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REVIEW

Dutch guidelines for diagnosis and treatment of chronic lymphocytic leukaemia 2011

A.P. Kater[1,*], S. Wittebol[2], M.E.D. Chamuleau[3], M. van Gelder[4], M.H. J van Oers[1,*], on behalf of the HOVON CLL working party

[1]Department of Hematology, Academic Medical Center, Amsterdam, the Netherlands, [2]Department of Hematology, Meander Medical Center, Amersfoort, the Netherlands, [3]Department of Hematology, VU University Medical Center, Amsterdam, the Netherlands, [4]Department of Hematology, Maastricht University Medical Center, Maastricht, the Netherlands, *corresponding authors: e-mail: a.p.kater@amc.nl; m.h.vanoers@amc.nl

ABSTRACT

One of the principal responsibilities of the Chronic Lymphocytic Leukaemia (CLL) Working Party of the Dutch/Belgium Haemato-Oncology Foundation for Adults in the Netherlands (HOVON) is to create up-to-date guidelines for CLL. In this article, the revised guidelines for diagnosis and treatment are summarised. Despite recent expansion in treatment options for patients with CLL, the disease remains incurable in most cases and the optimal treatment approach for several subgroups of patients is still unclear. Therefore, it remains highly important to treat patients within clinical studies as much as possible. In this article, the current studies initiated by the HOVON CLL working party are emphasised.

KEYWORDS

Chronic lymphocytic leukaemia, guidelines, HOVON

INTRODUCTION

During the past ten years, significant progress has been made in both the diagnostics and treatment options for patients with chronic lymphocytic leukaemia (CLL). In 2005 the Dutch/Belgium Haemato-Oncology Foundation for Adults in the Netherlands (HOVON) founded a separate CLL working party. Besides initiation of clinical trials (currently five), the working party is responsible for formulating national guidelines for diagnosis and treatment of CLL. Based on novel data from large international phase II/III trials, the group recently revised the previous guidelines.

Where possible, these revised guidelines are based on published randomised trials. If such evidence is lacking, the guidelines reflect the expert opinion of the members of the group. Despite recent expansion in treatment options for patients with CLL, the disease remains incurable in most cases and the optimal treatment approach for several subgroups of patients is still unclear. Therefore, it remains highly important to treat patients within clinical studies as much as possible. Outside such trials, these guidelines provide recommendations how to treat patients in a uniform and rational manner.

The recommendations are divided into:

- Diagnosis
  - peripheral blood
  - additional tests
  - prognostic factors
- Treatment
- Treatment indications
- Treatment choices
  - first-line
  - relapse
  - refractory
- Actual treatment guidelines within HOVON studies / outside studies.

DIAGNOSIS

The guidelines for the diagnosis of CLL are primarily based on the recently revised guidelines of the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL).

Blood

In case of clinical suspicion of CLL, it must be ruled out that the patient is suffering from another lymphoproliferative disease that can mimic CLL, such as hairy cell leukaemia, or leukaemic manifestations of mantle cell lymphoma, marginal zone lymphoma, splenic marginal zone lymphoma with circulating villous lymphocytes, or follicular lymphoma. Therefore, it is essential to evaluate both blood count and blood smear, and to perform immunophenotyping of circulating lymphoid cells.

The diagnosis of CLL requires the presence of at least 5 x 10^9/l clonal B lymphocytes (5000/µl) in the peripheral blood. The leukaemia cells found in the blood smear are characteristically small, mature-appearing lymphocytes with a narrow rim of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. Although these cells may be found admixed with larger or atypical cells, or pro-lymphocytes, the presence of more than 55% of such cells favours a diagnosis of pro-lymphocytic leukaemia (B-cell PLL). 'Gumprecht schollen' or smudge cells are characteristic morphological features of CLL.

