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Chronic Lymphocytic Leukemia

Guideline

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie

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Chronic Lymphocytic Leukemia

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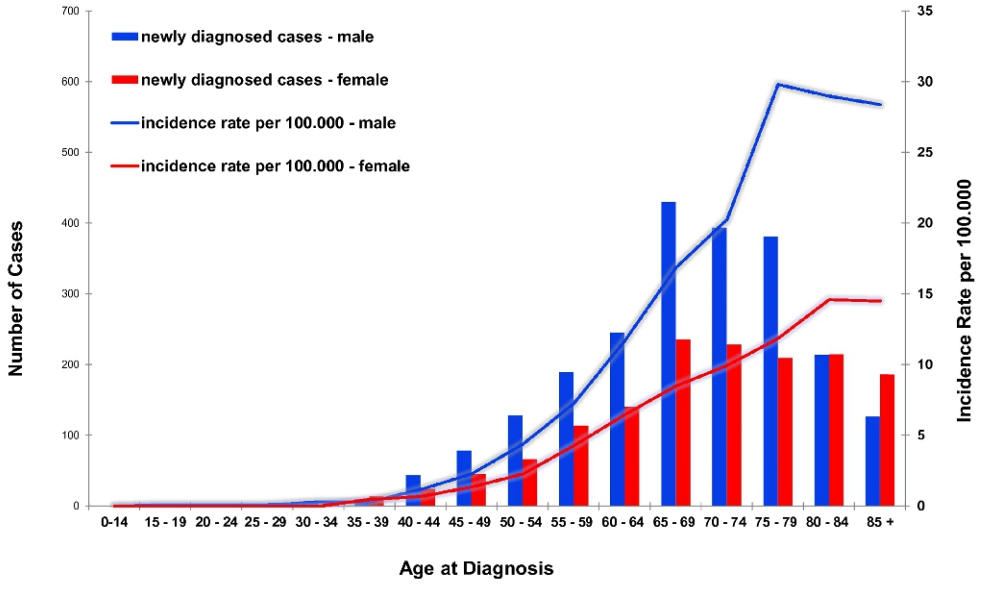
1 Definition and Basic Information

The WHO classification describes chronic lymphocytic leukemia (CLL) in terms of an indolent (lymphocytic) lymphoma, characterized by leukemic progression. According to the WHO CLL is invariably a B cell neoplasia, whereas the entity formerly designated T-CLL is now referred to as T cell prolymphocytic leukemia (T-PLL) .

1.1 Incidence Rate

CLL is the most frequent leukemic disease occurring in the western hemisphere. In Germany, approximately 2,250 men and 1,500 women annually acquire the disease. The age-standardized incidence rate for men is at 4.1 and for women at 2.1 per 100,000 inhabitants. The median age of men and women at diagnosis is 70 and 72 years, respectively, see Figure 1.

Abbildung 1: Incidence of CLL in Germany



(Source: Ulrich Gerdemann, Ron Pritzkuleit, Alexander Katalinic, Cancer Epidemiology Institute, Lübeck, Germany)

Projection of the Cancer Epidemiology Institute, Lübeck, for ICD10: C91.1 based on the number of new cases derived from the Cancer Registers of Bremen, Hamburg, Lower-Saxony, Münster, Saarland (for ICD 9: 204.1) and Schleswig-Holstein in the years 2007/8 (reference population ≈ 16 million inhabitants), September 2011

1.2 Risk Factors

The risk for CLL is increased by the factors below:

- acquired
- organic solvents
- genetic
- Persons with a positive family case history have an elevated risk for the diagnosis of CLL as well as any other lymphatic neoplasia.

CLL is almost invariably preceded by a clinically asymptomatic pre-stage characterized by an increase in the number of clonal B cells. These cells possess the biological features of leukemic cells and the pathological condition is referred to as monoclonal B lymphocytosis (MBL). MBL can be evidenced in >5 percent of seniors over 60 years of age. The risk of its transformation into CLL requiring treatment amounts to approximately one percent/year.

2 Prevention and Early Detection

There is no evidence of any efficient prevention or early-recognition actions.

