

Updated BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2016

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On behalf of the BHS Lymphoproliferative Working Party*

The Belgian Hematological Society Lymphoproliferative Working Party updated the 2012 recommendations on the best strategies for front-line and subsequent-line treatment of small lymphocytic leukaemia/chronic lymphocytic leukaemia. No treatment is necessary for patients without active and/or advanced disease, regardless of prognostic factors. When front-line treatment is indicated we recommend adding an anti-CD20 monoclonal antibody to chemotherapy except in frail patients: fludarabine, cyclophosphamide, rituximab for fit patients; bendamustine, rituximab for fit patients >65 years or unfit for fludarabine, cyclophosphamide, rituximab; and chlorambucil with obinutuzumab or rituximab for older patients with a geriatric profile, major comorbidities or a reduced performance status. The choice of treatment for patients with recurrent disease depends on the duration of response to the previous treatment, the type of treatment refractoriness and the presence of a 17p deletion/p53 mutation. As an alternative, chemoimmunotherapy can be proposed for patients with a late relapse. The novel B-cell receptor inhibitors are the best choice for those relapsing early, who have refractory disease or are unfit for chemoimmunotherapy. The B-cell receptor inhibitors are also first choice for each patient with a de novo or acquired 17p deletion/p53 mutation. Reduced intensity conditioning allogeneic stem cell transplantation should still be considered for patients with high-risk disease after response induction by the B-cell receptor inhibitors. We still have to encourage patients to enter clinical trials exploring new drug combinations.

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Introduction

The Belgian Hematological Society (BHS) Lymphoproliferative Working Party reviewed the recent literature on treatment of small lymphocytic leukaemia (SLL)/chronic lymphocytic leukaemia (CLL) to update the 2012 recommendations on the best strategies for front-line and subsequent-line treatment.

In 2014 the Belgian authorities extended the reimbursement of rituximab (R) for combination with chlorambucil (Chl) and bendamustine (B) as first-line treat-

ment in CLL. In 2015 ibrutinib, obinutuzumab (Ob) and idelalisib-R will also have gathered reimbursement, as these agents change the natural history of the disease. Ibrutinib and idelalisib-R are recommended for certain subgroups of relapsing/refractory (R/R) CLL and for any CLL with a 17p deletion/p53 mutation. Ob-Chl can be recommended as first-line treatment for patients with comorbidities unfit for full dose fludarabine. Ofatumumab (O) will not be reimbursed shortly in Belgium.

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Diagnosis and risk stratification

Criteria to diagnose and stage SLL/CLL have not been changed. The only prognostic factor that predicts treatment resistance and has to be known before the start of treatment, is the presence or absence of a 17p deletion and/or a p53 mutation.¹

Treatment

Criteria for initiating first-line or subsequent-line treatment still follow the 2008 guidelines of the International Workshop on Chronic Lymphocytic Leukaemia (IW-CLL), meaning that treatment should be reserved for patients with advanced (Stage Rai 3-4 or Binet C) and/or active disease.¹

Before initiating treatment, consideration must be given to: patient related factors (age, performance status (PS), comorbidities, renal and bone marrow function, and patient wishes), disease related factors (17p deletion and/or p53 mutation) and treatment related factors (degree and duration of response, contraindications to and side-effects from particular treatment modalities).

Frontline treatment of advanced and/or active disease in "Fit" patients

Fludarabine, cyclophosphamide, rituximab (FCR) chemotherapy (CIT) with fludarabine (F) (25 mg/m² d1-3), cyclophosphamide (C) (250 mg/m² d1-3), rituximab (R) (cycle 1 375 mg/m², from cycle 2 500 mg/m²) (q4wks, up to six cycles) remains the standard first-line therapy in patients who are fit, have no major comorbidities (cumulative illness rating scale (CIRS) <6) and have a normal renal function (creatinine clearance (CrCl) ≥70 ml/min).² This CIT (GCLLSG CLL 8: FCR versus FC) achieves the best possible response (overall response (OR) 95,1 versus 88,4%, complete response (CR) 44,1 versus 21,8%) with prolonging median progression free survival (mPFS) (51,8 versus 32 months (mo)) and three year and six year overall survival (OS) (87 versus 83% and 69.4 versus 62.3%). Especially patients with an 11q deletion and unmutated IGVH fare better when treated with FCR.³ Approximately one third of patients treated with FCR has not progressed after a median follow-up time of +/- fourteen years and may be cured of their CLL.⁴ Most of these patients seemed to have mutated IGV_H.⁵

