Diagnosis, treatment and supportive management of chronic lymphocytic leukemia

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REVIEW

Diagnosis, treatment and supportive management of chronic lymphocytic leukemia: recommendations of the Dutch HOVON CLL working group

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ABSTRACT

Management of patients with chronic lymphocytic leukemia (CLL) is changing due to considerable advances in the therapeutic armamentarium, and new therapies will possibly continue to emerge in the near future. Therefore, the CLL working group of the Dutch-Belgium Haemato-Oncology Cooperative Group for Adults in the Netherlands (HOVON) necessitated revising the Dutch CLL guidelines. The current guideline is based on the expert opinion of the HOVON CLL working group members and focusses on well-designed clinical trials taking into account efficacy with special emphasis on toxicity, treatment duration and treatment intensity. This article provides recommendations on diagnosis, treatment strategies in front-line and relapsed setting and provides supportive care measurements during novel-based therapies as well as for infectious CLL-related complications. The recommendations presented here are intended to provide guidance for the management of CLL patients in the Netherlands, and take into account the availability of treatment strategies at the time of this publication.

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Introduction

Chronic lymphocytic leukemia is the most common type of leukemia in Western countries, with an age-standardized incidence rate ranging from 3.8 to 5.0 person-years in a contemporary era [1–5]. Annually, 800–1000 additional cases are diagnosed in the Netherlands [1]. The disease is frequently diagnosed in the seventh decade of life and is referred to as a disease of the elderly. The male predominance is marked with an age-standardized incidence rate of 5.1 for males, as compared to 2.6 per 100,000 person-years for female individuals [1]. The management of CLL patients has undergone a transformational shift in the past decade. Refinement of diagnostic procedures, improvement in prognostic capabilities and the introduction of novel-based targeted agents have collectively made a tremendous impact to the paradigm of CLL [6,7]. Alongside these advances, the implementation of novel-based agents have led to a dramatic increase in societal costs [8,9]. Consequently, the CLL working group of the Dutch-Belgium Haemato-Oncology Cooperative Group for Adults in the

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Netherlands (HOVON) necessitated an update of the 2018 Dutch CLL guideline [10].

The revised guideline was formatted using the expert opinion of the members of the HOVON CLL working group based on results of well-designed clinical trials, preferably randomized controlled clinical phase-3 trials (RCTs), taking into account: (i) efficacy in terms of progression-free survival (PFS) and overall survival (OS) (ii) toxicity (iii) treatment duration and (iv) treatment intensity. Currently, the majority of the clinical trials uses PFS as a primary endpoint and statistics are based on the difference in the expected PFS as and statistics are based on the difference in the expected PFS. Moreover, OS differences are frequently not established and quality of life data is lacking and usually not correlated to PFS, OS or time-to-next treatment. Consequently, the HOVON CLL working group decided to establish treatment recommendations based on efficacy with special emphasis on toxicity, treatment duration and treatment intensity. The recommendations presented here are intended to provide practical guidance for the management of CLL patients in daily practices within the Netherlands, and take into account the availability of treatment strategies in the Netherlands at the time of this publication.

Diagnosis of CLL

CLL is a recognized entity in the WHO/WHO 2016 classification of hematopoietic and lymphoid tissues and is defined in the third edition of the International Classification of Diseases for Oncology (ICD-O-3) as 9823/3 [11,12]. The diagnosis of CLL should be suspected in case of a persistent lymphocytosis, sustained for at least 3 months, that morphologically shows smudge cells and mature small lymphocytes with dense nuclei and partially aggregated chromatin. Immunophenotyping of the peripheral blood is mandatory to assess the clonality [13,14]. A monoclonal B-cell count $\geq 5 \times 10^9$/L with a distinct immunophenotype profile is necessary to established the diagnosis [15]. More specifically, CLL cells co-express the surface antigen CD5 together with expression of the B-cell antigens CD19, CD23 and weak expression of CD20 [16–18]. Additionally, expression of CD43, CD200 and weak expression of CD79b can be present. Each leukemic clone is restricted to expression of the kappa or lambda light chain, which results into finding an aberrant kappa: lambda ratio [18]. The diagnosis of CLL does not require a bone marrow evaluation or a lymph node biopsy.

Small lymphocyte infiltration with a CLL-like phenotype in the lymph nodes, spleen or other extramedullary organs, in the absence of a lymphocytosis $\geq 5 \times 10^9$/L in the peripheral blood leads to the diagnosis of small lymphocytic leukemia (SLL). Of note, the diagnosis of SLL should always be confirmed by histopathological evaluation through a biopsy of a lymph node or another tissue.

In the presence of a clone in the peripheral blood at the level of $< 5 \times 10^9$/L, which is immunophenotypically identical to CLL and the absence of lymphadenopathy, organomegaly and bone marrow infiltration, the diagnosis of monoclonal B-cell lymphocytosis (MBL) should be made [19].

Clinical staging and indications for treatment

Historically, prognostication has relied on the clinical staging as per Rai and Binet [20,21]. These staging systems, developed approximately 40 years ago, are still widely used within the daily clinical practices and hold prognostic capabilities. Consequently, patients with Rai 0-II or Binet A or B should only be treated if there are signs of an active disease, whereas Rai III/IV and Binet C patients should always be treated. Of note, the etiology of an anemia or thrombocytopenia in patients with stable disease should be questioned prior to attributing it to CLL progression consequently leading to misclassification as Rai III/IV or Binet C. Active disease criteria has been defined by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) [13].

