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Hairy-Cell Leukemia

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

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DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
Alexanderplatz 1
D-10178 Berlin

Executive chairman: Prof. Dr. med. Michael Hallek

Phone: +49 (0)30 27 87 60 89 - 0
Fax: +49 (0)30 27 87 60 89 - 18

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

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Hairy-Cell Leukemia

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Authors: Bernhard Josef Wörmann, Anthony D. Ho, Mathias J. Rummel, Max Solenthaler, Michael Steurer

1 Definition and Basic Information

Hairy-cell leukemia (HCL) is a malignant disease which affects the B lymphocytes and belongs to the indolent lymphomas. The name is derived from the microscopical aspect of leukemic cells which display characteristic, fine cytoplasmic projections [1, 2].

1.1 Incidence

Hairy-cell leukemia is a rare disease. Its incidence is approximately 0.3/100,000 people. The median average age lies between 50 to 55 years. The age interval is very broad, however, children are not affected. The disease occurs up to five times more often in males than in females [1].

1.2 Risk Factors

The cause of hairy-cell leukemia is unknown. Amongst other exogenous risk factors, exposure to insecticides or herbicides is being discussed [3].

2 Prevention and Early Detection

There is no evidence that effective measures of prevention or early detection exist.

3 Clinical Presentation

The characteristic symptoms of hairy-cell leukemia are cytopenia and splenomegaly [4]. Cytopenia results on the one hand from progressive bone marrow failure, caused by a combination of leukemic infiltration, hematopoiesis-suppressive cytokines such as TNF alpha, and a reticulin fibrosis, and on the other hand the consequences of splenomegaly. The symptoms are generalized fatigue, weakness, and paleness due to the anemia, infections due to neutropenia, and a bleeding tendency due to thrombocytopenia. Approximately 70% of all hairy-cell leukemia patients are pancytopenic. Feeling of pressure in the left upper abdomen might be a sign of splenomegaly. Additional, less common symptoms are hepatomegaly (20%), lymphadenopathy (<10%), autoimmune phenomena (vasculitis, polyarthritis), skeletal manifestations (osteolyses) and B symptoms. The latter has to be distinguished from infectious complications, also with unusual pathogens. The progression of hairy-cell leukemia is slow and displays an individually variable, often undulating course.

4 Diagnosis

4.1 Classification

Two forms of the disease are distinguished, i.e. hairy-cell leukemia and a variant form, see Table 1 [5]. The variant form of hairy-cell leukemia (HCL-V) differs with regard to its cytology, immunology, and cytochemistry [6, 7]. HCL-V is typically accompanied by a leukocytosis, with cell counts ranging from 15,000 to 400,000 /µl. The morphology of these cells displays a central nucleus with dense chromatin and a prominent nucleolus, whereby the cells themselves somewhat resemble a mixture between a hairy cell and a prolymphocyte. As far as their immunophenotype is concerned, HCL-V cells are CD25-negative, as opposed to classical HCL cells. The expression of CD103 may vary.

New is our knowledge about the significance of the *BRAF* V600E mutation. It has been evidenced in 80-100% of the patients with hairy-cell leukemia, but not in the variant form [8, 9]. Neither does the *BRAF* V600E mutation occur in hairy-cell leukemia associated with IGHV4-34 gene rearrangements [9].

Table 1: Classification of Hairy-Cell Leukemia

	Hairy-Cell Leukemia	**Hairy-Cell Leukemia Variant**
Relative Occurrence (%)	90 – 95	5 – 10
Sex Distribution	4 : 1 (M : F)	1 - 2 : 1 (M : F)
Age (median, years)	50 – 55	> 70
Lymphocytosis in peripheral blood (%)	≤ 10	≥ 90
Monocytes in peripheral blood	Decreased	Normal range
Hemoglobin	Anemia in 85% of the cases	Often normal range
Thrombocytopenia	Thrombocytopenia in 80% of the cases	Often normal range
Immunophenotype[1]	Mature B cell, CD11c +, CD103 +, CD25 +	Mature B cell, CD11c +, CD103 +, CD25 -
Immunohistochemistry	DBA.44 + Cyclin D1 + Annexin A1 +	DBA.44 + Cyclin D1 + Annexin A1 -
Genotype	*BRAF* V600E mutation	BRAF wild type

Legend:
[1] acc. to CD classification - cluster of differentiation, analyzed by multiparameter flow cytometry

A second hairy-cell leukemia variant has been described in Japan. This variant is not subject of this Guideline.