CLL cells have a distinct surface marker expression pattern as compared with both normal B cells and other B-lymphoproliferative diseases. The four main immunophenotypical characteristics of CLL are:[1]

- expression of B-cell associated antigens including CD19, and CD23;
- weak expression of CD20 and CD79b;
- expression of CD5, a T-cell associated antigen;
- low expression of membrane-bound immunoglobulin, which is usually either IgM or IgM combined with IgD. Each clone of leukaemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains.

CLL cells are usually negative for CD10 and cyclin D1. FMC7 and CD22 are either negative or very weakly expressed.

In 5 to 20% of otherwise healthy adults over the age of 40, an absolute increase of monoclonal CLL-like lymphocytes can be detected, yet with an absolute number (much) less than 5 x 10^9/l. In the absence of lymphadenopathy or organomegaly (as defined by physical examination or CT scans), cytopenias, or disease-related symptoms, the presence of less than 5 x 10^9/l B lymphocytes is defined as monoclonal B lymphocytosis (MBL). MBL may progress to frank CLL at a rate of 1 to 2% per year, closely resembling the risk of development of multiple myeloma in patients with monoclonal gammopathy of undetermined significance (MGUS).[2]

Other investigations

Autoimmune haemolytic anaemia (Coombs positive and negative) and thrombocytopenia are frequently observed in CLL and might be hard to distinguish from cytopenias due to marrow infiltration. Therefore, in case of cytopenias, an active search for autoimmune features is needed. Although a bone marrow aspirate and biopsy are not strictly necessary for the diagnosis, they may be needed to differentiate bone marrow infiltration from autoimmune cytopenias. Before treatment initiation, active infections should be excluded. Because the clinical value of CT scans has not been demonstrated, CT scans are not recommended outside clinical trials.

Table 1 shows the minimum tests for diagnosis, initial treatment and evaluation of treatment.

Prognostic factors

The disease is very heterogeneous. In less than 30% of all patients the disease has a very indolent course, with patients eventually dying from causes unrelated to CLL. About 15% of patients die rapidly – within two to three years from diagnosis – from CLL and /or treatment-related causes, whereas in the remaining proportion of CLL patients the disease has a relative indolent course during the first five to ten years, followed by a terminal phase lasting one to two years with considerable morbidity, both from the disease itself and from complications of therapy.[3] Traditional clinical staging systems devised by Rai and Binet are the simplest and still best validated means of assessing prognosis for CLL patients, However, there is substantial heterogeneity in the course of the disease within defined stages. In recent years molecular and cellular markers have been correlated with disease aggressiveness: immunoglobulin VH (IgV_H) gene segment usage (mutated or unmutated), and the proposed surrogate markers CD38 and ZAP-70 (reviewed by Kay *et al.*[4]). Unfortunately these parameters thus far have only limited use in guiding when and how to treat and determining when and what type of therapy to use.[5] Given the above, the working party recommends assessing IgV_H mutational status or CD38 and ZAP-70 status only in the setting of clinical trials.

Cytogenetics using fluorescence in situ hybridisation (FISH) provides prognostic information, notably as to the probability of response to various therapeutic regimens. A deletion of chromosome 11q (11q22.3, the location of the ATM gene), and in particular deletion of chromosome 17p (17p13.1, the localisation of the p53 gene) is frequently associated with p53 dysfunction. Since most chemotherapeutic drugs currently used depend on p53 for their cytotoxic effect, such deletions strongly impair the efficacy of such treatments (reviewed by Kater and Tonino[6]). Although both 11q deletion and 17p deletion are associated with rapid disease progression, such deletions can not be used to initiate therapy in the absence of the current treatment criteria. Cytogenetic studies are of importance to determine the probability of responses to

Table 1. *Required tests for diagnosis, initial treatment and evaluation of treatment*