As FCR has some toxicities (prolonged cytopenia, infections, treatment related myeloid neoplasms, etc.), a search for less toxic alternatives has been started (GCLLSG CLL 10: FCR versus BR, CALGB 10404:

FCR versus FR). Results from the GCLLSG CLL 10 are already available in abstract form. BR (bendamustine (B) (90 mg/m², d 1-2) and rituximab (R) (cycle 1 375 mg/m², from cycle 2 500 mg/m²) (q4wks, up to six cycles)) versus FCR showed the same OR (95.7 versus 95.4%), but with a lower CR (30.8 versus 39.7%) and a lower minimal residual disease (MRD) negativity in bone marrow at final staging (11.1 versus 26.6%). The mPFS was superior for FCR (55.2 versus 41.7 mo) but without three year OS (90.6 versus 92.2%) benefit at the time of publication. The difference in mPFS was however not maintained in patients >65y. FCR treated patients experienced significantly more grade 3 adverse events (AEs) compared to patients treated with BR. Patients >65y treated with FCR had an infection rate that was double compared to that of patients ≤65y.⁶ This means that for patients >65y BR is an alternative treatment to FCR with similar outcomes but lower toxicities even in fit patients without major comorbidities or impaired renal function.

Frontline treatment of advanced and/or active disease in "Unfit" patients

Till recently, elderly patients with a geriatric profile, significant comorbidities or a reduced PS, were treated with chlorambucil (Chl) as this treatment option - due to its oral availability and low incidence of AEs - was still considered adequate to control disease symptoms. Although multiple randomised controlled trials (RCTs) comparing Chl versus F, B or alemtuzumab (A) showed a lower OR and a lower PFS for Chl, no loss of survival was observed.⁷⁻¹⁰

As adding anti-CD20 monoclonal antibodies to chemotherapy has improved OS of fit CLL patients who need treatment, several anti-CD20 monoclonal antibodies were combined with Chl in phase III trials to treat elderly patients inappropriate for an F-based treatment. Obinutuzumab (Ob), a glycoengineered fully humanised type 2 anti-CD20 monoclonal antibody targets an epitope distinct from that targeted by R. Type 2 antibodies induce increased cell death due to enhancement of direct cell death and antibody dependent cellular cytotoxicity. The GCLLSG CLL 11 enrolled treatment naive patients (median age 73y) in need of therapy and with a significant comorbidity burden (median CIRS 8). The trial compared Ob-Chl versus R-Chl versus Chl (Ob: cycle 1 d1-8-15 1000 mg, from cycle 2 d1 1000 mg, q4wks, up to six cycles; R: cycle 1 375 mg/m², from cycle 2 500 mg/m², q4wks, up to six cycles; Chl:

0.5 mg/kg oral d1 and d15, q4wks, up to six cycles). The study confirmed higher response rates for the combination arms (OR 77.3 versus 65.7 versus 31.4%, CR 22.2 versus 8.3 versus 0% and MRD negativity in bone marrow 20 versus 3 versus 0%) and a prolongation of mPFS (29.2 versus 15.4 versus 11.1 mo). OS of patients treated with Ob-Chl and R-Chl was significantly improved compared to patients treated with Chl monotherapy. Time to next treatment (TTNT) was longer for patients treated with Ob-Chl than with R-Chl (42.7 versus 32.7 mo). The combination arms induced more neutropenia although without an increase in infection rate. Ob also induces more infusion related reactions (IRRs), especially with the first infusions on day one and two (grade 3-4: 20%, no severe reactions during the subsequent infusions).^{11,12} Ofatumumab (O), a human type I anti-CD20 monoclonal antibody, binds a distinct epitope on the CD20 molecule, induces more effective complement-dependent cytotoxicity even in CLL cells with low CD20 expression and shows a slower off-rate compared to R. The Complement 1 trial (O-Chl versus Chl) (O: cycle 1 d1 300 mg, d8 1000 mg, from cycle 2 1000 mg); Chl 10 mg/m² oral d1-7 (q4wks, up to best response with a maximum of twelve cycles) showed a higher response rate (OR 82 versus 69%, CR 14 versus 1%), a longer mPFS (22.4 versus 13.1 mo) and a longer TTNT (39.8 versus 24.7 mo) although without 3y OS benefit (85.1 versus 83.2%) for O-Chl at the time of publication. The combination arm induced more neutropenia but did not result in a higher rate of infection. O induces grade 3-4 IRRs in 10% of patients, predominantly in cycles one and two.¹³ Bendamustine (B) (100 mg/m², d1-2, q4wks, up to six cycles) compared to Chl offers a higher response rate (67 versus 30%), a longer mPFS (21.2 versus 8.8 mo) and a longer mTTNT (31.7 versus 10.1 mo) with manageable toxicity and without compromising quality of life, even in the elderly.⁸⁻⁹ BR (B 90 mg/m², d1-2, R cycle 1 375 mg/m², from cycle 2 500 mg/m², q4wks, up to six cycles) increases OR and mPFS (88%, 34 mo) compared to B monotherapy in the previously mentioned trial.¹⁴ Both trials are however not really representative for old and unfit CLL patients as the median age varies between 63 and 66.5y and the number and/or severity of comorbidities were not reported. BR has been approved and reimbursed in Belgium for frontline treatment of patients with advanced CLL, not fit for FCR. We defined unfit for FCR in our previous guidelines as follows: renal function <70 ml/min, CIRS >6, active or a history of haemolytic anaemia or having a high infectious risk.

