



Updated BHS guidelines for the treatment of chronic lymphocytic leukaemia, mantle cell lymphoma and Waldenström macroglobulinemia anno 2018

A. Janssens, MD, PhD¹, V. Vergote, MD¹, V. Van Hende, MD², D. Bron, MD, PhD³, A. Van Hoof, MD⁴

On behalf of the BHS Lymphoproliferative Working Party (Members 2017-2018):

Marc André, Helène Antoine-Poirel, Christophe Bonnet, Dominique Bron, Alessandra Camboni, Charlotte Caron, Sarah Debussche, Hilde Demuynck, Virginie De Wilde, Vanessa Delrieu, Daan Dierickx, Radu Firescu, Pierre Heimann, Caroline Jacquy, Ann Janssens, Jan Lemmens, Marie Maerevoet, Fritz Offner, Liesbeth Schauvliege, Wilfried Schroyens, Sylvia Snauwaert, Joan Somja, Cécile Springael, Thomas Tousseyn, Eric Van Den Neste, Vanessa Van Hende, Achiel Van Hoof, Vibeke Vergote, Gregor Verhoef, Inge Vrelust, Ka Lung Wu.

SUMMARY

The Belgian Haematological Society Lymphoproliferative Working Party updated the existing recommendations on best strategies for frontline and subsequent line treatment of small lymphocytic leukaemia/chronic lymphocytic leukaemia, mantle cell lymphoma and Waldenström Macroglobulinemia according to new reimbursements and robust clinical data.

(BELG J HEMATOL 2018;9(3):101-12)

INTRODUCTION

The Belgian Haematological Society (BHS) Lymphoproliferative Working Party reviewed the recent literature on treatment of small lymphocytic leukaemia (SLL)/chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL) and Waldenström Macroglobulinemia (WM) to update the recommendations published in 2015.¹⁻³

RECOMMENDATIONS FOR THE TREATMENT OF SLL/CLL ANNO 2018

In May 2017, the Belgian authorities extended the reimbursement of ibrutinib monotherapy to first line treatment for CLL patients not suitable for fludarabine (F) treatment and without clinically significant cardiovascular disease. Venetoclax also has obtained reimbursement November 2017 as first line treatment in patients with a 17p deletion (del)/ p53 mutation (mut) who are unsuitable for treatment with ibrutinib and in relapsed/refractory (R/R) patients with a 17p del/p53 mut after failure of a B-cell receptor inhibitor (BCRi) or in R/R patients without a 17p del/p53 mut after failure of chemo-immunotherapy (CIT) and a BCRi. From April 2018, reimbursement of subcutaneous (SC) rituximab (R) for CLL has also been acquired. A fixed dose of 1600 mg can replace the intravenous (IV) dose of 500mg/m2 from the moment no infusion related events have occurred in the previous cycle.

¹Department of Haematology, Universitaire Ziekenhuizen Leuven, Leuven, Belgium, ²Department of Haematology, AZ Sint-Nikolaas, Sint-Niklaas, Belgium, ³Department of Haematology, Institut Bordet, Brussels, Belgium, ⁴Department of Haematology, AZ Sint-Jan, Brugge, Belgium.

Please send all correspondence to: A. Janssens, MD, PhD, Universitaire Ziekenhuizen Leuven, Department of Haematology, Herestraat 49, 3000 Leuven, Belgium, tel: 0032 16 34 68 80, email: Ann.janssens@uzleuven.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: chronic lymphocytic leukaemia, mantle cell lymphoma, Waldenström Macroglobulinemia, treatment guidelines.







FIGURE 1. Algorithm for treatment of CLL Frontline.

*unsuitable for treatment with ibrutinib

TREATMENT CLL

Criteria for initiating first line or subsequent line treatment have not to be changed. Only patients with active or progressive disease should start treatment. Before initiating treatment it is of utmost importance to consider patient related factors (age, performance status (PS), comorbidities, renal and bone marrow function and patient wishes), disease related factors (17p del and/or p53 mut) and treatment related factors (degree and duration (< or >24 months (mo)) of response, contraindications to and side-effects from particular treatment modalities, IV vs. oral treatment, defined treatment period vs. continuous treatment).⁴

FRONTLINE TREATMENT OF ADVANCED AND/OR ACTIVE CLL IN 'FIT' PATIENTS

Fludarabine (F)-cyclophosphamide (C)-R CIT stays the stan-

dard first line therapy in patients, who are fit, have no major comorbidities (cumulative illness rating scale (CIRS) <6) and a normal renal function (creatinine clearance (Cr Cl) \geq 70 ml/min).⁵ For patients >65 years (y) bendamustine (B)-R is an alternative treatment to FCR with similar outcomes but lower toxicities.⁶