Pretreatment assessment

At diagnosis the WHO performance score and the presence of constitutive symptoms should be determined. Physical examination should include palpation of all lymph nodes, spleen and liver. In addition to the above-mentioned complete and clinical evaluation, additional blood examination is also required. More specifically, a complete blood count with differentiation, hemolysis parameters (i.e. reticulocytes count, lactate dehydrogenase, haptoglobin and a direct antiglobulin test), kidney parameters (i.e. serum creatinine level and glomerular filtration rate) and liver parameters (i.e. transaminases, bilirubin and gamma-GT) should be performed. In addition, active or chronic infections that may be aggregated by therapy should be determined. Consequently, all patients should undergo serological testing for hepatitis B, hepatitis C and HIV. Performing a CT scan of the thorax, abdomen

Table 1. Pretreatment evaluation.

	Mandatory	Recommended	At indication
Clinical evaluation			
WHO performance score	X		
Constitutive symptoms	X		
Number of lymphadenopathies	X		
Hepatomegaly and/or splenomegaly	X		
Bone marrow biopsy[a]			X
Blood tests			
Complete blood count and differentiation	X		
LDH, reticulocyte count, haptoglobin and DAT	X		
Serum creatinine level and glomerular filtration rate	X		
Transaminases, bilirubin, gamma-GT	X		
HIV, hepatitis B and C serology	X		
Cytogenetics			
Del17p	X		
Del11q		X	
Del13q		X	
Trisomy 12		X	
Molecular diagnostics			
TP53 mutation	X		
IGHV mutational status[b]	X		
Imaging			
CT thorax abdomen pelvis[c]			X

[a]Only indicated in case of cytopenias with an unknown etiology.
[b]This test can be omitted if it does not have any therapeutic consequences.
[c]Only indicated if necessary for tumor lysis risk assessment or needed for response evaluation.
Abbreviations: DAT: direct antiglobulin test; IGHV: immunoglobulin heavy chain gene; LDH: lactate dehydrogenase; WHO: world health organization.

and pelvis is recommended for tumor lysis risk assessments, but is not mandatory for response evaluation [22]. As previously mentioned, a bone marrow biopsy is not needed to established a diagnosis of CLL. However, as marrow examination can help evaluate factors that might contribute to cytopenias it can be considered in case of cytopenias in patients with Binet A or Rai I/III, in stable CLL or whenever the cytopenia is of an unknown origin. A complete overview of all the required tests prior to start of therapy are provided in Table 1.

Cytogenetics

The assessment of aberrations in the *TP53* gene is essential for choosing the optimal treatment strategy. Consequently, cytogenetic assessment by fluorescence *in situ* hybridization (FISH) is mandatory for the deletion of the long arm of chromosome 17p (del17p). Additionally, the deletion of the short arm of chromosome 11 (del11q) and chromosome 13 (del13q) and trisomy 12 (tri12) can be assessed for prognostic information [23].

TP53 mutations

Since at least half of the CLL patients with an aberration in the *TP53* gene do not have a del17p, assessment of *TP53* mutations is also mandatory prior to start of therapy [24,25]. The HOVON CLL working group recommends the assessment of *TP53* mutations by next-generation sequencing (NGS) or Sanger sequencing in an ERIC-certified center. The presence of *TP53* mutations should be reported if the variant allele-frequency (VAF) is $\geq$10% [26]. Although NGS can detect smaller clones, the prognostic value and clinical relevance of smaller *TP53* clones with a VAF $<$10% remains under discussion [27]. Therefore, the HOVON CLL working group does not recommend the use of NGS over Sanger sequencing for *TP53* mutation assessment.

Somatic mutations of the immunoglobulin heavy chain gene (IGHV)

Approximately 50% of all untreated CLL patients have an unmutated IGHV, which is defined as $\geq$98% sequence homology as compared to the germ line. These patients have a poorer prognosis and respond poorly to chemoimmunotherapy, as compared to patients with mutated IGHV genes [28–30]. Moreover, approximately 40% of all CLL patients expresses stereotyped B cell receptors and can be assigned to different subsets, which in some cases are associated with a specific course of the disease [31]. For example, subset #2 is the largest subset and is characterized by a borderline IGHV expressing IGHV3-21 and is associated with a poorer prognosis, irrespective of the somatic hypermutation status [32]. At present, the HOVON CLL working group does not recommend the assessment