DIAGNOSTIC TEST	
Tests to establish the diagnosis	
Complete blood count and differential count, smear	Always
Immunophenotyping of lymphocytes	Always
Assessment before treatment	
History and physical, performance status	Always
Complete blood count and differential	Always
Marrow aspirate and biopsy	Desirable in case of anaemia without reticulocytosis and/or thrombocytopenia to differentiate between autoimmune phenomenon marrow infiltration
Serum chemistry, serum immunoglobulin, direct antiglobulin test	Always
Chest radiograph	Always
Infectious disease status	Always
Additional tests before treatment	
Cytogenetics (FISH) peripheral blood for del(13q), del(11q), del(17p), trisomy 12,	Desired at first-line, always at relapse
IgVH mutational status, ZAP-70, and CD38	Optional
CT scan of chest, abdomen, and pelvis	No
MRI, PET scans	No
Abdominal ultrasound	Possible
Treatment evaluation	
History and physical, performance status	Always
Complete blood count and differential count, smear	Always
Immunophenotyping of lymphocytes	In case a CR is suspected
Marrow aspirate and biopsy	In case of cytopenia ECI.
MRD (minimal residual disease) studies	No
CT scan of chest, abdomen, and pelvis	No
Abdominal ultrasound	Possible, when earlier abnormal

various treatment modalities. This is especially true in case of relapse. The value of cytogenetics for first-line treatment choices remains unclear. Despite the poor prognosis of 17p-deleted patients, it remains to be determined whether allogeneic stem cell transplantation in first remission improves survival. It will be clear that this group of patients should preferably be treated within clinical trials. Currently an international study in untreated symptomatic CLL patients harbouring a 17p deletion is being developed. Outside such a study, cytogenetics prior to first-line treatment is not strictly necessary. Because the percentage of patients with adverse cytogenetic abnormalities such as 17p deletion strongly increases with each subsequent treatment, it is advised to perform cytogenetics before each new treatment regimen, at least from the time of first relapse (*table 1*).

TREATMENT OF CLL

Indications for treatment

Because of the considerable heterogeneity in disease-related signs and symptoms and in the clinical course of the disease, along with the present lack of curative treatment modalities, the decision when and how to treat a CLL patient requires marked individualisation.

Early treatment of asymptomatic patients resulted in a delay of disease progression but yielded no improved survival. Importantly there is some evidence that early treatment increases the risk of acute myeloid leukaemia. *Table 2* shows the indications for treatment in daily practice. The situation is obviously different for clinical trials, and depends on the question and the inclusion criteria of the studies.

Key points in the choice of treatment

Because of the rapidly expanding treatment modalities the half-life of the current guidelines is limited. Important aspects in treatment choices are:

- age of the patient;
- performance status / comorbidity;
- cytogenetic risk profile (if known);
- response (duration) to previous therapy;
- toxicity of previous therapy;
- aim of treatment; palliative care or improved progression-free survival (PFS) and overall survival (OS).

Considerations as to first-line treatment

In 2006/2007 three phase III randomised trials were published, showing that the addition of cyclophosphamide to fludarabine (FC) significantly improves PFS of CLL

Table 2. *IWCLL/NCI treatment criteria*

Binet stage C or Rai stage III or Rai stage IV or Treatment of active/progressive disease*
*** For progressive disease at least one of the following criteria should be met:**

1 Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia
2 Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
3 Massive nodes (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
4 Progressive lymphocytosis with an increase of more than 50% over a two-month period or lymphocyte doubling time (LDT) of less than six months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of two weeks over an observation period of two to three months. In patients with initial blood lymphocyte counts of less than 30 x 10^9/l (30,000/µl), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded
5 Autoimmune anaemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
6 Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
- Unintentional weight loss of 10% or more within the previous six months
- Significant fatigue (i.e., ECOG PS 2 or worse; inability to work or perform usual activities)
- Fevers higher than 100.5°F or 38.0°C for two or more weeks without other evidence of infection, or
- Night sweats for more than one month without evidence of infection

Hypogammaglobulianaemia or monoclonal or oligoclonal paraproteinaemia does not constitute a basis for initiating therapy in itself. However, it is recommended to assess the change of these protein abnormalities if patients are treated.

patients.[7-9] However, despite increased PFS the OS was not different. This obviously reflects the lower efficacy of salvage therapy, following intensified first-line treatment. FC proved to be significantly more toxic than chlorambucil, with increased neutropenia / thrombocytopenia, neutropenic fever and need for hospitalisation.