3 Clinical Picture

The disease is characterized by lymphocytosis in the blood which is often discovered incidentally. As the disease progresses lymphadenopathy, splenomegaly and hepatomegaly, signs of bone-marrow failure, and sometimes autoimmunity-associated cytopenias may appear. Clinical symptoms can also manifest themselves in the sense of B symptoms and an increased susceptibility to infections.

4 Diagnosis

4.1 Diagnostic Criteria

According to the *International Workshop on CLL (IWCLL) in 2008* the diagnosis of CLL is defined by the criteria below:

- Identification of at least 5,000 clonal B lymphocytes per µl in the peripheral blood. Below this value, monoclonal B lymphocytosis (of uncertain significance) (“MBL”) can be “diagnosed”, if clinical symptoms of the disease are absent (B symptoms, lymphadenopathy, hepatomegaly, splenomegaly, cytopenia, etc.).
- Prevalence of small lymphocytes appearing mature in the cytological examination of blood smears
- Co-expression of the B cell antigens CD19, CD20, und CD23 with the T cell antigen CD5 in multiparametric immunophenotyping. Additionally characteristic is the relatively poor expression of surface immunoglobulin, CD20 and CD79b. The monoclonality of the cells can be evidenced by light-chain restriction (Ig-kappa or Ig-lambda), preferentially by double marking of CD19/kappa or CD19/lambda.

Characteristic findings of microscopy, immunophenotyping, and genetics are compiled in the Chronic Lymphocytic Leukemia Knowledge Base http://www.dgho-onkopedia.de/ wissensdatenbank/wissensdatenbank/chronische-lymphatische-leukaemie-cll .

4.2 Diagnostics

The diagnostic procedure depends on the primary constellation of findings, which is usually characterized by the cardinal symptom of lymphocytosis, present either with or without accompanying lymphadenopathy. If a patient is suspected of having CLL, the following tests are recommended, see Tables 1 and 2.

Tabelle 1: Diagnostics in Suspected Cases of CLL

Diagnostics	**Comment**
Medical Case History	Loss of physical fitness, B symptoms, susceptibility to infections etc., previous differential blood-cell counts / leukocyte counts, family case history
Physical Examination	Lymph-node status, organomegaly, signs of hemorrhage or anemia
Differential Blood Cell Count	Leukocytes in the differential blood-cell count, platelets, hemoglobin, reticulocytes (in case of signs of anemia)
Multiparametric Immunophenotyping	• Expression of CD19 and CD23 • Co-expression of CD5 • Poor or absent expression of CD20, CD79b, FMC7 • Monoclonality of IgKappa or IgLambda

Tabelle 1: Diagnostics in Suspected Cases of CLL

Bone-Marrow Puncture	Usually not necessary for diagnosis, but may be indicated at disease progression in order to assess unclear cytopenias and/or the quality of remission.
Lymph-Node Biopsy	Only indicated in case of absent lymphocytosis in the blood or suspected transformation into an aggressive lymphoma (Richter syndrome)

Tabelle 2: Additional Diagnostics before Therapy Initiation

Diagnostics	**Comments**
Genetics	• Deletion 17p13* • Additional genetic tests in case of atypical phenotype to distinguish from other indolent lymphomas
Supplementary Laboratory Analyses	Depending on symptoms and scheduled therapy, e.g.: • Haptoglobin and Coombs test in case of suspected hemolysis, and before initiation of therapy including fludarabine • GFR in case of planned therapy with fludarabine • Quantitative determination of immunoglobulins in case of suspected immunodeficiency • CMV status (serology) before initiating therapy with alemtuzumab
Sonography	Abdomen: lymph node

*Legende: * The data on the unfavorable prognosis of patients with 17p13 deletions rely on molecular cytogenetic analyses with FISH. The patient population with mutational inactivation of p53 overlaps to a great extent with those having 17p13 deletions, however, they are not fully identical. At present, the FISH analysis of the 17p13 deletion is therefore recommended as the standard.*

Recently identified biological prognosis factors, e.g. thymidine kinase, beta-2-microglobulin, m utation status of the variable segments of the immunoglobulin heavy-chain genes (IGHV), other genomic aberrations, CD38 or ZAP70 expression still require prospective validation and at present do not form the foundation of differential therapeutic considerations outside clinical studies. Their routine analysis is not indicated outside clinical studies.