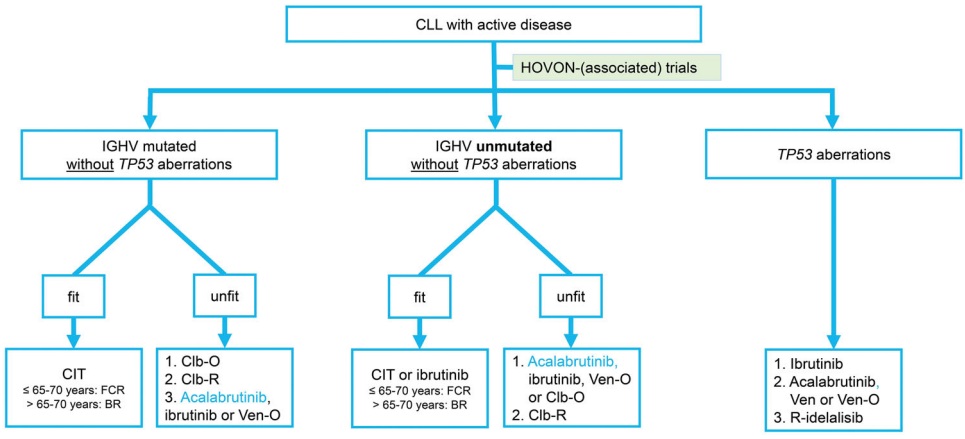

Figure 1. Recommendations for first-line therapy in previously untreated CLL patients with mutated IGHV genes without *TP53* aberrations, unmutated IGHV genes without *TP53* aberrations and for patients with *TP53* aberrations. Abbreviations: BR: bendamustine and rituximab; Cbl: chlorambucil: CLL: chronic lymphocytic leukemia; FCR: fludarabine cyclophosphamide and rituximab; IGHV: immunoglobulin heavy chain gene; O: obinutuzumab; R: rituximab; Ven: venetoclax.

of the different subsets in CLL as it does not have an implication for therapy. However, it is mandatory to assess the IGHV mutation status in an ERIC-certified center [13,33].

First-line treatment

Whenever there is an indication for start of therapy, it is important to consider several patient- and disease-specific aspects in the decision-making to establish the most suited treatment regimen for the patient [13,34]. Currently, the choice of therapy is determined by the risk profile of the CLL – in particular the presence of *TP53* aberrations and unmutated IGHV genes – and the age and fitness level of the patient. The HOVON CLL working group recommendations in first-line setting are discussed below and an overview of these recommendations is provided in Figure 1. An overview of all reimbursed treatment modalities in the Netherlands, as compared to the approval by the European Medicine Agency (EMA) at the time of this publication is provided in Supplemental Table S1.

Mutated IGHV genes without TP53 aberrations

The first selection criteria in the treatment decision-making process in this subgroup of CLL patients is the assessment of fludarabine-eligibility. Fludarabine-eligible patients are young individuals <65 years without significant comorbidities defined as a cumulative illness rating scale (CIRS) <6 and adequate renal function (GFR >60 mL/min). In fludarabine-eligible patients, the combination of fludarabine, cyclophosphamide and rituximab (FCR) remains the standard therapy. FCR has been proven to provide excellent responses and long-term remissions. More specifically, FCR heralded a plateau in mutated IGHV patients with at least half of all patients being in remission after a median follow-up period of 12.8 years [35–37]. Although FCR was found to be superior in terms of PFS as compared to bendamustine-rituximab (BR) in the CLL10 study, BR was associated with less toxic effects [38]. Consequently, since the infections rate of FCR is most pronounced in patients older than 65 years, the HOVON CLL working group recommends BR for elderly otherwise physically fit patients. Moreover, BR is also less associated with secondary bone marrow pathologies and other secondary malignancies as compared to FCR [38–40]. In the CLL11 study, chlorambucil-obinutuzumab (Cbl-O) was proven to be superior over chlorambucil-rituximab (Clb-R) and chlorambucil monotherapy, in patients with coexisting comorbidities [41]. Consequently, the HOVON CLL working group considers Clb-O to be the first therapy of choice and Clb-R the second. Since the optimal dose of chlorambucil has never been studied and many different treatment strategies exist, the HOVON CLL working group advises a chlorambucil dose of 10 mg/m^2 orally at day 1–7 for 4 weeks with a target of 6 cycles. Lastly, novel-based agents such as acalabrutinib, ibrutinib of venetoclax-obinutuzumab (Ven-O) can be considered. These agents are presented as a last option, since many clinical trials have demonstrated superior PFS for novel-based agents as compared to chemoimmunotherapy, but subgroup analysis did not confirm this benefit in patients with mutated IGHV genes [42–46]. Consequently, the HOVON CLL working group is of the opinion that chemoimmunotherapy remains the standard therapy for IGHV mutated patients without *TP53* aberrations, and considers only a little role for

novel-based agents in this patient group. Of note, at the time of this publication acalabrutinib therapy was not reimbursed in the Netherlands for IGHV mutated patients without *TP53* aberrations.