Second or subsequent-line treatment

Second or subsequent-line treatment should depend again on patient and disease related factors. Important treatment related factors to consider are type of prior treatment, encountered side effects and the duration of response to that treatment.

We proposed in our previous guidelines a different treatment approach according to duration of response, as duration of response < or >24 mo after the previous CIT changed outcome significantly.¹⁴ Several pro- and retrospective analyses have confirmed that PFS after first-line FCR predicts OS.^{4,15,16} Patients experiencing response duration of >36 mo after first-line FCR seem to survive approximately five years. These patients are considered treatment sensitive. Therefore first-line treatment can be repeated or an alternative CIT can be initiated. A lot of colleagues are reluctant to expose patients again to FCR due to accumulating risk of toxicities. BR (B 70 mg/m² d1-2, R cycle 1 375 mg/m², from cycle 2 500 mg/m², q4wks, up to six cycles) seems the most popular CIT after first-line FCR treatment. In a phase II trial, BR was effective (OR 59%, CR 9%, mPFS 15.2 mo, mOS 33.9 mo) and safe in R/R CLL. OR and PFS was equal for patients younger or older than 70y.¹⁷ These phase II results are in the meantime confirmed in the phase III Helios RCT (BR versus BR-ibrutinib). Two hundred and eighty-nine R/R CLL patients after at least one previous treatment were randomised to BR in the control arm and experienced an OR and CR of 69 and 7%, with a mPFS of 13.3 mo.¹⁸

However, patients relapsing in the first 12, 24 or 36 mo after FCR have a median OS of approximately one, two or three years despite salvage strategies.^{4,15} This means that this subgroup of patients has an outcome comparable to patients with a 17p deletion/p53 mutation or refractory to F or F and A. For this group of patients, we recommended in our previous guidelines after induction with A, O or an alternative CIT the consideration of an allogeneic stem cell transplantation (SCT).¹⁹

Data from treatment with the B-cell receptor inhibitors (BCRi) in this subgroup with a high unmet medical need have become mature and recommendations on how to incorporate these novel agents in the treatment algorithm of R/R CLL can be made. Ibrutinib is an oral, selective and irreversible inhibitor of the Bruton's tyrosine kinase (BTK) that signals BCR activation. After 3y follow-up of R/R CLL (n=101) patients receiving ibrutinib (420 mg, qod, oral, continuously) as monotherapy (PCYC-1102, PCYC-1103 trials), OR and CR