Rituximab monotherapy has some activity in CLL, albeit far lower than in other indolent B-cell lymphomas (as reviewed by Meerten and Hagenbeek[10]). The MD Anderson Cancer Center performed phase II trials of rituximab added to FC (FCR) in both previously untreated patients and in patients with relapsed CLL. The percentage of complete responses (CR) was 70% and 25% respectively.[11,12] As compared with historic controls these studies showed a survival advantage for the rituximab-containing therapy. At the end of 2010, the results of a large randomised German trial were published in which FC was compared with FCR. FCR was clearly superior: 90% response rate (44% CR), a nearly 20-month improvement of PFS and improved survival (after three years: 87 *vs* 82%, HR 0.664, p=0.012). This is the first study in which an upfront treatment regimen not only resulted in improved PFS, but also in a beneficial effect on overall survival. A limitation of this trial is that the patients studied do not optimally reflect the 'normal' CLL patients: they were fit (CIRS score ≤6, (*table 3*) creatinine clearance >70 ml/min) and relatively young. Only 10% of patients were over the age of 70 years. Yet, FCR has become the worldwide standard first-line treatment for fit patients (i.e. patients who are suitable for fludarabine-containing therapy). Although FCR improved survival of patients with an 11q deletion, this was unfortunately not the case for patients with a 17p deletion.[13] Several studies have shown that in the large group of, mostly less fit, elderly patients fludarabine-containing regimens have an unfavourable toxicity profile.[13-16] A randomised study of the German CLL study group in patients above the age of 65 indicated an inferior overall survival with fludarabine monotherapy as compared with chlorambucil.[17] To date, chlorambucil monotherapy is still widely used as first-line therapy in this population group. Despite obvious benefits of chlorambucil in the elderly and more vulnerable patients (such as low toxicity and oral administration) it is not very effective as monotherapy. In most studies, overall response rates (ORR) of chlorambucil are approximately 50% (31 to 72%) with virtually no complete remissions (CR), resulting in a PFS of less than 1.5 years (8.3 to 20 months).[18-20] In recent trials the clinical value of combining the anti-CD20 antibodies rituximab or ofatumumab with chlorambucil has been studied. In 2010, Hillmen and colleagues presented the results of an English phase II study in 100 previously untreated patients with the combination of chlorambucil and rituximab. They found an ORR of 82% with 9% CR, and a PFS of 23.5 months.[21] Although this seems slightly better than the results of chlorambucil monotherapy in the CLL4 trial (ORR 66%, 6% CR and 20 months PFS), these separate trials obviously cannot be compared.

In an attempt to improve the response rate (which is associated with increased PFS) the CLL working party has recently initiated a phase I/II trial studying the effect of addition of lenalidomide to chlorambucil and rituximab: the HOVON 109 study. The rationale behind this study is the possible synergistic effect of (mild) chemotherapy, monoclonal antibody treatment and an agent that exerts its effect by influencing the interaction of the malignant cells with their microenvironment, without an increase in toxicity.

Considerations as to treatment of relapse

At proven relapse, the presence of a 17p deletion should be analysed by FISH, even when previously found to be negative. When progression occurs following previous treatment it needs to be assessed whether it is rational to use the same treatment regimen again or whether

alternative regimens should be considered. An important issue for clinical decision making at relapse is whether the patient has relapsed or refractory disease. Relapse is defined by the IWCLL as development of progression following a period of at least six months of CR or PR after prior therapy. Refractory disease is defined by the IWCLL as either no response or progressive disease within six months after completion of previous therapy. Such a distinction between relapse and refractory disease is particularly relevant after treatment with fludarabine or chlorambucil monotherapy, since the majority of patients who develop progressive disease at least six to 12 months after these treatments can be treated successfully with the same regimen,[22] or with immuno-chemotherapy.[23] In patients with refractory disease, however, it is highly unlikely that responses will occur with immunochemotherapy.