Unmutated IGHV genes without TP53 aberrations

In patients with unmutated IGHV, the role of novel-based agents has much more been established over the past years. In short, ibrutinib was found to improve PFS, as compared to treatment with FCR, BR or Clb-O [43–47]. Also, acalabrutinib and Ven-O were superior in terms of PFS, as compared to Clb-O in this patient subgroup [43,46]. However, currently there is a discussion going on in the Netherlands concerning the clinical importance of PFS in a chronic disease such as CLL [48]. Differential findings in PFS are frequently based on the performance of routine CT scans within the framework of clinical trials. Indeed, the CLL14 trial demonstrated a major difference in PFS for Ven-O *versus* Clb-O, but the advantage for Ven-O sharply diminished in context of time to new antileukemic treatment, which is in the opinion of the HOVON CLL working group more clinically relevant as compared to PFS. In addition, an OS benefit has only been established in 1 out of 5 randomized controlled trials that compared novel-based agents to chemoimmunotherapy [42–46]. The only trial that reported an OS benefit was by Shanafelt *et al*. in which FCR was compared with R-ibrutinib [44]. However, this difference was based on small numbers, i.e. 4 deaths in the R-ibrutinib and 10 deaths in the FCR arm. More importantly, this trial did not contain a crossover design and therefore 4 out of 10 patients who died due to progression following FCR did not receive adequate salvage therapy. Moreover, preliminary data of the NCRI FLAIR trial that also examined R-ibrutinib *versus* FCR in previously untreated CLL patients failed to report a difference in the OS [49]. Although the rate of grade 3–4 toxicity is comparable for novel-based agents and chemoimmunotherapy, the toxicity profile is clearly different. More specifically, chemoimmunotherapy is associated with an increased risk for hematological malignancies (<2% in patients <65 years), whereas ibrutinib is associated with an increased bleeding risk and cardiac toxicity including atrial fibrillation/flutter (6.5%) and sporadically sudden death due to ventricular arrythmias (1%) [39,50,51]. As for the latter, in some population-based studies examining ibrutinib the reported adverse events were more severe and included long-term grade I-II toxicities that led to a higher discontinuation rate as compared to those in clinical trials [52–55]. Lastly, although there is accumulating evidence on novel-based agents, potential long-term complications are still unknown and prospective trials have provided little data in the context of novel-based agent sequencing and the effective potential of salvage therapy after novel-based therapies [56,57].

Considering all the above named arguments, the HOVON CLL working group considers novel-based agents equivalent to chemoimmunotherapy in this subgroup. Since the HOVON CLL working group prefers the institution of time-limited options, FCR and BR are recommended in fit patients and Ven-O or Clb-O in unfit patient. However, continuous treatment with ibrutinib or acalabrutinib are considered to be equivalent. Of note, acalabrutinib is only available for unfit IGHV unmutated patients without *TP53* aberrations, but has not been reimbursed for this indication in the Netherlands at the time of this publication. Lastly, Clb-R can be considered as a second choice therapy in unfit IGHV unmutated patients without *TP53* aberrations.

TP53 aberrations

Patients with aberrations in the *TP53* gene have an inferior prognosis and a poor response to chemoimmunotherapy [58]. As such, patients with *TP53* aberrations always require treatment with novel-based agents. Currently, ibrutinib and venetoclax-based therapies are being compared in a head-to-head fashion in the CLL17/HOVON500 clinical trial [59]. At present, there is no knowledge on which treatment regimen is superior in patients with *TP53* aberrations. However, the HOVON CLL working group considers ibrutinib to be the first therapy of choice in this patient subgroup due to the availability of more extensive follow-up data, as compared to other novel-based agents [60,61]. If there is a relative contraindication for ibrutinib therapy, e.g. use of anticoagulants or a strong CYP3A4 inhibitor and/or a history of cardiovascular diseases, treatment with Ven or Ven-O can be considered as a second option. Also, acalabrutinib therapy is a second option which is reimbursed for this subgroup. Lastly, idelalisib-rituximab (R-idelalisib) can be considered as a last option in this patient subgroup. However, the HOVON CLL working group only recommends the use of R-idelalisib in case of a contraindication for both ibrutinib and venetoclax-based therapies due to the unfavorable toxicity profile including immune-mediated colitis, pneumonitis and

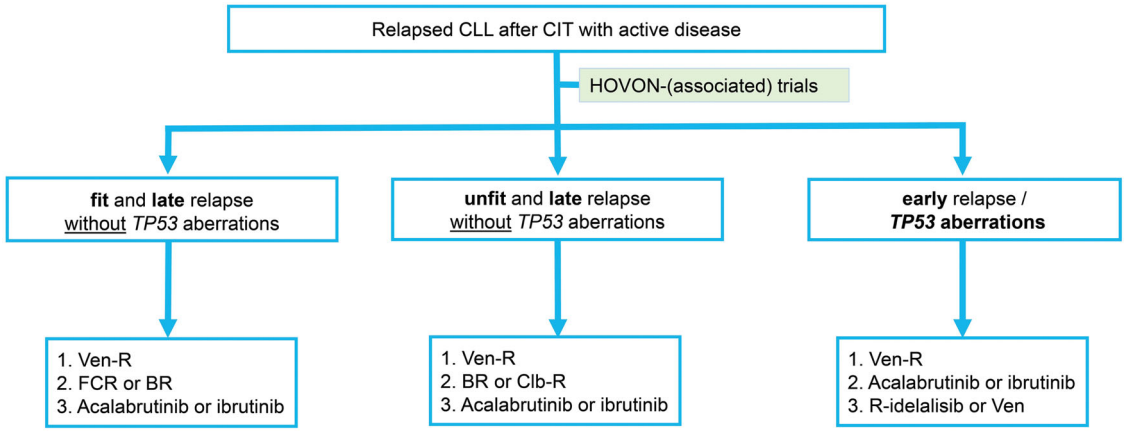

Figure 2. Recommendations for relapsed therapy after previous treatment with chemoimmunotherapy in physically fit CLL patients with a late response without *TP53* aberrations, physically unfit patients with a late response without *TP53* aberrations and for patients with an early relapse or the presence of *TP53* aberrations. Abbreviations: BR: bendamustine and rituximab; Clb: chlorambucil; CLL: chronic lymphocytic leukemia; FCR: fludarabine cyclophosphamide and rituximab; R: rituximab; Ven: venetoclax.

transaminitis as well as risk of opportunistic infections [62,63].