4.3 Staging and Prognostic Factors

Staging after Binet (the most common in Europe, see Table 3) or Rai merely requires a physical examination and a differential blood-cell count. Test results from methods depending on imaging (organomegaly detected by means of sonography, CT) are irrelevant to staging.

Tabelle 3: Staging after Binet

Stage	Definition	Median Survival
A	Hemoglobin $\geq$ 10 g / dl Platelets $\geq$ 100.000 / µl < 3 affected regions[2](LN[1], liver or spleen)	> 10 years
B	Hemoglobin $\geq$ 10 g / dl Platelets $\geq$ 100,000 / µl $\geq$ 3 affected regions[2](LN[1], liver or spleen)	5 years
C	Hemoglobin < 10 g / dl Platelets < 100,000 / µl	2 - 3 years

Legende: [1]LN = lymph nodes;[2]Regions are cervical, axillary, and inguinal LN enlargements (unilateral or bilateral), as well as enlargements of liver and spleen (only by means of physical examination).

4.4 Differential Diagnosis

The most frequent differential diagnoses are:

- Monoclonal B lymphocytosis
- Reactive lymphocytosis (viral infections, collagenoses)
- Other leukemic lymphomas (follicular lymphoma, cf. Follicular Lymphoma Guideline ; lymphoplasmacytic lymphoma, marginal zone lymphoma, cf. Marginal Zone Lymphoma Guideline ; mantle cell lymphoma, cf. Mantle Cell Lymphoma Guideline ; B cell prolymphocytic leukemia (B-PLL)).
- Hairy cell leukemia, cf. Hairy Cell Leukemia Guideline

5 Therapy

According to the current state of knowledge CLL is not curable by conventional chemotherapy or antibody-based therapies. Allogeneic stem-cell transplantation is the only curative option.

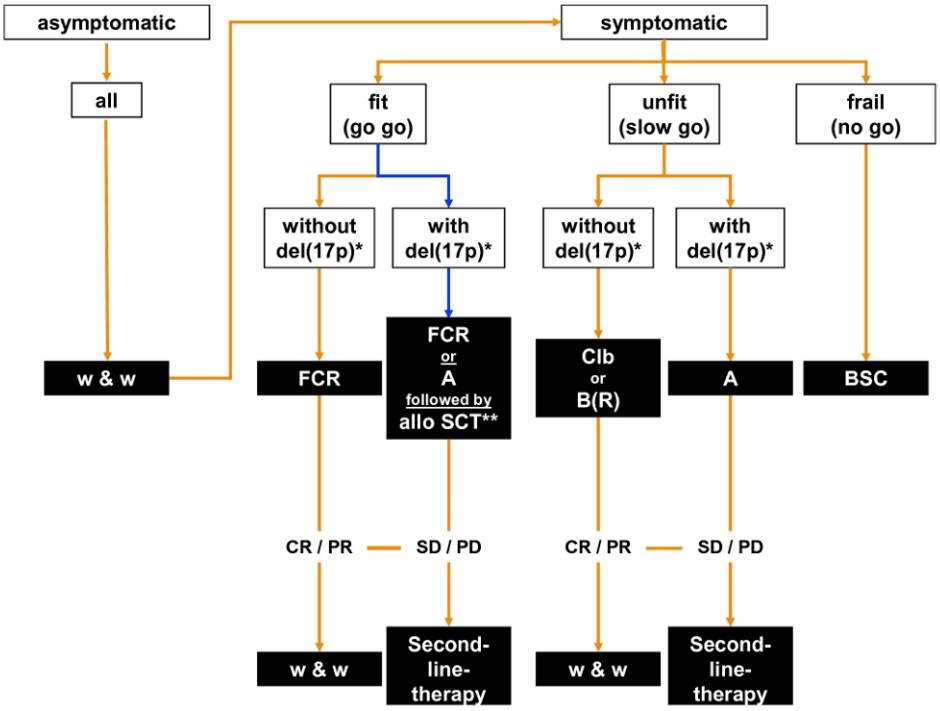
An indication for therapy commonly exists in Stage Binet C as well as in Binet Stage B or A, if other criteria for therapy requirement are fulfilled:

- Occurrence/exacerbation of anemia / thrombocytopenia
- Massive (> 6cm under the costal arch), progressive or symptomatic spleno-megaly; note: the size of the spleen varies among individuals depending on height and body weight
- Massive (measuring > 10cm in diameter), progredient or symptomatic lymphadenopathy
- Lymphocyte doubling time less than 6 months or a 50% rise within two months, after other causes of lymphocytosis have been excluded
- Refractory autoimmune cytopenia upon standard therapy
- One of the following constitutional symptoms
  - unintentional weight loss > 10 % in 6 months
  - fever of unknown origin lasting more than 2 weeks
  - night sweating for more than one month without evidence of infection
  - serious fatigue

5.1 First-Line Therapy

The choice of therapy depends on comorbidity (e.g. determined by applying the CIRS Score), the genetic status, renal function, and less on chronological age, see Figure 2. Whenever possible, patients should be included in clinical trials.

Abbildung 2: First-Line Therapy of CLL



Palliative therapy approach; Curative therapy approach;

* for methods see Chapter 4.1.2. Diagnostics ** allo SCT in patients who are eligible;

A - Alemtuzumab, allo SCT - Allogeneic Stem-Cell Transplantation, B - Bendamustine, BSC - Best Supportive Care, C - Cyclophosphamide, Clb - Chlorambucil, C - Cyclophosphamide, CR - Complete Remission, F - Fludarabine, P - Prednisone, PD - Progress, PR - Partial Remission, R - Rituximab, SD - Stabile Disease, w & w - watch and wait;

In physically fit patients (e.g. CIRS < 6) with normal renal function and absence of clinically relevant comorbidity, the first-line therapy of choice outside clinical studies consists in a combination therapy of fludarabine, cyclophosphamide and rituximab (FCR), see Chronic Lymphocytic Leukemia - Systemic Therapy .

An alternative to FCR might consist of combining bendamustine with rituximab (BR), particularly in cases of uncontrolled autoimmune hemolysis or impaired renal function. However, only data derived from single-arm phase-II studies are as yet available for this combination. Results of a study which examined BR in a randomized comparison with FCR administered in first-line therapy are still pending.

There are at least two options available to patients with impaired renal function and/or increased comorbidity: chlorambucil and/or bendamustine. In direct comparison, bendamustine was shown to be superior to chlorambucil with regard to ORR, CR, and PFS. Monotherapy with chlorambucil should be reserved for patients with significant comorbidity. According to data obtained in phase-II studies the addition of rituximab to bendamustine or chlorambucil improves the efficacy of both regimens. Phase-III studies focusing on this issue are currently in progress. Thus this new combination might also present an option to unfit patients in the future.

Monotherapy with standard-dosed fludarabine is not recommended in patients with significant comorbidity because of its increased toxicity and no improvement in survival parameters as compared to chlorambucil therapy.

As a standard, the dosages of chemotherapies and immune therapies are based on the specifications of multicenter studies. A dose reduction may be required in older and comorbid CLL patients, occasionally upon initial administration, more often in the course of further therapy cycles as an adjustment to individual susceptibility.

Patients with 17p13 deletion and/or p53 mutation have lower response rate as well as shorter progression-free survival and total survival rate subsequent to chemotherapy (chlorambucil, fludarabine-containing regimes, bendamustine, also in combination with rituximab). In patients without relevant comorbidity, but with therapy-requiring CLL and 17p13 deletion, alternative therapy approaches (e.g. alemtuzumab with subsequent consolidating allogeneic blood stem-cell transplantation) should be endeavored, if possible, in the scope of clinical studies, in order to achieve long-term disease-free survival.