FRONTLINE TREATMENT OF ADVANCED AND/ OR ACTIVE CLL IN 'UNFIT' PATIENTS

Obinutuzumab (Ob)-chlorambucil (Chl) or R-Chl stays the standard treatment for elderly patients unsuitable for a F based treatment regimen.^{7,8} Although today no randomised trials (RCTs) for BR in unfit patients are available, BR can be considered as an alternative treatment as retrospective data have shown that BR is an effective and safe treatment in the elderly even with comorbidities.⁹ In the phase III





FIGURE 2. Algorithm for treatment of relapsed/refractory CLL.

RESONATE-2 study of older patients (n=269) (median age 73 y) with treatment naive CLL/SLL, single-agent ibrutinib (given until progressive disease) was compared to Chl (given for maximum 12 mo). Reasons for initiating therapy included progressive marrow failure (38%), lymphadenopathy (37%), splenomegaly (30%), fatigue (27%), and night sweats (25%). Patients with progressive disease in the Chlarm could cross-over to ibrutinib. The initial publication with a median (m) follow up of 18.4 mo showed an impressive reduced risk of progression or death by 84% for ibrutinib vs. Chl (p<0.001).¹⁰ The most recent update with a median follow up of +/-3 y showed an overall response rate (ORR) and complete response (CR) of 92% and 18% with a progression free survival (PFS) rate at 30 mo for ibrutinib of 85% vs 28% for Chl and a reduced risk of death of 57% for ibrutinib.11 Therefore, in May 2017 the Belgian authorities have extended the reimbursement of ibrutinib monotherapy to first-line treatment for CLL patients not suitable for F treatment and without clinically significant cardiovascular disease.

Rituximab 1600 mg SC, combined with FC, achieved trough serum concentrations that were pharmacokinetically noninferior to those achieved with rituximab 500 mg/m² IV, with a similar safety and efficacy profile.¹² Reimbursement of rituximab SC for the treatment of CLL has been obtained from April 2018 as this administration route could be a more convenient delivery method than the IV route. Hopefully it can replace rituximab IV also in other combination regimens especially together with the novel oral drugs.

SECOND OR SUBSEQUENT LINE TREATMENT FOR CLL

In patients with R/R disease in need for treatment fitness, presence or absence of a 17p del and/or a p53 mut and degree and duration of response to the previous treatment (< or >24 mo) must help us to select treatment. CIT is only preferred for patients with a long response to the previous treatment. The duration of response is defined by the Belgian reimbursement criteria as 30 mo from the start of the previous treatment. Today, BR is the most frequent



<u>104</u>



FIGURE 3. Algorithm for treatment of MCL Frontline.

chosen alternative CIT after first line FCR. However, in the two phase III RCTs (BR with placebo compared to BR with idelalisib or ibrutinib) patients treated with BR in the control arm experienced an ORR of 45 and 69% with a mPFS of 11.1 and 13.3 mo.^{13,14} Very recently the results of the third RCT comparing BR vs. venetoclax-R where presented. The ORR and CR were respectively 67.7 and 93.3% and 8.2 and 26.8%. The mPFS was 17 mo vs. not reached.¹⁵ When BR was combined with idelalisib or ibrutinib ORR raised to 70% and 86% with a mPFS of 20.8 mo and not reached.^{13,14} With a 5 y follow-up, R/R CLL patients (PCYC-1102, PCYC-1103 trials) (n=101) receiving ibrutinib, showed an ORR and CR of 89% and 10% with a mPFS of 52 mo and a 5 y OS of 57%.¹⁶ In updated analyses it has been once more confirmed that responses to BCRi are independent of mutational

status and the presence of unfavourable genetic aberrations (11q del, complex karyotype or novel gene mutations).^{17,18} The mPFS for patients with a 17p del/p53 mut was inferior but still 26 mo.¹⁶ Therefore, experts wonder if CIT has still a place in treatment of R/R CLL or if it must be reserved for patients with at least a response duration of >60mo after the previous CIT. No RCTs are available comparing BR with a novel agent vs. the novel agent alone to decide which treatment option should be preferred. In addition, there is a concern in terms of secondary malignancies after CIT treatment and retreatment.