Relapse treatment

In the relapse setting, the choice of therapy depends on the timing of the relapse, the fitness of the patient and the presence of *TP53* aberrations. Consequently, the presence of *TP53* aberrations should always be determined again prior to the start of second or subsequent lines of therapy. A distinction should be made between an early and a late relapse [64]. A relapse within 4–6 years after FCR, within 3 years after BR and within 12 months after chlorambucil-containing therapy is classified as an early relapse; whenever the relapse occurs later, it is classified as a late relapse [10]. Patients with an early relapse and/or *TP53* aberrations are considered to be poor risk and require different treatment options. An overview of the recommended therapies in all subgroups in the relapsed setting is provided in Figure 2.

Late relapse without TP53 aberrations

Regardless of the physically fitness of the patient, venetoclax-rituximab (Ven-R) is considered to be the first therapy of choice [65]. This recommendation is based on the MURANO study, in which Ven-R was found to be superior in terms of PFS, OS and treatment-free survival as compared to BR [42,65]. Due to the time-limited nature of chemoimmunotherapy, the HOVON CLL working group recommends to repeat chemoimmunotherapy as a second option. However, we only recommend this in limited cases who had a very-long term remission after front-line chemoimmunotherapy, which was also well tolerated. Lastly, continuous therapy with ibrutinib or acalabrutinib is also an option for this patient subgroup [66,67]. As previously mentioned, although Ven-R and ibrutinib or acalabrutinib can be considered as equivalent strategies, the HOVON CLL working group prefers the use of time-limited options over continuous therapies.

Early relapse and/or TP53 aberrations

Due to the fact that patients with an early relapse after front-line treatment and/or *TP53* aberrations represent an extremely poor prognostic subgroup, they should always be treated with novel-based agents [65,67–69]. Ven-R is the first therapy of choice followed by ibrutinib or acalabrutinib as a second option. Continuous Ven or R-idelalisib is the last therapy of choice, of which the latter should only be considered when neither Ven-R, Ven, ibrutinib or acalabrutinib can be used [62,63].

Relapse after novel-based agents

In case of a relapse after Ven-R or continuous Ven, treatment with ibrutinib or acalabrutinib is recommended and vice versa [70] (Figure 3). Lastly, a switch to R-idelalisib is also an option but does not have the preference of the HOVON CLL study group due to low response rates and the rather unfavorable toxicity profile [70]. Importantly, patients that exercise a relapse after two lines of novel-based therapies should always be considered to enter a clinical trial. However, for patients without the presence of *TP53* aberrations, it might be considered to apply chemoimmunotherapy outside of clinical trials. Of note, the efficacy of

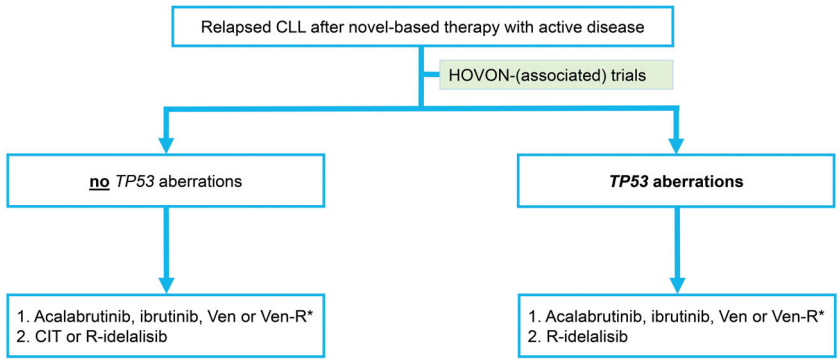

Figure 3. Recommendations for relapse therapy after previous treatment with novel-based agents in CLL patients without *TP53* aberrations and for patients with *TP53* aberrations. Abbreviations: CLL: chronic lymphocytic leukemia; R: rituximab; Ven: venetoclax.

chemoimmunotherapy following novel-based therapies has not been thoroughly investigated. As such, chemoimmunotherapy should only be considered if there was a very long-term response to previous chemoimmunotherapy (4–6 years after FCR or >3 years after BR or >1 year after Clb-containing therapy) and previous chemoimmunotherapy was well tolerated. Allogeneic stem cell transplantation should be considered in patients with (i) a relapse after treatment with a kinase inhibitor (i.e. ibrutinib or acalabrutinib) and venetoclax, or (ii) a relapse after a kinase inhibitor or venetoclax in patients harboring *TP53* aberrations, or (iii) a relapse after treatment with chemoimmunotherapy and a kinase inhibitor or venetoclax and (iv) after a clonal related Richter's transformation (Figure 4) [71]. In the consideration of an allogeneic stem cell transplantation, the estimated 2-year non-relapse mortality (NRM) needs to be taken into account [72,73].

Supportive care and novel-based therapies

Venetoclax

Tumor lysis syndrome management

The risk of tumor lysis should be determined prior to start of venetoclax therapy and special measurements should be taken for prevention of this syndrome. The risk of tumor lysis can be calculated based on the diameter of the largest lymph nodes, the absolute lymphocyte count and the kidney function (Supplemental Table S2). Severe renal dysfunction defined as a glomerular filtration rate (GFR) <30 ml/min, is a relative contra-indication for venetoclax because of the high risk for tumor lysis and the lack of studies investigating the efficacy of venetoclax in this subpopulation. Adequate prophylactic measurements as depicted in Supplemental Table S3 should be applied according to the risk category. The ramp-up scheme in Supplemental Figure S1 should be used until the therapeutic dose is reached. Laboratory checks need to be performed before (hemoglobin, leukocytes, lymphocytes, thrombocytes, sodium, potassium, calcium, albumin, phosphate, uric acid, creatinine and LDH) and after 6–8 h and after 24 h after each ramp-up and should include assessment of potassium, calcium, phosphate, uric acid and creatinine.