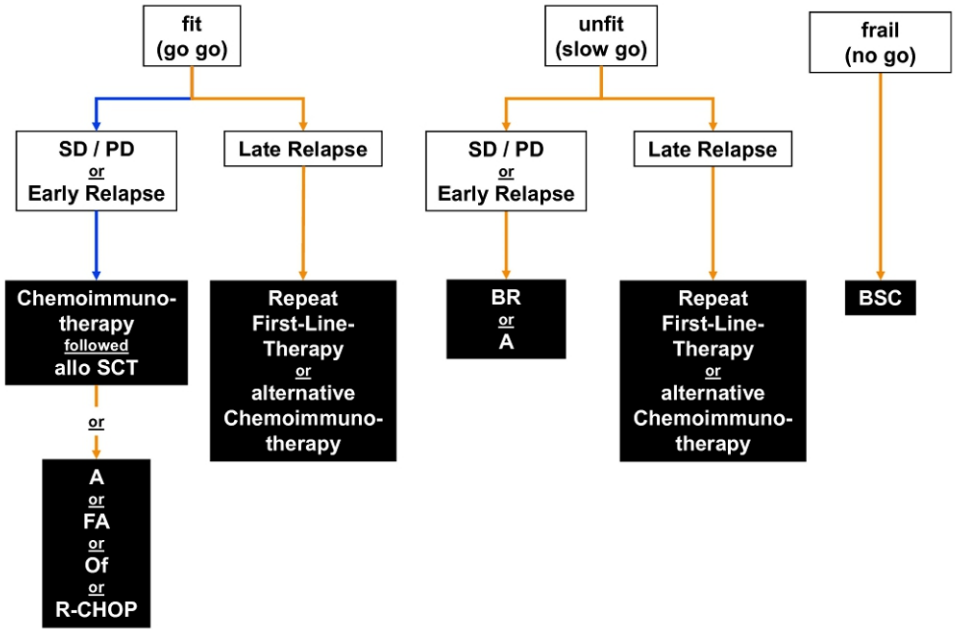
5.2 Drugs

Information about the authorization status of drugs that qualify for CLL therapy is listed in Chronic Lymphocytic Leukemia - Authorization Status for Germany, Austria, and Switzerland.

5.3 Second-Line Therapy

The choice of relapse therapy depends on individual factors. Such factors are, apart from the age of the patient and the existence of patient comorbidity, especially clinical parameters, like the type of primary therapy and the duration of previous remission. An algorithm is shown in Figure 3. Whenever possible, therapy should proceed in the context of clinical studies.

Abbildung 3: Second-Line Therapy of CLL



→ Palliative therapy approach; → Curative therapy approach;
A - Alemtuzumab, allo SCT - Allogeneic Stem-Cell Transplantation, B - Bendamustine, BSC - Best Supportive Care, C - Cyclophosphamide, d - dose-adapted t, F - Fludarabine, H - Doxorubicin, O - Vincristine, Of - Ofatumumab, P - Prednisone, PD - Progress, R - Rituximab, SD - Stabile Disease;

5.3.1 Progress / Refractoriness / Early Relapse

Patients who are refractory to current standard therapies (FC, FCR, BR) or experience only a short remission (< 2 years), have a bad prognosis. Their median total survival period amounts to 1-2 years, starting with the onset of salvage therapy.

Applicable in this situation is the pan-lymphocyte antibody alemtuzumab, cf. Appendix to Chronic Lymphocytic Leukemia - Authorization Status . An application of alemtuzumab will require extensive anti-infection prophylaxis and frequent infectious monitoring. CMV reactivations must be expected if CMV serology turns out positive.

The monoclonal anti-CD20 antibody Ofatumumab is registered for application to patients who were refractory to a fludarabine-containing regime and alemtuzu-

mab (Germany, Austria) and/or patients who were not eligible for these therapies (Switzerland).

Alternatively, in cases in which the patient is in good general health or an aggressive course of CLL exists, chemoimmunotherapy can be conducted like in cases of non-Hodgkin lymphomas, e.g. R-CHOP.

In addition, several new substances are currently being evaluated for their efficacy in cases of refractory / relapsing CLL (among others, lenalidomide, flavopiridol, ABT263, CAL101, PCI32765 etc.). A therapy outside of studies cannot be recommended on account of the limited availability of published data.