Although the response rates, duration of response (DOR) and the tolerability to the BCRi are high, some patients relapse or are intolerant and need another treatment. Venetoclax is the first bcl-2 antagonist available as single PRACTICE GUIDELINES



FIGURE 4. Algorithm for treatment of relapsed/refractory MCL.

agent for treatment of CLL. The M13-982 trial consisted of R/R CLL patients with a 17p del (n=107), who received at least one prior treatment.¹⁹ 51 patients were included additionally in the expansion cohort. The m age of the patients was 67 y, 65% was male and the median number of prior treatments was two (range 1-10). The time to response was very short (median of 0.8 mo). In an investigator-assessed analysis, including all 158 patients, the ORR was 77% (18% CR/CR with incomplete recovery of blood counts (CRi) and 6% nodular partial remission (nPR)). The mDOR was 27.5 mo with a mPFS of 27.2 mo. Using a cut-off of one CLL cell per 10⁴ leukocytes, 27% of patients (42/158) were shown to have no minimal residual disease (MRD) in the peripheral blood (pb) (fifteen also MRD-negative in bone marrow (BM)).20 In the M14-032 trial, 64 CLL patients who were refractory while on treatment with ibrutinib (n=43) or idelalisib (n=21) or progressed after ibrutinib/idelalisib discontinuation were treated with venetoclax. The m age in this study was 67 y and 75% of patients were male. The

median number of prior treatments was four (range 1-12). The ORR was 64%, with a CR/CRi of 9% and a nPR of 3%. The six and twelve mo PFS were 89% and 72%. Venetoclax could induce MRD negativity in 25% (16/64) of tested patients in the pb (one also in BM).²¹ Venetoclax has gathered reimbursement November 1st 2017 as first line treatment in patients with a 17p del/p53 mut who or unsuitable for treatment with ibrutinib and in R/R patients with a 17p del/p53 mut after failure of a BCRi or in R/R patients without a 17p del/p53 mut after failure of CIT and a BCRi.

Data on optimal sequencing of the new oral agents are limited (n=178). The most common reasons for BCRi discontinuation were toxicity (51%), CLL progression (29%), and Richter transformation (RT) (8%). Today, a proposal could be to treat patients who discontinue BCRi due to toxicity with an alternate BCRi and to switch progressive patients to the bcl-2 antagonist.^{22,23} The outcome after RT stays infaust. Check point inhibitors seem to have some activity but further investigation is warranted.²⁴





FIGURE 5. Algorithm for treatment of WM Frontline.

TREATMENT OF CLL WITH 17P DEL OR TP53 MUT: FRONT-LINE OR AT RELAPSE

Patients showing a 17p del/p53 mut are poor responders to conventional treatment (chemotherapy, immunotherapy, CIT, corticosteroids) resulting in an inferior outcome. The BCRi ibrutinib and idelalisib are approved for the treatment of patients with a 17p del/p53 mut even as frontline treatment.¹ Although mPFS and mOS are shorter for patients with the p53 aberration, the outcome is still better than for any treatment available for this bad prognostic subgroup.¹⁶ Due to safety concerns (infections), it has been advised to treat patients with a 17p del/p53 mut frontline with R-idelalisib only when the patient is unsuitable for ibrutinib. Venetoclax can be nowadays an alternative in this situation. In R/R CLL patients with a p53 alteration, venetoclax is also a new treatment option after ibrutinib or R-idelalisib.

ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) FOR CLL

Reduced intensity allogeneic SCT should still be considered as a reasonable therapeutic option for younger, fit, high-risk (F refractory, early relapse after CIT or having a 17p del/p53 mut in need for treatment) CLL patients. These patients should today 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 (< 70 y, 17p del/p53 mut, no comorbidities, well matched donor) or deferred till treatment failure (> 70 y, multiple or severe comorbidities, partially matched donor). At treatment failure disease control must be sought again with an alternative novel agent (other BCRi, venetoclax, clinical trial, etc.) and the need of a consolidating allogeneic SCT reconsidered at response.^{25,26}

FUTURE TREATMENT APPROACHES FOR CLL

Although responses and DOR are exceptionally high and long with the use of the new oral agents, the search for new agents or combinations must continue and patients must be encouraged to enter clinical trials. The challenge stays to identify the best combination or sequence to achieve long-term CLL control with optimal quality of life. RCTs are ongoing to compare chemo-free regimens to the traditional CITs in front-line. As the new oral agents for the moment are given till progression or intolerance, ongoing trials are exploring stopping treatment after a well-defined time period or at the achievement of a MRD negativity. Further research projects on clonal evolution and treatment resistance are ongoing.





FIGURE 6. Algorithm for treatment of relapsed/refractory WM.

RECOMMENDATIONS FOR THE TREATMENT OF MCL ANNO 2018

Very recently the Belgian authorities have granted the reimbursement of rituximab (original and biosimilar) for the treatment of MCL patients in combination with chemotherapy and in maintenance. Induction with R-DHAP (cisplatinum, cytarabine, dexamethasone) (4x) could be an alternative to alternating R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone)/R-DHAP (6x) before autologous SCT.