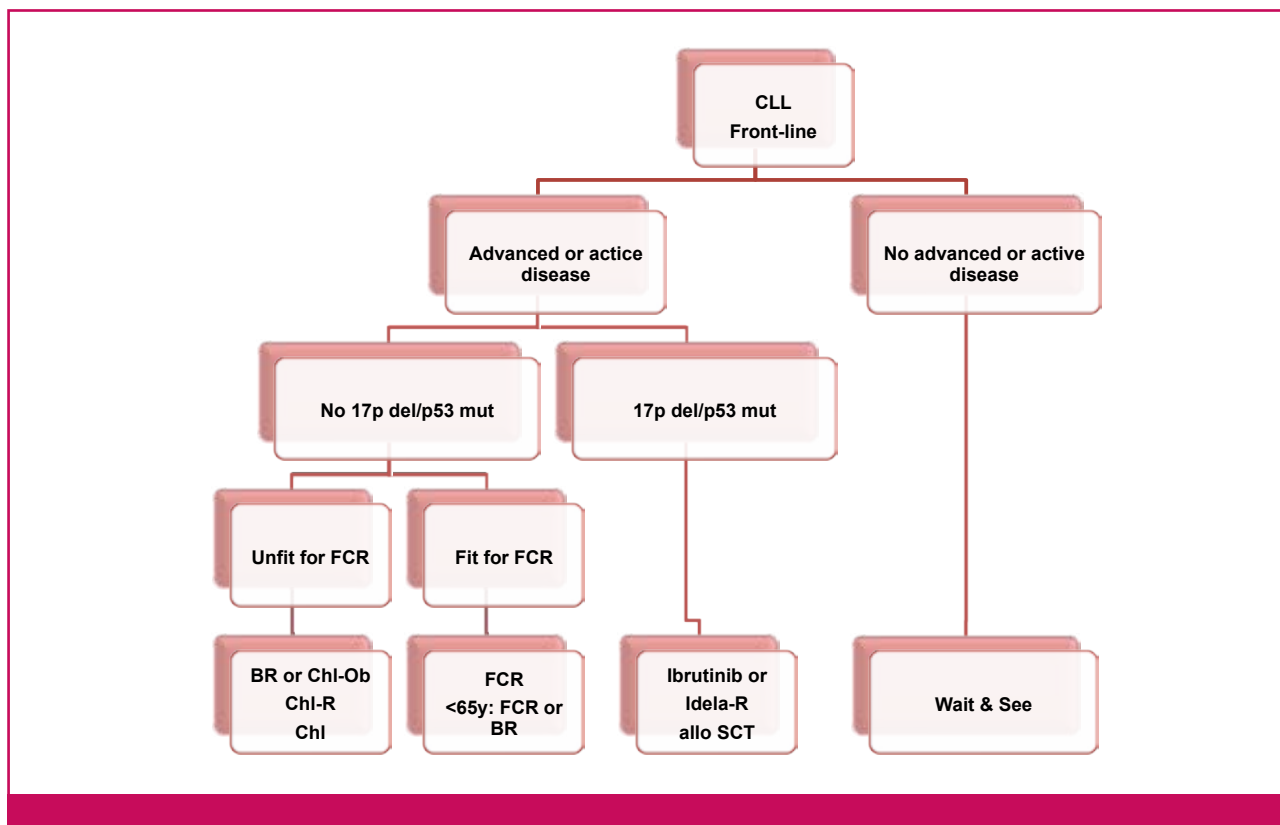


Figure 1. Algorithm for Frontline treatment of CLL.

Unfit for FCR: renal function impairment, comorbidities, frequent infections, history of or active haemolysis.

FCR: fludarabine, cyclophosphamide, rituximab; BR: bendamustine, rituximab; Chl: chlorambucil, Ob: obinutuzumab; idela: idelalisib.

was 90 and 7% with an estimated PFS and OS at 30 mo of 69 and 79% (median age 64y, median prior therapies four, CrCl <60 81%).²⁰ The phase III Resonate trial randomising R/R CLL patients, inappropriate for purine analogues (relapsing <24 mo after previous treatment, 17p deletion, >70y, comorbidities) between ibrutinib or O, showed that ibrutinib was more efficacious than O (investigator versus independent review committee (IRC) assessment OR 83 versus 63% and CR 23 versus 4%, mPFS not reached versus 8.1 mo and a 1y OS of 90 and 81%).²¹ Responses were independent of mutational status and the presence of unfavourable genetic aberrations (FISH, complex karyotype or novel gene mutations).²² The efficacy of ibrutinib-R has also been tested. Longer follow-up is needed to see if the combination with R improves PFS and/or OS, besides blunting and shortening lymphocytosis.²³ The phase III Helios trial randomised R/R CLL between BR and BR-ibrutinib. The study has been unblinded on the following results: IRC assessed OR and CR of 67.8 versus 82.7% and 2.8 versus 10.4% with a mPFS of 13.3 mo versus not reached. OS was not different at the time of publication with 90 patients crossed over to ibrutinib at progres-