4.2 Diagnostics

The diagnostic algorithm is divided in basic and special tests, see Table 2. Despite the typical lymphocytopenia, hairy cells are found in the peripheral blood of most patients. Standard procedure in diagnostics is multiparameter flow cytometry at least four fluorescent parameters and a sensitivity of < 1/1,000 cells. The cytochemical determination of tartrate-resistant acid phosphatase (TRAP) is only of historical interest. Frequently, the bone marrow cannot be aspirated (dry tap). Most cases do not require molecular genetic analysis. Evidence of the *BRAF*

V600E mutation can be useful for the differential diagnostic distinction from other indolent non-Hodgkin lymphomas and the variant form of hairy-cell leukemia.

Table 2: Diagnostics in case of Suspected Hairy-Cell Leukemia

	Material / Method	Test
Basic	Peripheral blood	Complete blood cell count including leukocyte count with microscopic differential, reticulocytes
		AST (GOT), ALT (GPT), AP, CRP, Ferritin, LDH, Vitamin B12, Folic Acid
	Sonography	Abdomen
Special	Peripheral blood	Immunophenotyping
	Bone marrow aspirate	Panoptic stain, Multiparameter Flow Cytometry
	Bone marrow biopsy	Histology, Immunohistochemistry, Reticulin staining

4.3 Differential Diagnosis

The differential diagnostics of cytopenia and splenomegaly is broad. An overview of the most common diseases is shown in Table 3.

Table 3: Differential Diagnosis in Cases of Suspected Hairy-Cell Leukemia

Panzytopenia	Splenomegaly (Hypersplenism)	Hemocytopenia and Splenomegaly
Reactive / toxic bone-marrow disorders	Portal-vein thrombosis of unknown origin	Non-Hodgkin Lymphoma • Splenic Marginal Zone Lymphoma (with villous lymphocytes) • Other: Follicular Lymphoma, Lymphocytic Lymphoma (CLL[1]), PLL, Morbus Waldenström
Vitamin B12- Deficiency	Budd – Chiari syndrome	Hematolytic Anemia, Evans Syndrome
Folic Acid Deficiency	Liver cirrhosis with portal hypertension	Felty Syndrome
Myelodysplastic Syndrome		Primary Myelofibrosis
Acute Leukemia		Morbus Gaucher
Non - Hodgkin Lymphoma, Stage IV		Hemophagocytic Syndrome
Aplastic Anemia		
Paroxysmal Nocturnal Hemoglobinuria (PNH)		
Primary Myelofibrosis		