DIAGNOSIS: LEUKEMIC NON-NODAL MCL

Most patients with MCL follow an aggressive or rapidly progressive clinical course, however a small subset of patients may exhibit a more indolent evolution. These patients have a distinct pathogenesis and are now recognised as a separate subtype of MCL according to the 2016 WHO classification (named leukemic non-nodal MCL). These cases are often hard to distinguish, but have a typical clinical presentation with BM involvement and splenomegaly only. Also SOX11 negativity may help to identify these cases. In this small group of patients with low tumour burden, a course of 'watch and see' under close observation seems to be appropriate.^{27,28} Throughout the rest of the manuscript we will use MCL to refer to the classical MCL.

TREATMENT MCL

FIRST LINE TREATMENT MCL: LOCALISED DISEASE (STAGE I-II)

The small group of patients presenting with limited stage disease can be treated with radiotherapy (RT) or a shortened conventional chemotherapy followed by consolidation RT.





In case of stage I-II disease with large tumour burden or adverse prognostic features (high MCL international prognostic index (MIPI), blastoid morphology, high Ki67, B-symptoms, etc.), systemic therapy as indicated for advanced stages should be applied.^{28,29}

ADVANCED DISEASE (STAGE III-IV) MCL: YOUNGER PATIENTS (<66Y, ELIGIBLE FOR AUTOLOGOUS SCT)

As was presented in our previous guidelines, the optimal treatment for younger patients consists of an induction with an Ara C containing regimen, followed by high dose (HD) chemotherapy and autologous SCT.² The most commonly used induction therapy is R-DHAP alternating with R-CHOP, as this regimen has shown to significantly improve PFS, and show a trend towards improved OS, when compared to R-CHOP alone.³⁰ Recently, the final results of the LyMa trial have been published. In this phase III trial, patients were randomly assigned to receive R maintenance (375 mg/m² every 2 mo for 3 y) or undergo observation, after induction with four cycles R-DHAP and autologous SCT. This study showed that R maintenance after autologous SCT significantly prolongs PFS (83% vs. 64% at 4 y) and OS (89% vs. 80%).³¹ Since the recent expansion of the reimbursement of R in Belgium, we advise that R maintenance after autologous SCT should be standard of care in younger MCL patients. Notably, R-DHAP (4x) induction produces high ORR (89%) and CR (77%) and can be considered as an alternative induction therapy to R-CHOP/R-DHAP (6x) if followed by an autologous SCT and maintenance R. No RCTs comparing these two induction treatments are however available.

ADVANCED DISEASE (STAGE III-IV) MCL: ELDERLY PATIENTS (>65Y, NON-ELIGIBLE FOR AUTOLOGOUS TRANSPLANT)

For the main group of elderly patients, CIT followed by R maintenance appears to be the gold standard. R in combination with chemotherapy such as CHOP or B should be used.^{2,28,32} The benefit of R maintenance (375 mg/m² every 2 mo until progression) has been proven after induction with R-CHOP.³³ However, preliminary results from the MAINTAIN trial showed no significant benefit (both in PFS and OS) for R maintenance after BR.³⁴ Other alternatives include VR-CAP (R-CHOP regimen, replacing vincristine with bortezomib at a dose of 1.3 mg/m²) (bortezomib not reimbursed in Belgium for the treatment of MCL) or R-BAC (bendamustine, AraC).^{35,36}

SALVAGE TREATMENT MCL

Despite the advances in first line treatment, most patients

will eventually relapse. For younger patients re-induction followed by allogeneic SCT should be considered.³⁷

The choices for salvage treatment include novel therapies (ibrutinib, lenalidomide, temsirolimus, and bortezomib) or classical CIT. In case of early relapse (<12-24 mo) or refractory disease we strongly advise the use of novel agents. Among these compounds ibrutinib achieves the highest response rates and most durable remissions (mPFS 13 mo).³⁸ Based on these data ibrutinib has gained reimbursement in Belgium for the treatment of MCL at first relapse. Lenalidomide (preferably in combination with R) has also shown efficacy in relapsed MCL and can be considered as an alternative therapy, however lenalidomide is not yet reimbursed in Belgium for this indication.^{28,39} Temsirolimus has shown limited efficacy in MCL (mPFS 4.8 mo), and is reimbursed at second relapse in Belgium.⁴⁰

In case of late relapses (>12-24 mo) a non-cross resistant scheme of CIT can be considered for re-induction (e.g. BR, R-DHAP, HD Ara C, etc.).^{2,28}

