Prophylaxis	*Pneumocystis and zoster prophylaxis* No international consensus on systematic prophylaxis [59] → 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

[a] Contraindications from the FILO group.

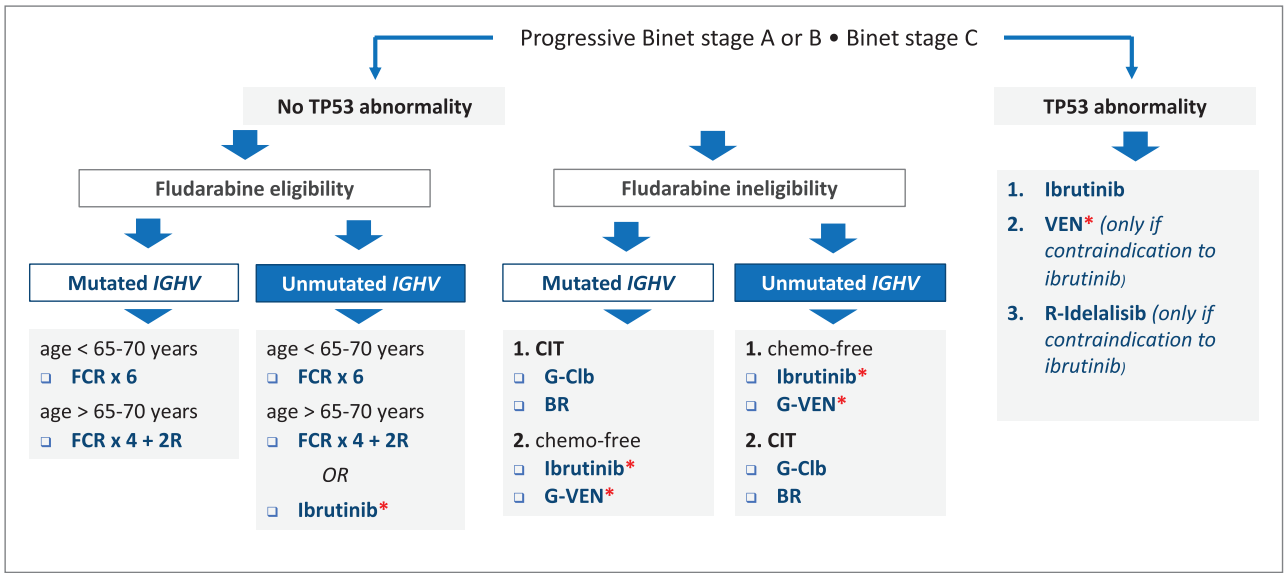

Figure 1. First-line treatment of CLL. BR = bendamustine and rituximab; CIT = chemoimmunotherapy; Clb = chlorambucil; FCR = fludarabine, cyclophosphamide and rituximab; G = obinutuzumab; R = rituximab; VEN = venetoclax. *no reimbursement in France for this indication.

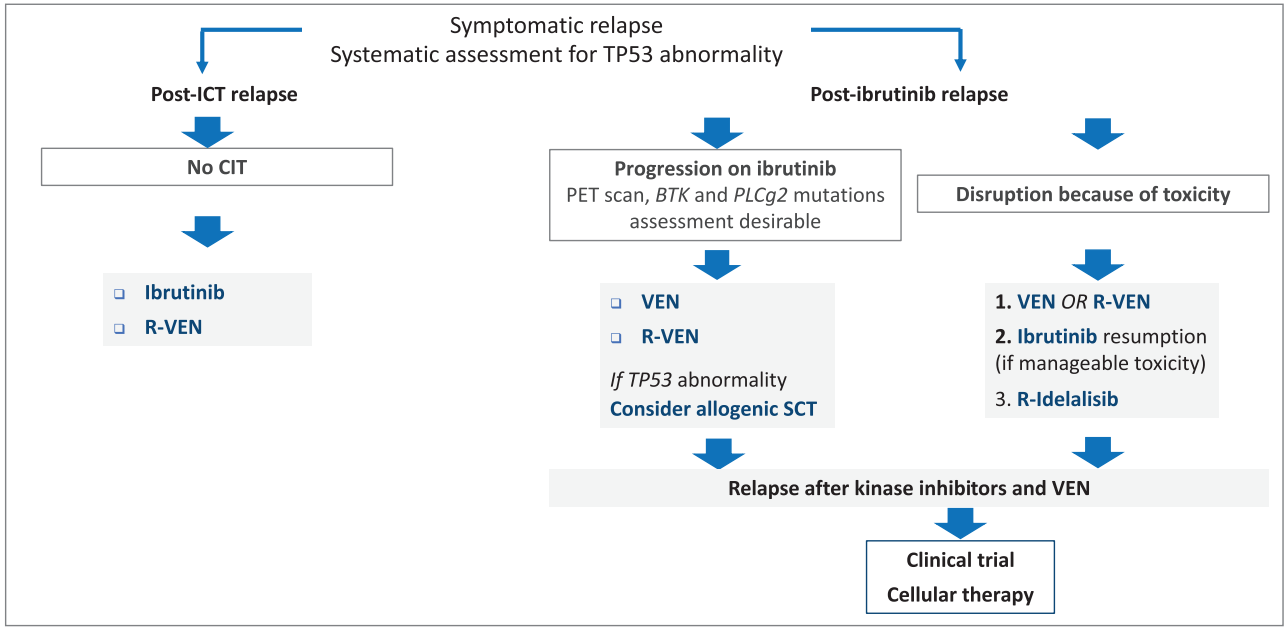

Figure 2. Treatment of relapsed CLL. BTK = Bruton's tyrosine kinase; CIT = chemoimmunotherapy; PLCg2 = phospholipase C gamma-2; R = rituximab; SCT = stem-cell transplantation; VEN = venetoclax.

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.[19–21] 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.[28] In older subjects, a strategy based on 4 cycles of FCR followed by 2 injections of rituximab may be proposed.[29] 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.[19] 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)[30,31] or the combination of chlorambucil plus obinutuzumab (G-CLB).[32] 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 is the best option to date.[19,33] 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.[34,35]

In the presence of *TP53* inactivation

CIT is not effective in patients with p53 pathway inactivation (8%–10% of patients requiring first-line treatment).[24,28] Continuous ibrutinib treatment is therefore the standard of care as a first-line treatment for these patients.[36,37] 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[2] 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.[36,37] 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).[38] 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.[39] Venetoclax is the treatment of choice after progression on ibrutinib either as continuous monotherapy[40] or in combination with rituximab for a total of 2 years.[38] 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.[41] In relapsed patients with *TP53* abnormalities, the indication for allogeneic stem-cell transplantation (AlloHCT) should be discussed.[42]

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.[43]

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.[42] 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.[42]

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).[44,45]

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.[46]

Autoimmune cytopenia

Autoimmune cytopenia (AIC) is a frequent complication of CLL, occurring in 4% to 14% of patients.[47] 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.

Autoimmmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP)

Corticosteroid therapy with predniso(lo)ne 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 polyvalent 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 (RCD) association,[48] but this combination might not provide long-lasting control of the tumor clone. The efficacy of the BR combination has also been demonstrated.[49] Kinase inhibitors (ibrutinib and idelalisib) can be used, but the risk of CAI relapse is high after treatment discontinuation.[50] 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

of invasive fungal infection, and zoster and pneumocystis prophylaxis is mandatory.[51]

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 ciclosporin. 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.[52] 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.[53,54] 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 haemoathologist. 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.[55] 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.[56] 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.[57] 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.[58] 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.[55]

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