If a patient is eligible for an allogeneic stem cell transplantation, a broader, EBMT-based definition of 'refractory' or more precisely high-risk disease is being used: relapse within one year after fludarabine-containing chemotherapy, or relapse within two years after fludarabine-rituximab containing immunochemotherapy or any relapse in patients with a 17p deletion.[24]

Treatment of relapsed CLL

Currently, the optimal choice of treatment for patients with relapsed disease is unknown. In the absence of a 17p deletion patients can be successfully treated with either the same regimen as used previously, or by switching to other more potent treatment combinations, depending on the last remission duration.

In a randomised trial in CLL patients relapsed following monotherapy with fludarabine or chlorambucil, FCR induced a PFS that was ten months longer than with FC (30.6 *vs* 20.6 months). No difference in overall survival was observed.[23] An important consideration is the fact that the median survival following relapse after FCR treatment is just 2.5 years for patients not eligible for allogeneic stem cell transplantation.[25]

Recently, a HOVON-led international trial was initiated in patients with a second or third relapse of their CLL (HOVON 101 or PROLONG) to study the value of maintenance therapy with ofatumumab (administered once every two months for up to two years), following a CR or PR obtained by any induction treatment.

Treatment of high-risk relapsed/refractory CLL

In fit younger patients (<70 years) with relapsed CLL within one year after fludarabine-based chemotherapy or within two years after fludarabine and rituximab-containing immunochemotherapy or with any relapse in patients with a 17p deletion (EBMT 'high risk' definition[24]) a reduced-intensity stem cell transplantation (RIST) with an HLA-identical (family / MUD) donor should be considered, preferably in the context of a clinical trial (HOVON 88, see below). Response to induction treatment prior to RIST is found to be an important determinant of long-term outcome as patients with a high disease burden, particularly bulky lymphadenopathy at the time of transplantation or poor response to last treatment, have the tendency to relapse more often, whereas patients with progressive disease uniformly do badly.[25] Currently, no optimal induction regimen, especially for patients with chemo-refractory disease, has been established. Options for induction treatment can be found below.

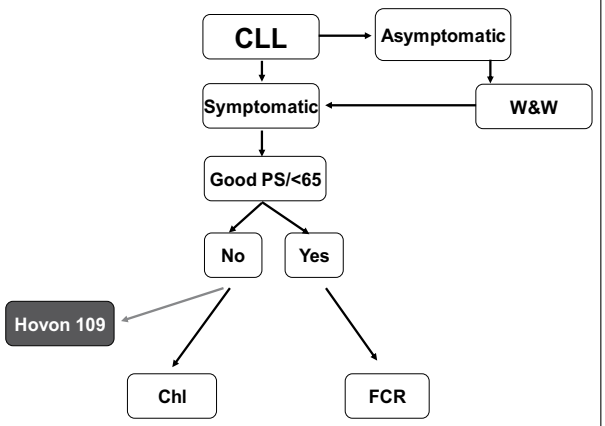
If patients do not qualify for a RIST, the therapeutic goal should be to induce responses resulting in improved quality of life. The following options are reported to be effective in patients with chemo-refractory disease:

- Alemtuzumab (Campath-1H®), an anti-CD52 humanised monoclonal antibody, has been investigated extensively in CLL. It has significant anti-leukaemic activity, predominantly in the peripheral blood compartment, bone marrow, and spleen, whereas activity is lower in lymph nodes. Response rates of alemtuzumab in chemo-refractory patients are around 30% with a median response duration of approximately nine months.[26,27] The efficacy of alemtuzumab is significantly reduced in patients with large lymph node masses (>5 cm diameter);
- An alternative regimen is a combination of rituximab or alemtuzumab with high-dose steroids (dexamethasone or methylprednisolone), especially in patients with large lymph node masses. Although the response seems better, the published phase II studies are rather small.[28,29] Recently, an international forum of experts stressed that alemtuzumab-containing chemotherapy should only be applied within clinical trials because of very high risks of severe (opportunistic) infections;
- Ofatumumab (HuMax CD20;Arzerra®) is a fully human, high-affinity monoclonal antibody that binds to a different CD20 epitope to that targeted by rituximab. It induces complement-derived cytoxicity more effectively than rituximab. A pivotal phase II study of ofatumumab in relapsed CLL patients showed impressive activity both in patients refractory to both fludarabine and alemtuzumab (double refractory or DR, n=59) and in patients with bulky lymphadenopathy refractory to fludarabine (bulky fludarabine refractory or BFR, n=79). ORR, time to next therapy, and OS were similar for the DR (51%, 9.0 months, 13.7 months) and BFR groups (44%, 7.9 months, 15.4 months).[28-30] Based on these findings, ofatumumab has recently been registered for CLL patients who are refractory to fludarabine and alemtuzumab. In the Netherlands, the Health Care Insurance Board (CVZ) has advised to include ofatumumab on the list of expensive orphan drugs.

GUIDELINES FOR THE TREATMENT OF CLL

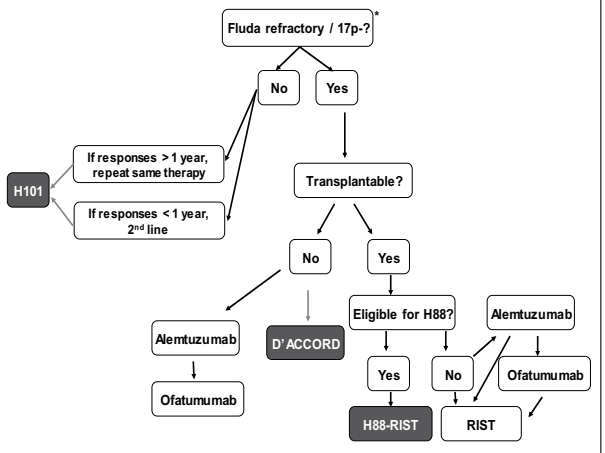
Based on the above considerations, the Dutch CLL working party has formulated the following guidelines (see algorithm, *figures 1* and *2*).

Figure 1. *Guidelines CLL 2011, first line*



Black indicates HOVON studies. CLL = chronic lymphocytic leukaemia; W&W = watch and wait; PS = performance score; Chl = chlorambucil; FCR = fludarabine, cyclophosphamide and rituximab.

Figure 2. *Guidelines CLL 2011, relapse*



Black indicates HOVON studies
*** If patient is eligible for allo-SCT; the answer is yes if refractory or relapsed within one year after the fludarabine chemotherapy or two years after fludarabine-containing immunochemotherapy or relapse or 17p deletion**
*** If eligible for allo-SCT; the answer is yes in case of refractory disease (lack of response) following fludarabine-containing (immuno) chemotherapy treatment or first signs of relapse within six months after an initial response or on fludarabine-containing (immuno) chemotherapy treatment or 17p deletion.**

First-line treatment of CLL (*figure 1*)

In clinical trials

- HOVON 68. This trial was closed on 11 September 2010; the first results are expected at the end of 2011;
- HOVON 109. Phase I/II study on the value of addition of lenalidomide to chlorambucil and rituximab. Inclusion criteria: Patients ≥65 years or <65 but not eligible for fludarabine (containing) therapy (CIRS score >6 (*table 3*)).