FUTURE TREATMENT APPROACHES FOR MCL

Several new agents for the treatment of MCL are currently under investigation. The novel Bruton's tyrosine kinase inhibitor (BTKi) acalabrutinib induces a high rate of ORR (81%) and CR (40%) in R/R MCL, leading to its FDA approval in October 2017.⁴¹ Another promising therapy is the bcl-2 inhibitor venetoclax, showing high ORR (75%) and an acceptable safety profile in a phase I trial.42 Results from trials with immune checkpoint inhibitors in MCL have been disappointing so far. Further studies are needed to determine the role of these novel agents, as well as the role of combination therapies such as R-ibrutinib and BR-ibrutinib. In light of the development of these potent novel agents, the need for an autologous SCT in first remission needs to be evaluated. The Hovon 133-TRIANGLE trial is a phase III RCT, comparing classical induction with R-CHOP/R-DHAP with or without ibrutinib followed by autologous SCT and/or ibrutinib maintenance. Results are expected in 2021.

RECOMMENDATIONS FOR THE TREATMENT OF WM ANNO 2018

Ibrutinib has gathered reimbursement in Belgium in September 2016 for the treatment of adult patients with a MYD88-L265P mutated WM, an Ig M level >2x upper limit of normal (ULN) after two or more prior treatment regimens, including at least one treatment with R. Very recently the Belgian authorities have extended the reimbursement of R (original and biosimilar) also for the treatment of WM patients.



DIAGNOSIS WM

In the 2016 revision of the WHO classification of lymphoid disorders testing for MYD88-L265P mutation has been included as a diagnostic criteria for WM (mutated in >90% of WM) next to an Ig M monoclonal protein along with histological infiltration of BM by clonal lymphoplasmacytic cells.²⁷ WM patients without MYD88-L265P are reported to have a more aggressive and treatment-resistant disease.⁴³ The presence of the MYD88-L265P mutation is necessary to obtain reimbursement for ibrutinib in R/R WM in Belgium. CXCR4 mutations are found in about 30% of WM.⁴⁴ Routine testing of the CXCR4 mutation is however not recommended. In patients with nodal disease imaging with CT scan should be performed before starting therapy.

TREATMENT WM

FIRST LINE TREATMENT WM

Treatment indications have not been changed. A watch and wait approach is still the standard strategy in asymptomatic patients. However, the occurrence of cytopaenia (Hb <10 g/dl, platelets <100000/µl), hyperviscosity, moderate or severe polyneuropathy (PNP), extramedullary symptomatic disease (large lymphnodes, organ involvement, effusions, Bing Neel syndrome), symptomatic cryoglobulinemia, cold agglutinin disease and amyloidosis must lead to the start of treatment.³ The combination of R with chemotherapy is among the most effective treatments and remains the first option for fit patients. As front line treatment the majority of patients receive a combination of R with C and dexamethasone (R-CD) or prednisolone (R-CP). These schedules give an ORR of 70-80%, and a CR in approximately 10% of patients. Schedules with an anthracycline and/or vincristine have proven to be equally effective but with more adverse events, particularly treatment related PNP and febrile neutropenia.^{3,45,46}

BR and bortezomib-RD show the same efficacy data. Treatment choice must therefore depend on individual patient related factors and expected treatment toxicities. As longlasting cytopaenias occur after BR especially in elderly patients, it's advised to lower the dose of B.⁴⁷

TREATMENT IN R/R WM

Approval of the BTKi ibrutinib in the United States and Europe represents a novel and effective treatment option for relapsing patients. MYD88 mutation evokes BTK activation and therefore BTKi, such as ibrutinib are highly active in WM. The prospective study of ibrutinib in symptomatic WM patients who received at least 1 previous treatment (n=63) showed an ORR of 91% with a major response rate of 73% and a 2 y PFS of 69% and a 2 y OS of 95%. The m

time to obtain at least a minor response was 4 weeks. Treatment-related AEs of grade 2 or greater included neutropenia (22%) and thrombocytopenia (14%), both more common in heavily pretreated patients. Atrial fibrillation was present in 3% of patients.⁴⁸ These impressive results were confirmed in the iNNOVATE trial (single-agent ibrutinib in 31 R/R WM patients with an ORR of 90% and an 18mo PFS and OS of 86% and 97% and a m time to best response of 2 mo). AEs included grade 1-2 diarrhoea (36%), thrombocytopenia (13%), grade 3 neutropenia (10%) and hypertension (10%). A vast majority of serious AEs were related to infections.49 Although ibrutinib may increase the risk of bleeding, WM patients with acquired von Willebrand disease associated with a high IgM level showed benefit after treatment with ibrutinib due to disease control. In the recent published treatment recommendations from the Eighth International Workshop on WM, the panel recommends that testing for von Willebrand activity in patients with a history of bleeding diathesis before starting ibrutinib is reasonable.⁵⁰ Ibrutinib is reimbursed in Belgium for the treatment of adult patients with WM presenting a MYD88-L265P mutation and an Ig M level >2 x ULN. Patients should have received at least two prior regimens, including at least one treatment with R.