Legend:
[1] CLL – Chronic Lymphocytic Leukemia, PLL – Prolymphocytic Leukemia

5 Therapy

5.1 Therapy of Hairy-Cell Leukemia

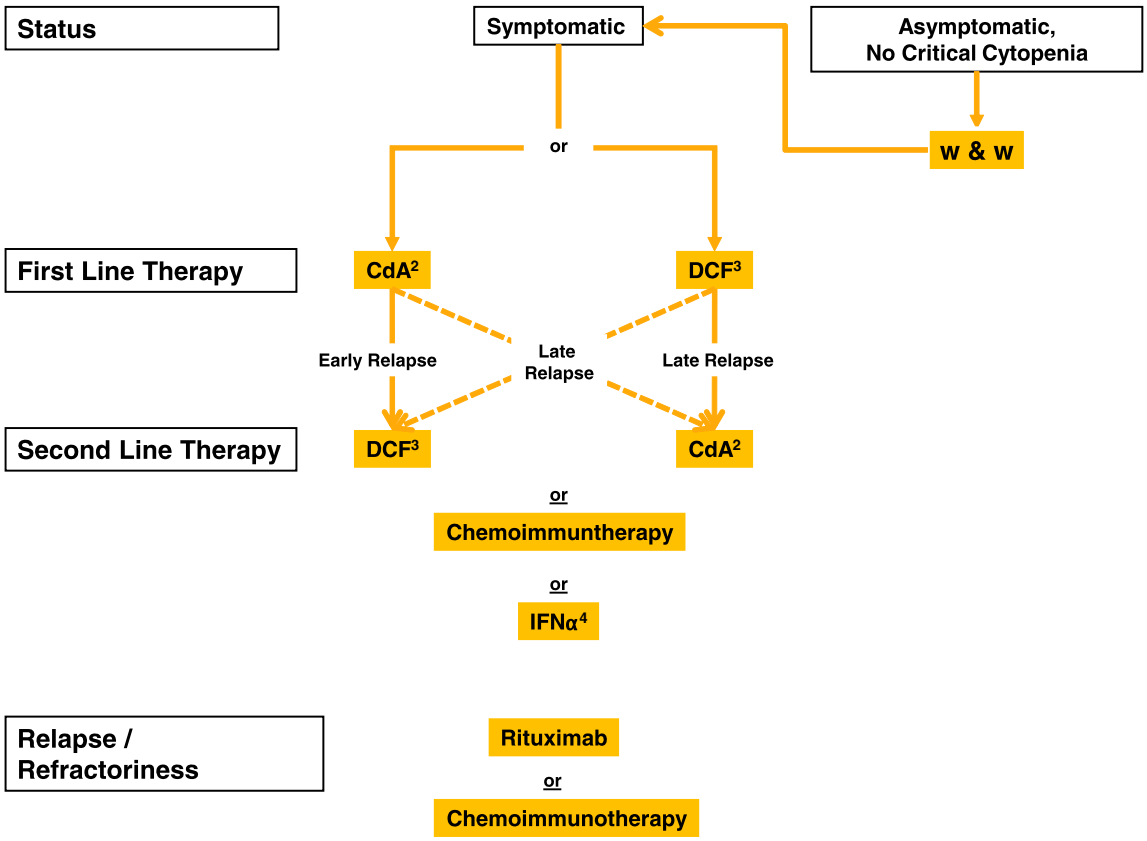
Hairy-cell leukemia is a highly treatable disease. An initiation of first-line therapy is indicated in symptomatic patients or in asymptomatic patients with progressive and moderate to severe cytopenia. In case of asymptomatic patients differential blood cell counts should be checked

regularly in at least three-monthly intervals, in order to assess the dynamics of the disease. The criterion for deciding on the onset of therapy consists in the progression of cytopenia, including

- neutrophils < 1,000 / µl and / or
- platelets < 100,000 / µl und / or
- hemoglobin < 11 g / dl

An algorithm for differential therapy is shown in Figure 1 [10- 12].

Figure 1: Therapy Algorithm



Legend:
[1] *w & w - watch and wait, observant behavior;*
[2] *2CdA - cladribine, 2-chlorodeoxyadenosine;*
[3] *deoxycoformicin,*
[4] *IFN alpha - interferon alpha*

The minimum goal of therapy is a sustained normalization of the differential blood cell counts. Reaching complete remission is associated with a prolonged period of progression-free survival, however, the rate of total survival remains unaffected. The value of consolidation therapy to eradicate the minimal residual disease has not been established. .

5.1.1 Chemotherapy

Purine analogues display the highest efficacy. Both 2-chlorodeoxyadenosin (cladribine, 2-CdA) and deoxycoformicin (pentostatin, DCF) are effective. A prospective randomized study comparing the two substances has not been conducted. 2-CdA has gained wide-spread acceptance in Germany. In Austria and Switzerland, it is the only authorized purine analogue.

5.1.1.1 Cladribine (2-Chlorodeoxyadenosine, 2-CdA)

Patients with hairy cell leukemia achieve response rates of 95 - 98%, more than 75% of which are complete remissions [13- 15]. Cladribine can be applied in different ways. Response rates are similar (see Systemic Therapy):

1. Subcutaneous application: daily over 5 days [16]
2. Intravenous application: daily over 5 - 7 days [14, 15]
3. Intravenous application: weekly over 6 weeks [14, 15]

Subcutaneous application is performed once daily as a bolus. Intravenous application can be applied either as an infusion over two hours or as a continuous infusion over 24 hours.

Standard is the application of one cycle. Evaluation of the remission status should be performed not earlier than four months after completion of the cladribine cycle because the time required to attain an optimal remission is characteristically longer in cases of HCL. A second course may be taken into consideration only if the hematological and / or clinical response is poor.

Approximately 50% of the patients relapse within a time span of 15 years. A second therapy with purine analogues is possible in relapse, particularly if the previous remission after cladribine has been long (> 3 years). Patients who have a relapse subsequent to initial interferon therapy, or become resistant to interferon, might respond well to cladribine. In principle, the response does not differ from previously untreated HCL patients.