sion. Longer follow-up is needed to see if duration of response is longer than for ibrutinib alone.¹⁸ Idelalisib is an oral, selective phosphatidylinositol-3-kinase delta (PI3K δ) inhibitor that also signals BCR activation. Idelalisib-R versus R monotherapy (phase III, primary study 116 and cross over in extension study 117) (idelalisib 150 mg bid, oral, continuously; R: dose 1 375 mg/m², from dose 2 500 mg/m² q2wks, 4x, q4wks, 4x) was tested in R/R CLL patients (after one CIT or two cytotoxic treatments) with a decreased renal function, therapy-related myelosuppression or major coexisting illnesses (CIRS \geq 6). The combination arm improved OR (81 versus 13%), mPFS (not reached versus 5.5 mo) and also 1y OS (92 versus 80%). All prognostic subgroups benefit from the combination of idelalisib-R not only for OR but also for PFS.²⁴ The phase III trial Idelalisib-O (idelalisib 150 mg bid, oral, continuously; O: 1000 mg q1w 8x, q4wks, 4x) versus O (2000 mg q1w 8x, q4wks, 4x) randomised patients with early relapse. The observed responses were best for the idelalisib-O combination with an OR of 75 versus 18% and a mPFS of 16.2 versus 8 mo.²⁵ MRD negativity seems unlikely either with ibrutinib or idelalisib-R.

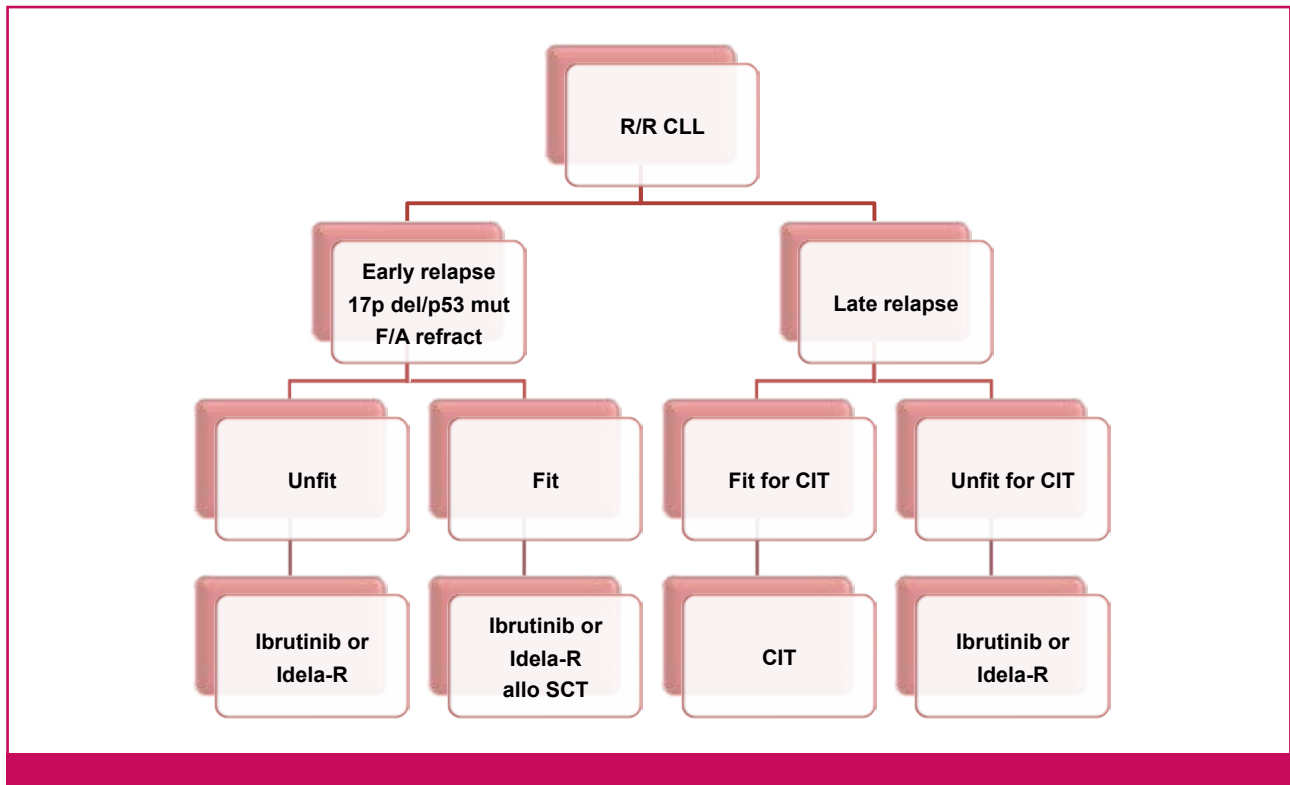


Figure 2. Algorithm for treatment of R/R CLL.

