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## Guidelines for Diagnosis and Treatment of Chronic Lymphocytic Leukaemia (CLL)

### Diagnosis

The guidelines on diagnosis are based on and represent a summary of the recently revised guidelines from the IWCLL (International Workshop on Chronic Lymphocytic Leukaemia):

Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. *Blood*. 2008 111: 5446-5456

LINK: <http://bloodjournal.hematologylibrary.org/cgi/content/full/111/12/5446>

### Requirements for diagnosis of CLL

- Morphology
- Immunotyping: CD 5+, CD19+, CD23 +; weak expression of CD20, membrane immunoglobuline and CD79b. FMC7 negative.
- > 5 x 10<sup>9</sup>/l circulating monoclonal B cells.

Please note: For diagnosis bone marrow investigation is NOT required. Morphology and immunotyping of the peripheral blood suffice.

Table 1 shows the minimum required examinations for diagnosis, start of treatment and evaluation of treatment. A clear differentiation is made between daily practice and clinical studies.

TABLE 1

Diagnostic Test	Daily practice	Clinical study
<b>Diagnosis CLL</b>		
Hb, thrombos, leukos +diff	always	always
Immunotyping lymphos PB	always	always
Case history, ALO, Performance status	always	always
Bone marrow aspirate and biopsy	desirable when anemia and thrombocytopenia	desirable
Serum chemistry (incl haptoglobin), Igs, direct Coombs	always	always
X-thorax	always	always
Examination of active infections	always	always
Cytogenetics (FISH) in PB (17p del;11q del; trisomia 12, deletion 13q; possibly del 6q	desirable	always
IgVH mutation status	desirable	always
Zap70 and CD38	no (value as surrogate marker to use for mutation status is doubtful)	always
CT-scan neck, thorax, abdomen	no	Desirable. Always, if CR is intended end point
MRI, gallium scan, PET scan, lymph angiogram	no	no
Echo abdomen	possible	no
<b>Evaluation of treatment</b>		
Case history, ALO	always	always
Hb, thrombos, leukos +diff	always	always

Immunotyping lymphos PB	If clinical and haematological response suggests CR	If clinical and haematological response suggests CR
Bone marrow aspirate/biopsy	For cytopenia eci	For (suggestion of) CR or cytopenia eci
MRD determination (minimal residual disease)	no	if long-term CR is clinical end point
CT-scan neck, thorax, abdomen	no	if previously non-conforming and if there is possibility of CR
Echo abdomen	Possible, if previously non-conforming	no

## GUIDELINES FOR THE TREATMENT OF CLL

### Indications for starting treatment of CLL

Table 2 shows the indications for treatment in daily practice. The situation in clinical studies is of course different and will depend on the underlying question and inclusion criteria for the study.

**Table 2**

	Daily practice	Clinical study
Treatment Rai 0/Binet A	No	Depending on research question*
Treatment Rai I/II or Binet B	Possible (if active disease; see table 3)	Depending on research question*
Treatment Rai III/IV of Binet C	yes	yes
Treatment if <b>no</b> progression or active illness	no	Depending on research question
Treatment if <b>there is</b> progression or active illness	yes	yes

\* With almost all studies a treatment indication (see table 3) is required!

### IWCLL/NCI CRITERIA FOR ACTIVE CLL

At least one of the following criteria must be present:

**Table 3**

1.	At least one of the following disease-related symptoms: a. Weight loss greater than or equal to 10 % in the previous 6 months b. Extreme fatigue (WHO performance status greater than or equal to 2) c. Fever greater than or equal to 38.6 degrees Celsius during a period of longer than or equal to 2 weeks, in the absence of infections d. Night sweating without infections
2.	Increased bone marrow failure, expressed in the development of or worsening of anaemia or thrombocytopenia
3.	Auto-immune anaemia and/or thrombocytopenia that responds poorly to treatment with steroids
4.	Massive (> 6 cm below left ribcage) or progressive splenomegalia
5.	Massive glands or packets (> 10 cm in largest diameter) or progressive lymph adenopathia
6.	Progressive lymphocytosis with an increase > 50% within 2 months, or anticipated doubling time of less than 6 months

Considerable hypogammaglobulinemia, the occurrence of an M-protein or a high leukocyte count in **the absence** of one of the above mentioned criteria is not sufficient for starting treatment.