5.1.1.2 Pentostatin (Deoxycoformicin)

Pentostatin is a specific inhibitor of adenosine deaminase (ADA). The enzyme ADA is indispensable for the development of T and B lymphocytes. An inhibition of ADA is therefore toxic to lymphocytes. Therapy with pentostatin achieves remission rates of > 90%, and complete hematologic remission in > 75% of the patients [17- 19].

Pentostatin application proceeds intravenously in intervals of two to three weeks over a period of at least three months (total of 6-9 cycles). In a randomized study, pentostatin was found to be superior to interferon α [20]. Retherapy after long remission durations is also possible with pentostatin (> 3 years). If a patient responds poorly to cladribine, switch to pentostatin is an alternative treatment option [20].

5.1.1.3 Supportive Measures in Case of Chemotherapy

Since both cladribine and pentostatin are eliminated via the kidneys, special attention must be given to the surveillance of functional renal parameters. Protracted elimination might results in prolonged cytopenia.

If the T helper cells (CD4+) are <200/µl cotrimoxazole/trimethoprim should be given as a continuous prophylaxis against *Pneumocystis jirovecii*, perhaps along with another type of antibiotic and antimycotic prophylaxis. The benefit of a routine application of G-CSF is not recommended, however, may be considered in the individual case.

5.1.2 Immunotherapy

5.1.2.1 Interferon alpha (IFN alpha)

Interferon alpha was the common and only available therapy in the 1980s. It was the first drug therapy applicable in the treatment of hairy-cell leukemia. Response rates amounted to 75-80%, whereby < 20% of the patients reached a complete remission [21, 22]. Interferon is applied by subcutaneous injection. The effective dose is 2-3 million units 3-5 x/week over 18 to 24 months, but in some cases over an even much longer period of time. The effects of interferon only occur gradually, in some cases even in association with a transitory exacerbation of the differential blood cell count parameters within the first 2-3 months. The relapse rate greatly exceeds 50 percent within the first ten years. Randomized studies demonstrated the superiority of pentostatin over IFN alpha as far as the rates of remission and the time to relapse was concerned. There was no difference in overall survival, however, pentostatin was applied in cases of interferon refractoriness or in relapse [22].

5.1.2.2 Rituximab

The cells of hairy-cell leukemia are CD20-positive and thus susceptible to treatment with rituximab. The remission rates in phase-II studies range at 50 - 80 %, whereas complete hematological remissions are obtained in 20-50% of the patients [23]. However, the remissions are mostly not of long duration. Rituximab is applied intravenously every 4 weeks over 2 - 4 courses.

5.1.2.3 Chemoimmunotherapy

Chemotherapy with purine analogues combined with rituximab is more effective in other indolent B-cell lymphomas than chemotherapy alone. This has been shown for remission rates, progression-free survival, and in some entities overall survival. In hairy-cell leukemia, two concepts are being tested:

- Chemotherapy, followed by rituximab
  The object of this concept is the eradication of the minimal residual disease in hematological remission after cladribine or pentostatin. In a phase-II pilot study all 36 patients reached complete remission after rituximab [24]. Long-term data are not available yet.
- Chemotherapy, combined with rituximab
  This therapy is being evaluated in relapse patients subsequent to therapy with a purine analogue. Cladribine, pentostatin, or fludarabine are applied in combination with rituximab. Rates of complete hematological remission are up to 90 percent [25, 26].

The question whether first-line chemoimmunotherapy improves the survival time of patients with hairy-cell leukemia still remains unanswered.

5.1.3 Additional Systemic Therapy

Drugs usually applied in other cases of indolent non-Hodgkin lymphomas have only little effect in hairy-cell leukemia. Toxin-coupled monoclonal antibodies are a further development in immunotherapy [27].

The evidence of a *BRAF* V600E mutation represents a new target site for molecular therapy of patients with hairy-cell leukemia, e.g. with vemurafenib [28]. However, this therapy is only indicated in the scope of clinical studies because of significant adverse effects.

5.1.4 Splenectomy

Splenectomy used to be the first effective therapy for hairy-cell leukemia and made it possible to obtain hematological remissions in up to 70 percent of all patients [29]. However, the relapse rate lies at >90 percent. Splenectomy no longer belongs to the standard therapy of hairy-cell leukemia, however, it may be considered for therapy-refractory patients after treatment with purine analogues and interferon alpha, and in cases of symptomatic splenomegaly.