FUTURE TREATMENT APPROACHES FOR WM

Several new molecules, as well as new combinations with ibrutinib are being investigated in WM. In the before mentioned iNNOVATE trial combination of R with ibrutinib is tested in previously untreated patients.⁴⁹ IRAK1 is a protein downstream of BTK. WM cells with MYD88 mutation show preferential IRAK1 rather than IRAK4 signalling. Theoretically ibrutinib in combination with IRAK inhibitors can overcome ibrutinib resistance by augmenting the NF $\kappa\beta$ blockade.⁵¹ Idelalisib targets the PI3K pathway and is activated in patient with MYD88 mutation. Recently, a phase II study evaluating the safety and efficacy of idelalisib in patients with R/R WM was prematurely closed due to the high incidence of hepatotoxicity.⁵² The bcl-2- antagonist, venetoclax, seems also effective in WM with CXCR4WHIM mutation that is known to cause resistance to BTK and PI3K inhibitors. Activity of venetoclax as a single agent has also been demonstrated in cell lines with CXCR4WT mutations what is believed to be due to overexpression of BCL2 by the WM cells.⁵³

CONCLUSION UPDATE: RECOMMENDATIONS FOR THE TREATMENT OF SLL/CLL, MCL AND WM ANNO 2018

The 2018 treatment guidelines for SLL/CLL incorporate two major changes. Ibrutinib monotherapy is available as first



KEY MESSAGES FOR CLINICAL PRACTICE

- 1 No immediate treatment is necessary for CLL/MCL/WM patients in the absence of active and/or advanced disease.
- 2 The CLL treatment guidelines has been adapted:
 - a. Ibrutinib monotherapy is available for first line patients not suitable for F and without severe, uncontrolled cardiovascular disease and is an alternative to Ob-Chl or BR.
 - b. Venetoclax is available as first line in patients with a 17p del/p53 mut unsuitable for treatment with ibrutinib.
 - c. Venetoclax is available to treat R/R CLL with a 17p del/p53 mut after failure of a BCRi.
 - d. Venetoclax is also available for R/R patients without a 17p del/p53 mut after failure of CIT 'and' a BCRi.
 - e. Reimbursement of R SC has been gained since April 2018 and can replace R IV from the moment no infusion related events has occurred in the previous cycle.
- 3 The MCL guidelines are updated as follows:
 - a. R (original and biosimilar) is reimbursed for the treatment of MCL.
 - b. R maintenance (q2mo/3y) after induction with a HD Ara C containing CIT followed by autologous SCT is now standard of care in younger patients.
- 4 The WM guidelines need also to be changed:
 - a. Ibrutinib is reimbursed for the treatment of adult patients with a MYD88-L265P mutation and an Ig M level >2x ULN. Patients should have received at least two prior regimens, including at least one treatment with R.
 - b. R (original and biosimilar) is reimbursed for the treatment of WM.
- 5 Patients must still be encouraged to enter clinical trials exploring new agents or combinations.

line treatment for CLL patients not suitable for treatment with F and without severe, uncontrolled cardiovascular disease. Venetoclax as first line treatment in patients with a 17p del/p53 mut is available for those who or unsuitable for treatment with ibrutinib. Venetoclax is also available to treat R/R CLL with a 17p del/p53 mut after failure of a BCRi and R/R patients without a 17p del/p53 mut after failure of CIT and a BCRi. In 2018 reimbursement of R SC is expected also for CLL.

The updated guidelines on the treatment of MCL in Belgium advice to incorporate R maintenance also in younger MCL patients after induction with R-chemotherapy including HD Ara C followed by autologous SCT. For elderly patients induction with R-CHOP followed by R maintenance is still standard of care. BR can be used as an alternative induction therapy. In case of relapse treatment choices consist of allogeneic SCT in younger patients, classical CIT or a novel therapy (such as ibrutinib).