### Choice of treatment

This is a field that has undergone much change over the past few years. As a result, the half-life of the guidelines is limited. Important aspects in making a choice are:

- Age of the patient
- Performance status/ co-morbidity
- Risk profile (if known)
- Response (duration) to previous therapy
- Toxicity of previous therapy
- Importance attached by patient/treating physician to improved progression-free survival (PFS)

In 2006/2007, three phase III randomised studies were published, all of which demonstrate that the addition of cyclophosphamide to fludarabine (FC) considerably improves the PFS survival of CLL patients. The overall survival, however, was not different and in the 3-arm UKCLL4 study, was in fact not even better than in the chlorambucil arm. This of course reflects the effects of rescue therapy, which following more intensive first-line treatment may possibly not be as good. FC was however clearly more toxic, with more neutropenia/ thrombocytopenia, fever and hospitalisation.

During the ASH 2008 the results were presented of the CLL 8 study in which FC and FC+rituximab (FCR) in first line were compared. FCR resulted in an approval of the PFS with 10 months. The overall survival is not yet different when compared due to the short follow-up period. Remarkable was that the patients with Binet C stage or a 17p deletion did not have a longer PFS when treated with FCR. On the basis of this study, the rituximab in combination with (any) chemotherapy has been registered for first line treatment of CLL.

Of importance is to note that the follow-up of the MD Anderson study showed that patients with a relapse after FCR and being no candidate of allogenic stem cell transplant (and treated before with a range of treatment schedules) had a median survival of just 2,5 years.

Only relatively small phase I/II studies have been published for many newer options such as high dose Methylprednisolon plus rituximab or alemtuzumab, CFAR, Ofatumumab (humanised CD20), Limulixumab (antiCD23), lenalidomide, etc. Evidence based guidelines are therefore not possible here. Benamustine seems promising, but is not (yet) available in the Netherlands at this time.

In the event of relapse, chromosome study using FISH should be repeated or (if not previously requested) carried out for the first time. This is of vital importance, because 17p-deletions increase in frequency in the event of repeated therapy, and go hand in hand with resistance to the majority of cytostatics. Amongst this group of patients, alemtuzumab (monotherapy or in combination) would appear to still be effective.

Recently, an international expert forum stressed that alemtuzumab-containing immuno chemotherapy should only be applied within a study environment.

In young patients with a quick relapse after and/or resistance against first or second line therapy, a RIST should be considered with an HLA-identical (family/MUD) donor (preferably as part of a trial: HOVON 88).

On the basis of these considerations, the CLL working group has drawn up the following guidelines.

### **First-line treatment CLL**

#### TRIAL

- High risk CLL (Del 17p, del11q, trisomia 12, non-mutated IgVH genes, VH3-21 )

TRIAL : [HOVON 68](#)

#### OUTSIDE STUDY

- Chlorambucil. (e.g. 10 mg/m<sup>2</sup> per day, x7 q 4 weeks, up to maximum response or 12 x)  
Alternative is FC (maximum 6x), to be considered in the case of a young patient, an absence of co-morbidity, or wish for quick response.

### **Treatment of Relapse CLL**

#### TRIALS

- [HOVON 101](#)  
Ofatumumab maintenance in relapsed CLL; a randomized phase III intergroup study (in preparation):
- [HOVON 88](#)  
Reduced intensity allogene stemcelltransplantation
- [D' ACCORD STUDIE](#) (Dasatinib ± Fludarabine)

#### OUTSIDE STUDY

- If response time to non-immunochemotherapy in first-line > 1 year: repeat is defensible
- If response time to non-immunochemotherapy in first line < 1 year: second-line therapy, e.g. FC (possibly FCR)

- If 17 p-deletion: alemtuzumab (containing) therapy, certainly if in the past a fludarabine treatment was given.
  - In the event of fludarabine-resistance or relapse within 6 (-12) months following monotherapy or within 1(-2) years following first-line immunochemotherapy : consider inclusion in studies
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