Neutropenia management

Neutropenia often occurs during treatment with venetoclax. The HOVON CLL working group, advises the use of G-CSF, pegfilgrastim or filgrastim. Usually pegfilgrastim 6 mg once every 4 weeks or filgrastim 5 mg/kg 1–2 times per week is sufficient (see Supplemental Figure S2). An overview of all recommendations for venetoclax treatment is given in Table 2.

Ibrutinib and acalabrutinib

Hemorrhagic risk management

Although the risk of severe hemorrhagic complications is low, treatment with ibrutinib is associated with bleeding complications such as ecchymosis and hematoma [74]. Consequently, concurrent use of double thrombocyte aggregation inhibitors or double anticoagulant therapy is an absolute contra-indication for ibrutinib therapy. Furthermore, if the patient is using vitamin K antagonists it is recommended to switch to a direct oral anticoagulant (DOAC) due to more available knowledge with this anticoagulant drug and simultaneous use of ibrutinib therapy. Moreover, the HOVON CLL working group advises to stop ibrutinib 3–7 days prior to surgical interventions or invasive procedures. If a severe bleeding complication occurs during ibrutinib therapy, it is recommended to interrupt ibrutinib and to apply a thrombocyte transfusion.

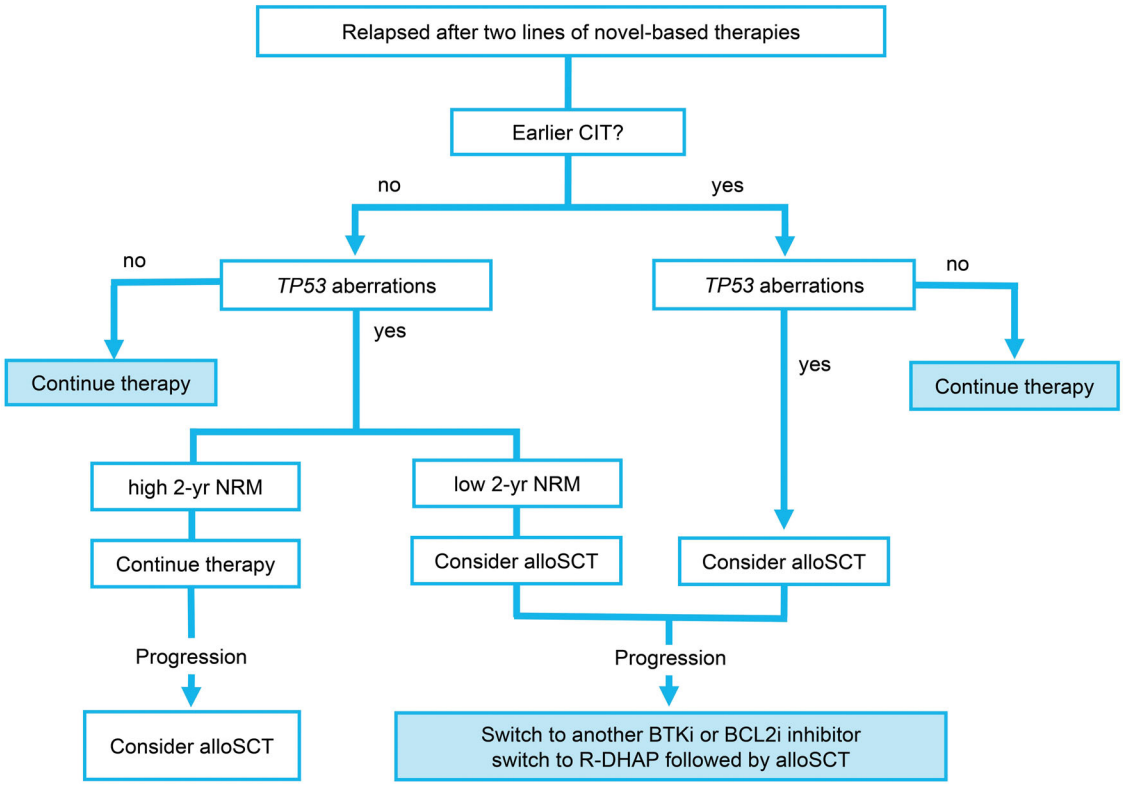

Figure 4. Recommendations for relapse therapy after two lines of novel-based agents and considerations for allogeneic stem cell transplantation. Abbreviations: alloSCT: allogeneic stem cell transplantation; BCL2: anti-apoptotic protein B-cell lymphoma-2; BTK: Bruton's kinase inhibitor; CLL: chronic lymphocytic leukemia; NRM: non-relapse mortality; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin.