Since the publication of the BHS WM guidelines in 2015, three major changes occurred in the diagnostic work up and treatment. During the diagnostic work up molecular testing for MYD88-L265P mutation is essential. This mutation is present in >90% of WM. The presence of the mutation is predictive for response to BTKi. Since 2016 ibrutinib is reimbursed for patients who had at least two prior treatments, one containing R. R (original and biosimilar) is reimbursed for WM from 2018 on.

REFERENCES

1. Janssens A, Van Den Neste E, Offner F, et al. Updated BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2016. Belg J Haematol. 2015;6:195-202.

2. Vergote V, Janssens A, Van Den Neste, et al. Practice guidelines: Treatment of mantle cell lymphomas: Updated recommendations of the Belgian Hematological Society 2015. Belg J Haematol. 2015;6:203-8.

 Van Hende V, Bron D, Van den Neste E, et al. Waldenström's macroglobulinaemia: Belgian Haematology Society guidelines. Belg J Hematol. 2015;6:142-150.
Hallek M, Cheson BD, Catovsky D, et al. Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. Blood. 2018 Mar 14. [Epub ahead of print].

5. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376:1164-74.

6. Eichhorst B, Fink A, Busch R, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab (R) in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17:928-42.

PRACTICE GUIDELINES

 Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Eng J Med. 2014;370:1101-10.
Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukaemia: updated results of the CLL11 study. Leukemia. 2015;29;1602-4.

9. Kleeberg U, Linde H, Günther G, et al. Bendamustin-rituximab combination is a safe and effective, ambulatory treatment for elderly patients with chronic lymphocytic leukaemia: retrospective real-world analysis by age from a German registry and review of the literature. Anticancer Res. 2016;36:2827-38.

10. Burger J, Tedeschi A, Barr P, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukaemia. N Eng J Med. 2015;373:2425-47.

 Barr P, Robak T, Owen C, et al. Updated Efficacy and Safety from the Phase
Resonate-2 Study: Ibrutinib As First-Line Treatment Option in Patients
Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Blood, 2016;128:234.

12. Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. Lancet Haematol. 2016;3:e128-38.

13. Zelenetz A, Barrientos J C, , et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, doubleblind, placebo-controlled trial. Lancet Oncol. 2017;18:297-311.

14. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): CLL/SLL: a randomized, double blind, phase 3 study. Lancet Oncol. 2016;17:200-11.

15. Seymour J, Assouline S, Jaeger U, et al. Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukaemia: results from pre-planned interim analysis of the randomized phase 3 Murano study. ASH 2017, Abstract BA-2.

 O'Brien S, Furman R, Coutre S, et al. Five year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia/ small lymphocytic lymphoma. ASH 2016 abstract 233.
Kipps T, Fraser G, Coutre S, et al. Integrated analysis: outcomes of ibrutinibtreated patients with chronic lymphocytic leukaemia/small lymphocytic leukaemia (CLL/SLL) with high-risk prognostic factors. Hematol Oncol. 2017;35 S2:109-11.
Brown J, Hillmen P, O'Brien, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. Leukemia. 2017. [Epub ahead of print].

19. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17:768-78.

20. Stilgenbauer S, Chyla B, Eichhorst B, et al. Venetoclax in relapsed/refractory chronic lymphocytic leukaemia (CLL) with 17p deletion: outcome and minimal residual disease from the full population of the pivotal M13-982 trial. Haematologica. 2017;102,S2:S771.

21. Jones J, Choi M, Mato A, et al. Venetoclax monotherapy for patients with chronic lymphocytic leukaemia who relapsed after or were refractory to ibrutinib or idelalisib. ASH 2016, abstract 637.

22. Mato R, Hill B, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib and venetoclax in chronic lymphocytic leukaemia: results from a multicentre study of 683 patients. Ann Oncol. 2017;28:1050-6.

23. Jones J, Mato A, Wierda W, 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(1):65-75.

24. Ding W, LaPlant B, Call T, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. Blood. 2017;129:3419-27.

25. Montserrat E, Dreger P. Treatment of Chronic Lymphocytic Leukemia with del(17p)/TP53 Mutation: Allogeneic Hematopoietic Stem Cell Transplantation or BCR-Signaling Inhibitors? Clin Lymphoma myeloma Leuk. 2016;16 Suppl: S74-81.

26. Selleslag D. Is there a place for allogeneic stem cell transplantation in chronic lymphocytic leukaemia in the era of new molecules? Belg J Haematol. 2017;8:185-91.

27. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375-90.

 Dreyling M, Campo E, Hermine O, et al. ESMO Guidelines Committee. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv62-iv71.
Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol. 2003;14:1555-61.

30. Hermine O, Hoster E, Walewski J, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. Lancet. 2016;388:565-75.

 Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stemcell transplantation in mantle-cell lymphoma. N Engl J Med. 2017;377:1250-60.
Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet, 2013;38:1203-10.