5.2 Therapy of Hairy-Cell Leukemia Variant

in contrast to the classic HCL which has a chronic, insidious course variant HCL-V presents more aggressively with shorter overall survival and poor responses to conventional types of therapy [6]. The response rate to purine analogues is at about 50%. HCL-V patients also respond poorly to IFN alpha or to cytostatics such as alkylating agents. Splenectomy is a therapy option for patients who fail to respond to purine analogues or who suffer a relapse in the short term.

6 Check-Up / Follow-Up

Hairy-cell leukemia is a chronic disease. Late relapses are possible as well. A prospectively evaluated check-up program does not exist. Recommended is a risk-adapted procedure: Four weekly differential blood cell count checks are recommendable within the first six months after achievement of an optimum response, and sonography of the abdomen every three months in order to check the size of the spleen. Once a stable hematological remission has been obtained the follow-up intervals for the differential blood cell counts can be extended to three months, whereas those for sonography may be extended to six months or longer.

7 Prognosis

About 70% of all patients with hairy-cell leukemia have a regular life expectancy. Crucial is the response to systemic drug therapy [20]. A recent evaluation of a long-term study with 242 patients revealed that 81% of the patients experienced complete hematologic remission, while the median period of disease-free survival amounted to 16 years [20, 30]. Some studies reported an increased rate of secondary neoplasms [31]. However, the data published and the spectrum of observed malignancies is not conclusive. Patients with hairy-cell leukemia should participate in the regular programs of cancer prevention and screening.

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9 Active Studies

- First Line
  StiL NHL 3-2004: The HCL primary therapy study recommends one cycle with a dose of 0.14mg/kg b.w./d of subcutaneously applicable cladribine on five consecutive days. It is to be tested whether patients who do not respond optimally to a cycle of cladribine, i.e. patients with a still measurable residual disease (reaching partial remission or a demonstrable residual infiltration into the bone marrow, also by applying immunohistochemistry) will benefit from a second cycle of cladribine; http://www.stil-info.de/index.php?id=258
- Relapse of classic hairy-cell leukemia or variant hairy-cell leukemia irrespective of the stage of the disease
  StiL NHL 4-2004: The combination of subcutaneous cladribine and rituximab is also currently under investigation in the scope of StiL study. The study is testing the efficacy (rate of complete remissions, total remission rate, and length of remission) and the toxic effects (acute toxicity and long-term toxicity) of immuno/chemotherapy combined with subcutaneous cladribine plus rituximab in patients with relapsed hairy-cell leukemia requiring therapy or patients with variant hairy-cell leukemia irrespective of any previous therapies.

10 Systemic Therapy – Protocols

- Hairy-Cell Leukemia – Systemic Therapy

12 Links

http://www.haarzell-leukaemie.de

13 Authors' Affiliations

Prof. Dr. med. Bernhard Josef Wörmann
Amb. Gesundheitszentrum d. Charité
Campus Virchow-Klinikum
Med. Klinik m.S. Hämatologie & Onkologie
Augustenburger Platz 1
13344 Berlin
Tel: 030 450553219
bernhard.woermann@charite.de

Prof. Dr. med. Anthony D. Ho
Universitätsklinikum Heidelberg
Medizinische Klinik V
Im Neuenheimer Feld 410
69120 Heidelberg
Tel: 06221 56-8001
Fax: 06221 56-5813
anthony_ho@med.uni-heidelberg.de

Prof. Dr. med. Mathias J. Rummel
Klinikum der Justus-Liebig-Universität Giessen
Medizinische Klinik IV
StiL-Studienzentrale
Klinikstr. 36
35392 Gießen
Tel: 0641 985-42600
Fax: 0641 985-42609
Mathias.Rummel@innere.med.uni-giessen.de

Dr. Max Solenthaler
Spital STS AG Thun
Onkologiezentrum Thun-Berner Oberland
Krankenhausstr. 12
CH-3600 Thun
Tel: 0041 33 2263601
max.solenthaler@spitalstsag.ch

Ao. Univ. Prof. Dr. Michael Steurer
Medizinische Universität Innsbruck
Klinik f. Innere Medizin V
Anichstr. 35
A-6020 Innsbruck
Tel: 0043 512 504-81386
Fax: 0043 512 504-25615
Michael.Steurer@i-med.ac.at