Cardiac risk management

Since ibrutinib is associated with an increased risk of atrial fibrillation and other cardiac arrhythmias, it is recommended to perform an electrocardiogram and blood pressure measurement prior to ibrutinib therapy. A recent interim-analysis of the phase III ECOG-E1912 suggested that the risk of sudden or cardiac death in patients treated with R-ibrutinib was increased in patients that were concurrently using an ACE inhibitor, as compared to patients randomized to FCR arm that were also using his drug [75,76]. As such, physicians should be aware of this warning and should reconsider the use of an ACE inhibitor before commencing therapy with ibrutinib [76]. Furthermore, ibrutinib can be continued in case of atrial fibrillation and the CHADSVASC score should be used for risk-assessment. If anti-arrhythmic therapy is indicated, beta-blockers are recommended.

Other risk management

Ibrutinib is metabolized by the CYP3A enzyme. Therefore, there should be awareness about the interaction with CYP3A4 inhibitors or inductors such as anti-arrhythmias (i.e. verapamil, diltiazem and amiodarone), anti-fungal therapies (i.e. voriconazole and itraconazole) and P-glycoprotein substrates (i.e. digoxin).There is an absolute contra-indication for ibrutinib therapy while using ketoconazole since this drug is a strong CYP3A inhibitor [77]. As for acalabrutinib, the recommendations are comparable to those of ibrutinib. Additionally, the use of proton pomp inhibitors (PPI) is not advised during acalabrutinib treatment as it increases the gastric pH, which may decrease acalabrutinib exposure due to its pH-dependent solubility.

Dose reduction and interruption

Dose reduction of ibrutinib can be considered in case of severe toxicity. Reduction of the dose from 420 mg to 280 mg is associated with less adverse events and also a reduction of the grade I-II symptoms, without impairment of efficacy [78,79]. However, since data on dose reduction are scare it is only recommended to reduce the ibrutinib dose in case of toxicity. Temporally discontinuation of ibrutinib can be considered in the case of severe infections. In the Netherlands, we have experienced several cases that developed an atraumatic splenic rupture shortly after interruption or discontinuation of ibrutinib [80]. Consequently, the HOVON CLL working group established additional guidelines for supportive care

Table 2. Supportive care recommendations for the use of novel-based agents.

Venetoclax	
Pretreatment assessment	Medical history, medication
	Tumor lysis risk assessment
Relative contra-indications	Severe renal dysfunction defined as a GFR $<$ 30 mL/min
Tumor lysis prevention	Dose-ramp up of venetoclax
	Hospitalization of high-risk patients
	Laboratory checkups prior to administration and after 6–8 h and 24 h after each ramp-up
	Hydration: orally for all patients and additionally intravenously for high-risk patients
	Anti-hyperuricemia therapy: allopurinol for all patients, rasburicase for high-risk patients
	Hospitalization of high-risk patients
	Blood chemistry monitoring prior to administration, after 6–8 h and 24 h after each ramp-up
Neutropenia management	Filgrastin in case of severe infections or persistent neutropenia without signs of infection
	Antibiotics in case of neutropenia in combination with fever
Ibrutinib and acalabrutinib	
Pretreatment assessment	Medical history, medication, scheduled operations
	Medication reconciliation: avoid CYP3A4 inhibitors and/or inducers, switch anticoagulant therapy to DOAC in patients using vitamin K antagonists, be aware of the use of ACE inhibitors and the risk of sudden (cardiac) death for ibrutinib, avoid PPI during acalabrutinib therapy,
	Cardiac evaluation: electrocardiogram for all patients and Holter in elderly patients and in case of cardiac events in the medical history
	Regular blood pressure measurement and start of anti-hypertensive therapy if necessary
Absolute contra-indications	Double anticoagulant therapy
	Double thrombocyte aggregation inhibitors
	Concomitant ketaconazole therapy
Idelalisib	
Pretreatment assessment	Start PJP prophylaxis with cotrimaxazol for 6 months
	CMV monitoring prior to treatment and each month during treatment

Abbreviations: CMV, cytomegaly virus; DOAC, direct anticoagulant; GFR, glomerular filtration rate; PPI, proton pomp inhibitor.

measurement for the discontinuation of ibrutinib therapy. The working group advises to taper off ibrutinib stepwise in order to prevent flare of the CLL if ibrutinib therapy was started less than 6 months ago, for example reduce the ibrutinib dose from 420 mg to 280 mg in week 1 decrease to 140 mg in week 2 and stop ibrutinib afterward. Whenever ibrutinib is combined with venetoclax therapy and discontinued due to progression, it is recommended to taper off ibrutinib after the venetoclax ramp-up. During this stepwise reduction of ibrutinib regular blood count should be performed alongside the monitoring of symptoms of the patient. If the patient experiences symptoms, it could be considered to temporarily increase the ibrutinib dose or start 20 mg prednisone. An overview of all recommendations for ibrutinib and acalabrutinib therapy is given in Table 2.

Idelalisib

The toxicity profile of idelalisib is rather unfavorable and includes diarrhea, pneumonitis and transaminitis. Idelalisib needs to be interrupted in case of grade I-II diarrhea, which lasts for more than three days or grade III–IV diarrhea. Also, idelalisib should be interrupted in case of high-resolution CT imaging abnormalities that are not compatible with a lobular pneumonia. Corticosteroids can be prescribed for ongoing diarrhea with negative cultures or for lung abnormalities with a negative broncho-alveolar lavage (BAL). Alternative anti-leukemic treatment is strongly recommended if the complaints do not resolve [63]. Moreover, idelalisib can cause hepatotoxicity, characterized by an evaluation of alanine transaminase (ALT) and aspartate transaminase (AST) blood levels. ALT and AST needs to be monitored frequently especially in the first 3 months and corticosteroids can be prescribed [63]. Pneumocystic jirovecii pneumonia (PJP) prophylaxis with cotrimoxazol 480 mg daily is recommended in patients treated with R-idelalisib. This prophylactics should be continued until 6 months after treatment. Lastly, as reactivation of virus infections are possible during idelalisib therapy monitoring of CMV is recommended every months. An overview of all recommendations for idelalisib treatment is given in Table 2.