33. Kluin-Nelemans HC, Hoster E, Hermine O. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367:520-31.

34. Rummel MJ, Knauf W, Goerner M, et al. Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: First results of a prospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial). J Clin Oncol. 2016;34:15 Suppl:7503.

35. Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med. 2015;372:944-53.

36. Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamus-



112

PRACTICE GUIDELINES

tine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. J Clin Oncol. 2013;3:1442-9. 37. Dietrich S, Boumendil A, Finel H, et al. Outcome and prognostic factors in patients with mantle-cell lymphoma relapsing after autologous stem-cell transplantation: a retrospective study of the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol. 2014;25:1053-8.

 Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: Updated safety and efficacy results. Blood. 2015;126:739-745.

39. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1-2 clinical trial. Lancet Oncol. 2012;13:716-723.

40. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2009;27:3822-9.

41. Wang M, Rule S, Zinzani P, et al. Efficacy and safety of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma in the Phase 2 ACE-LY-004 study. ASH annual meeting abstract. 2017. Abstract 155.

42. Davids M, Roberts A, Seymour J, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Onco. 2017;35:826-33.

43. Treon SP, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinaemia. N Engl J Med. 2012;367:826-33.

44. Hunter Z, et al. The genomic landscape of Waldenström macroglobulinaemia is characterised by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014;123:1637-46. 45. loakimidis L, et al. Comparative outcomes following CP-R, CVP-R, and CHOP-R in Waldenström's macroglobulinaemia. Clin Lymphoma Myeloma. 2009;9:62-6.

46. Dimopoulos M, Anagnostopoulos A, Kyrtsonis M, et al. Primary treatment of Waldenström macroglobulinaemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol.

47. Laribi K, Poulain S, Willems L, et al. The bendamustine plus rituximab regimen is active and safe in previously untreated patients with Waldenström macroglobulinemia, a study on behalf of the French Innovative Leukemia Organization (FILO). ASH 2017;abstract 4046.

48. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med. 2015;372:1430-40.

49. Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an openlabel substudy of an international, multicentre, phase 3 trial. Lancet Oncol. 2017;18:241-50.

50. Leblond V, Kastritis E, Advani R, et al. Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia. Blood. 2016;128:1321-8.

51. Yang G, Liu X, Chen J, et al. Targeting IRAK1/IRAK4 signalling in Waldenström's macroglobulinemia. Blood. 2015;126:4004.

 S2. Castillo JJ, Gustine JN, Meid K, et al. Idelalisib in Waldenström macroglobulinemia: high incidence of hepatotoxicity. Leuk Lymphoma. 2017;58:1002-4.
S3. Cao Y, Yang G, Hunter Z, et al. The BCL2 antagonist ABT-199 triggers apoptosis, and augments ibrutinib and idelalisib mediated cytotoxicity in CXCR-4Wild-type and CXCR4WHIM mutated Waldenström macroglobulinaemia cells. Br J Haematol. 2015;170:134.

ABBREVIATIONS

17p del/p53 mut: 17p deletion/p53 mutation	R: rituximab
Allo-SCT: allogeneic stem cell transplantation	R-CHOP: rituximab-cyclophosphamide-adriamycine-
AIC: auto-immune cytopaenia	vincristin-corticosteroids
Auto-SCT: autologous stem cell transplantation	R-CD: rituximab- cyclophosphamide-dexamethasone
BR: bendamustine, rituximab	R-Chl: rituximab-chlorambucil
BRD: bortezomib- rituximab-dexamethasone	R-CP: rituximab- cyclophosphamide -prednisolone
Chl: chlorambucil	R-DHAP: rituximab-cisplatinum-cytarabine-dexamethasone
CIT: chemo-immunotherapy	R/R: relapsed/refractory
CLL: chronic lymphocytic leukaemia	R/R MCL: relapsed/refractory mantle cell lymphoma
FCR: fludarabine, cyclophosphamide, rituximab	R/R WM: relapsed/refractory Waldenström
IF RT: involved field radiotherapy	macroglobulinemia
HD ARA-C: high dose cytarabine	unfit for FCR: Cr Cl <70 ml/min, CIRS >6, therapy-related
HD CT: high dose chemotherapy	cytopaenia, history of autoimmune cytopaenia
MCL: mantle cell lymphoma	VR-CAP: bortezomib-rituximab-cyclophosphamide-
Ob: obinutuzumab	adriamycine-corticosteroids
PNP: polyneuropathy	WM: Waldenström macroglobulinemia

VOLUME9june2018