Outside clinical trials

- Fit patients (CIRS score ≤6 (*table 3*) creatinine clearance >70 ml/min, which will generally be patients ≤65 years): FCR (fludarabine, cyclophosphamide, rituximab, a maximum

Table 3. *Cumulative Illness Rating Scale(CIRS)*[31]

Rating Strategy of Comorbity		
0	No problem	Organ system not compromised.
1	Mild	Illness/impairment with or without requirement of therapy, excellent prognosis, patient with normal activity.
2	Moderate	Illness/impairment requiring therapy, good prognosis, compromised activity of patient.
3	Severe	Illness/impairment with urgent requirement of therapy, prognosis unclear, marked restriction in activity.
4	Extremely severe	Life threatening illness/impairment, emergency case of therapy, adverse prognosis.

Please take into account that CLL induced illness or organ damage are not included in this rating scale! The goal of this rating scale is to assess comorbidity other than CLL in the patient. If there are two or more illnesses/impairments of one organ system, the illness/impairment with the highest severity should be evaluated!

Organ system	If illness/impairment present, please specify	Score
1. Heart		☐
2. Blood pressure		☐
3. Vascular		☐
4. Respiratory		☐
5. Ear/nose/throat		☐
6. Upper gastrointestinal		☐
7. Lower gastrointestinal		☐
8. Liver		☐
9. Renal		☐
10. Genitourinary		☐
11. Musculoskeletal		☐
12. Endocrine/metabolic		☐
13. Neurological		☐
14. Psychiatric		☐
15. Score:	Total	☐

of six cycles). Fludarabine: 40 mg/m² orally, days 1-3, cyclophosphamide 250 mg/m² orally days 1-3; rituximab: the first infusion 375 mg/m², 500 mg/m² thereafter;
- Patients with comorbidities and older patients (>65 years): chlorambucil (for example 10 mg/m² daily for seven days, every four weeks, until maximum response, or x 12).

Treatment of relapsed CLL (*figure 2*)

In clinical trial
- HOVON 101 (PROLONG); randomised phase III ofatumumab maintenance study. Inclusion criteria: Relapsed CLL second or third remission, and within three months after reaching the second or third CR/PR with any induction regimen.

Outside clinical trials
- Response duration following first line >1 year: repeat same treatment;
- In case of a response duration <1 year: second-line therapy, e.g. FCR;
- In both cases, then consider HOVON 101 (PROLONG; see above).

In case of refractoriness to fludarabine, or relapse <1 year, following fludarabine-containing chemotherapy or relapse <2 years following fludarabine-containing immunochemotherapy, or in case of 17p deletion *AND* if the patient is eligible for an allogeneic allo-SCT:

In clinical trial
- HOVON 88 (R-DHAP followed by RIST). Inclusion criteria: <70 years and refractory or relapsed within one year after the fludarabine chemotherapy or two years after fludarabine-containing immunochemotherapy or relapse and 17p deletion.

Outside clinical trial
- Induction treatment as described in treatment options for refractory CLL (below), if possible followed by RIST.

In case of fludarabine refractoriness:

In clinical trial
- D'ACCORD study, dasatinib ± fludarabine. Inclusion criteria: refractory disease following fludarabine-containing (immuno) chemotherapy treatment or first signs of relapse within six months after an initial response on fludarabine-containing (immuno) chemotherapy treatment. The patient may have received additional treatments following fludarabine.

Outside clinical trials
- Alemtuzumab therapy (first week 3 mg, 10 mg, 30 mg followed by 30 mg three times a week for up to three months);
- In case of bulky disease or contraindications for alemtuzumab (high risk of infection): Consider:
- Ofatumumab (2000 mg once a week for eight weeks, followed by 2000 mg once a month for four months);
- Rituximab in combination with high-dose prednisone (375 mg/m² rituximab twice a week combined with HDMP 1 g/m² once a day for five days every four weeks up to a maximum of three cycles).

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