R/R CLL: relapsed/refractory CLL; F/A refract: fludarabine/alemtuzumab refractory; CIT: chemoimmunotherapy; unfit for CIT: CrCl <70 ml/min, CIRS >6, therapy-related cytopenia, history of autoimmune cytopenia.

Treatment of CLL patients with 17p deletion or TP53 mutations: front-line or at relapse

Patients showing a 17p deletion or a p53 mutation are poor responders to conventional treatment (chemotherapy, immunotherapy, CIT, and corticosteroids). Patients with a de novo 17p deletion treated in the GCLLSG CLL 8 trial (n=22) with FCR have an OR with CR of 65 and 5% with a mPFS and mOS of only 11 and 23 mo.²⁶ Alemtuzumab (A), a humanised anti-CD 52 monoclonal antibody, with corticosteroids (methylprednisolone and dexamethasone) in treatment-naïve patients with p53 defects (UK CLL206 trial (n=17), German/French study CLL20 (n=42)) seemed the most effective induction regimen (OR 88-92%, CR 65-21%).^{27,28} For the UK cohort the mPFS and OS was 18.3 and 33 mo.²⁶ For the CLL20 trial a mPFS of 33 mo was seen with randomisation to alemtuzumab maintenance or allogeneic SCT after induction. Outcome of patients was superior for allogeneic SCT, as all patients on maintenance have relapsed or died by 5y. Alemtuzumab/corticosteroids appeared to be the best rescue treatment for R/R CLL and a 17p deletion with an OR and CR of 79 and 4% but again with a short PFS and OS (10.3 and 21.3 mo).²⁷ The BCRi ibrutinib and idelalisib have gained FDA and

EMA approval for the treatment of patients with a 17p deletion/p53 mutation as front-line treatment. The phase II Resonate 17 treated 144 R/R CLL patients with a 17p deletion with ibrutinib. The investigator and IRC assessed OR was 83 and 65%. At 12 mo 79.3% of patients were alive and progression free with an OS of 83.5%.²⁹ In the PCYC 1102/1103 trials, 34 patients had R/R CLL with a 17 p deletion. OR was 79% with 6% CR. mPFS was 28 mo with a 30 mo OS of 65%. Although mPFS and mOS are shorter for patients with the 17p deletion, the outcome is still better than for any other treatment available for this poor prognostic subgroup.²⁰ In the Resonate trial 63 and 62 patients with a 17p deletion were treated respectively with ibrutinib and O. mPFS was not reached for patients on ibrutinib versus 5.9 mo for those treated with O. No statistically significant difference in PFS was seen for patients with or without 17p deletion.³⁰ Idelalisib-R (study 116) has been given to 42 R/R CLL patients with 17p deletion/p53 mutation. Median PFS for patients with the p53 defect was not different from patients with wild type p53 (16.6 versus 20.3 mo). The 101-08 study treated naïve CLL/SLL patients with idelalisib (150 mg bid, oral, continuously) and R (375 mg/m²

q1wk, 8x).³¹ The response rate of the 9/62 patients harbouring a 17p deletion/p53 mutation was not different from patients with a wild type p53 (OR 97 versus 100 %, CR 19 versus 33%).³² Thirty-three previously untreated patients with a 17p deletion/p53 mutation received ibrutinib and showed an OR at 24 weeks of 97%.³³

Allogeneic stem cell transplantation

Reduced intensity conditioning is still preferred because non-relapse mortality is lower compared to conventional myeloablative allogeneic SCT. This is a feasible procedure up to 70 years of age with a better outcome if the disease is chemosensitive, bulky adenopathies are absent and the patient was not exposed to alemtuzumab in the last twelve months.