5.3.2 Late Relapse

Despite the limited database it appears generally justified after primary therapy to apply the same regime a second time, if the response was good and the duration of remission lasted long enough, i.e. at least 1-2 years (depending on the intensity of therapy). It may be generally assumed that efficacy will be enhanced once rituximab is added. Apart from intensive fludarabine-containing combination therapies, e.g. FCR combination therapy, BR or the antibody alemtuzumab are also applicable in relapse therapy.

5.4 Autoimmune Disorders

Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are frequent phenomena associated with CLL. AIHA is usually Coombs-positive. The concomitant occurrence of cold agglutinins along with identified IgM antibodies is exceptional. Coombs-negative hemolytic anemias have been described after a preceding therapy with purine analogues. The patients must be informed about the particularly high risk resulting from crises associated with infections. The appearance of pure red-cell aplasia (PRCA) is rare. Therapy with corticosteroids will be indicated in case of the exclusive appearance of AIHA or ITP, occurring without other symptoms of therapy-demanding CLL (see above). Therapy options applicable to patients failing to respond to corticosteroids are, for example, RCD, R-COP, or R-CHOP. M onotherapy with purine analogues is contraindicated in case of active autoimmune phenomena.

5.5 Allogeneic Stem-Cell Transplantation

Allogeneic stem-cell transplantation presents a reasonable option to patients with therapy-refractory or early-relapsing CLL (see Chapter 5.3), provided that the course of the disease and the physical condition of the patient so allows. Another indication for allogeneic stem-cell transplantation is the detection of a 17p deletion or TP53 mutation in the event of a therapy-demanding disease.

Indication, time-point, and performance of the transplantation, including the search for a donor, should be clarified in close collaboration with a transplantation center before the initiation of salvage or first-line therapy. An important prognostic factor to gain long-term control over the disease is the existence of

a remission at the time of allogeneic transplantation. If possible, transplantation should proceed in the context of clinical studies.

5.6 Autologous Stem-Cell Transplantation

High-dose therapy with autologous transplantation results in an increase of remission rates, compared to a standard chemotherapy, but not to an improvement of survival rates, cf. Chronic Lymphocytic Leukemia Study Results . Comparisons with an immunochemotherapy do not exist. At present, a high-dose therapy with autologous stem-cell transplantation outside of studies cannot be recommended.

5.7 Supportive Therapy and Therapy of Complications

CLL patients often have complications due to infections in the course of the disease, which are enhanced by the decrease in immunoglobulin concentrations and other mechanisms of acquired immune deficiency. A particularly careful surveillance of intensive general medical therapies, e.g. in cases of chronic or relapsing bronchitides, is indicated. The prophylactic substitution with immunoglobulins reduces the risk of contracting serious infections, however, it has no significant influence on mortality [11]. Immunoglobulins can be applied to patients with hypogammaglobulinemia and concomitantly elevated infection frequency.

Age-correlated vaccinations (e.g. against influenza or pneumococci) are being recommended despite the fact that the formation of specific antibodies might be reduced. Travel vaccinations should only be done after consulting the attending physician, as live vaccines could become hazardous for the patient.

6 Follow-Up

The follow-up of asymptomatic patients should include a differential blood-cell count in a time interval of approx. 3-6 months, apart from a clinical examination of lymph nodes, liver, and spleen. In this context, attention should be paid to the appearance of autoimmune cytopenias (AIHA, ITP) and infections. Furthermore, rapid lymph-node enlargements, B symptoms and/or an increase of LDH activity should prompt further diagnostics to rule out a transformation into a highly malignant lymphoma (Richter syndrome) apart from the occurrence of a CLL relapse.

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8 Active Studies

9 Systemic Therapy - Protocols

Chronic Lymphocytic Leukemia - Systemic Therapy - Protocols

10 Drugs - Authorization Status

11 Study Results

Chronic Lymphocytic Leukemia - Study Results (RCT, Metaanalysis)

12 Links

Malignant Lymphoma Competence Network
www.kompetenznetz-leukaemie.de

Deutsche Leukämie - und Lymphom - Hilfe e. V.
www.leukaemie-hilfe.de

German CLL Study Group
www.dcllsg.de

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14 Disclosures