CLL and the risk of infections

CLL patients have a higher risk of community-acquired infections. To prevent infectious complications vaccination should be offered to CLL patients according to

the Dutch guideline of the National Institute for Public Health and the Environment Ministry of Health, Welfare and Sport (RIVM) [81]. In short, patients should receive the annually influenza vaccination and the 13-valent pneumococcal vaccine (PCV13, PREVENAR13®) followed by at least 8 months later by the 23-valent polysaccharide vaccine (PPV23, PNEUMOVAX®) [81]. The HOVON CLL working also provides recommendations for the treatment of recurrent infectious (Supplemental Figure S3). At first, antibiotics on demand are recommended. Whenever a patient experiences $\geq$3 infections per year, prophylactic antibiotics with co-trimoxazole 960 mg daily or azithromycin 250 mg 3 times a week is recommended. Immunoglobulin supplementation (100 mg/kg/week or 300–400 mg/kg per 3–4 weeks i.v. or subcutaneous) can be considered in case of hypogammaglobulinemia in combination with $\geq$3 infections per year or complications such as bronchiectasis or hearing damage despite adequate antibiotic treatment. The IgG level for supplementation is $>$ 6 g/L and $>$8 g/L in case of persistent infections or complications. Treatment with immunoglobulin supplementation should be evaluated after $6-12$ months. If the infections have resolved, the dose can be reduced or supplementation can be stopped while monitoring future infections. The treatment should be continued indefinitely in case of relapsing infections or complications such as bronchiectasis or hearing damage [82].

COVID-19

The 2019 pandemic of SARS-CoV-2 (COVID-19) has challenged the health care systems in the Netherlands and across the entire globe. This particularly accounts for elderly individuals with significant comorbidities. Given the advanced age at diagnosis, comorbidities and immune dysfunction, CLL patients might be at a higher risk of infection and poor outcomes following a COVID-19 infection. Two large international multicenter studies have reported outcomes for CLL infected with COVID-19 in the period of February to May 2020 and reported a similar COVID-19 prevalence in CLL cases, as compared to the general population but a higher mortality rate in CLL patients reflected by a case fatality ratio between 31% and 33% [83,84]. More recently, an updated analysis revealed a drop in the case fatality rate to 11% and an improved OS for CLL patients diagnosed with COVID-19 after May 2020 [85].

At present, there is no clear consensus about the use of anti-neoplastic therapy in CLL patients during the SARS-CoV-2 pandemic. Mato *et al*. found that the overall survival of patients was not affected by anti-neoplastic therapy in particular ibrutinib [84]. On the other hand, the ERIC study and CLL campus study demonstrated that the hospitalization rate for severe COVID-19 was lower in patients treated with ibrutinib *versus* other therapies or patients on a watch-and-wait approach, potentially suggesting a protective effect for ibrutinib therapy [83]. Moreover, it has been demonstrated that COVID-19 outcomes for cancer patients are generally more favorable when the disease is in remission, as compared to those with active, uncontrolled malignancies at the time of COVID-19 diagnosis [86,87]. Consequently, the HOVON CLL working group advises physicians to balance the risk of treatment while keeping in mind that uncontrolled, progressive CLL in combination with severe COVID-19 infection is the worst scenario [88]. In addition, due to the susceptibility of CLL patients to infections it is recommended to protect patients through COVID-19 vaccination. In the Netherlands, patients with immune dysfunction such as CLL were initially vaccinated with two doses of vaccine. Later, in November 2021 a third vaccine became available for patients with immune dysfunction followed by a booster vaccine, which is currently available for the entire Dutch population [89].

Autoimmune cytopenias

Immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) are a frequent complication of CLL, occurring in 4% to 14% of all patients. These autoimmune cytopenias should initially be treated with glucocorticoids. Prednisone or prednisolone at an initial dosage of 1 mg/kg/day is the recommended first-line therapy. Although approximately 70% of all patients will respond to initial glucocorticoid therapy, the response will be durable in a minority. If the patient does not respond, rituximab 4×375 mg/m^2 is recommended. Alternative treatment includes splenectomy, intravenous immunoglobulins and/or immunosuppressive therapy with agents such as cyclosporine. Treatment refractory autoimmune cytopenias or autoimmune cytopenias in combination with other features of CLL progression can be treated with standard therapy directed to the underlying CLL [13].

Follow-up and response evaluation

All CLL patients should receive life-long follow-up. Blood count and physical examination should be performed every 3–12 months in asymptomatic patients

depending on the dynamics of the disease. Patients with stable CLL can be referred back to the general practitioner for follow-up with good instructions. Response evaluation should be performed at least 2 months after completion of therapy. Assessment of response should include physical examination, assessment of the blood and, if necessary, bone marrow.

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Author contributions

The HOVON CLL working group designed the guideline; LvdS wrote the manuscript under supervision of GR with contributions from all authors, who also interpreted the data, and read, commented on, and approved the final version of the manuscript.

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