According to the recommendations of the European Group for Blood and Marrow Transplantation (EBMT), allogeneic SCT should still be considered as a reasonable therapeutic option for younger, fit, high-risk CLL patients. High-risk CLL is defined as F-refractory, early relapse after CIT and having a 17p deletion/p53 mutation. These patients should first be offered a novel agent to induce disease control. Once maximum disease control has been achieved, a consolidating allogeneic SCT could be performed immediately (young, 17p deletion, no comorbidities, well matched donor) or deferred till treatment failure (older, comorbidities, partially matched donor). At treatment failure, disease control must be sought again with an alternative novel agent.³⁴

Ibrutinib after allogeneic SCT can also induce responses that appear durable (OR 88% with a 24 mo PFS of 76.6% and a 24 mo OS of 75%). Ten of these patients had a 17p deletion and showed an OR of 80% and a 24 mo PFS and OS of 64%.³⁵

Maintenance or consolidation treatment

Guidelines 2012 need no change.

Future treatment approaches

Although responses and duration of response are exceptionally high and long with the use of the available BCRi, responses are not forever and the search for new agents must continue. Several ongoing clinical trials are exploring new agents in monotherapy or in combination. These include monoclonal antibodies (e.g. novel anti-CD20 (e.g. ublituximab), anti-CD37 (e.g. BI836826), anti-CD19 antibodies), next generation PI3K (e.g. IPI-145 and TGR-1202) and BTK inhibitors (e.g. ACP-196), Syk-inhibitors (e.g. entospletinib), modulators of the microenvironment (e.g. lenalidomide), apoptosis indu-

cing agents (bcl-2 antagonists (e.g. venetoclax)), and chimeric antigen receptor-engineered T-cells.

Although most of these agents have an acceptable safety profile as monotherapy, combination trials must test not only synergistic activity but also cumulative toxicity. Combining an anti-CD20 monoclonal with a PI3Ki and a BTKi appears safe as the combination of an anti-CD20 monoclonal with a PI3Ki and lenalidomide or a PI3Ki with a Syki induce unacceptable toxicities.^{36,37}

RCTs are also necessary to test if chemo-free regimens are superior to the traditional CITs.

The current challenge is to identify the best combination and sequence to achieve long-term CLL control with optimal quality of life. One option could be to combine the best available agents in a short-term treatment to attain MRD negative CR (CIT-BCRi or -venetoclax). Another option could be to use sequential monotherapies of new and old drugs. A third strategy could be to use a short debulking therapy followed by a combination of a monoclonal with a BCRi as long as remission improves or until CR and then follow-up using single agent maintenance with MRD monitoring. Treatment could be stopped three months after achieving MRD negativity.³⁸

Richter transformation

Guidelines 2012 need no change.

Autoimmune complications

Guidelines 2012 need no change.

Conclusion

The BHS Lymphoproliferative Working Party recommends:

- No treatment for patients without active and/or advanced disease, regardless of prognostic factors (*Figure 1*).
- Ibrutinib or idelalisib-R for patients with a de novo or acquired 17p deletion/p53 mutation.
- Front line treatment (*Figure 1*):
 - FCR for fit patients as this treatment can prolong OS.
 - BR for patients fit and >65y or unfit for FCR (renal function impairment, comorbidities, frequent infections, history of or active haemolysis) as this treatment prolongs PFS.
 - Chl with an anti-CD20 monoclonal antibody for older patients with a geriatric profile, major comorbidities or a reduced PS as this treatment can prolong OS.
 - Chl monotherapy or supportive care for frail patients to control symptoms.

Key messages for clinical practice

1. No treatment is necessary for patients without active and/or advanced disease, regardless of prognostic factors.
2. FCR for fit patients, BR for patients fit but >65y or unfit for FCR and Ob- or R-ChI for older patients with a geriatric profile, major comorbidities or a reduced PS is recommended as front-line treatment.
3. For patients with recurrent disease, CIT can be recommended for late relapse after the previous treatment and the BCRi can be recommended for those with early relapse or refractory disease.
4. The BCRi are also recommended for treatment patients with a 17p deletion and/or p53 mutation.
5. RIC allogeneic SCT should still be considered after remission induction with the BCRi according the EBMT recommendations.
6. Patients must be encouraged to enter clinical trials exploring new agents and/or combinations.

– Second or subsequent treatment for patients with R/R CLL and no 17p deletion/p53 mutation:

- Repeat previous CIT or start an alternative CIT if the duration of response has lasted >2-3y following CIT.
- Ibrutinib or idelalisib/R are recommended for patients unsuitable for purine analogues defined as early

relapse (<2-3y after CIT), refractory disease, CrCl <70 ml/min, CIRS >6, therapy-related cytopenia, or history of autoimmune cytopenia.

- RIC allogeneic SCT should still be considered at response or immediately at first sign of relapse after remission induction with BCRi.

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