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Hairy-Cell Leukemia

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

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Hairy-Cell Leukemia

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

HCL (HCL) is a rare lymphoproliferative disorder and belongs to the indolent B-cell lymphomas. Approximately 95% of patients have classic HCL. It is clinically characterized by cytopenias, splenomegaly, general symptoms, and a slow course. Therapy with purine analogs achieves remission rates >95%. Other effective drugs include anti-CD20 monoclonal antibodies, interferon alpha, cytostatics, and targeted inhibitors of BRAF, MEK, and BTK. HCL is a chronic disease. With a good response to therapy, the majority of patients have an almost normal life expectancy. HCL variant is distinguished from classic HCL as a biologically distinct entity with a more aggressive clinical course and poorer response to standard therapy.

2 Basics

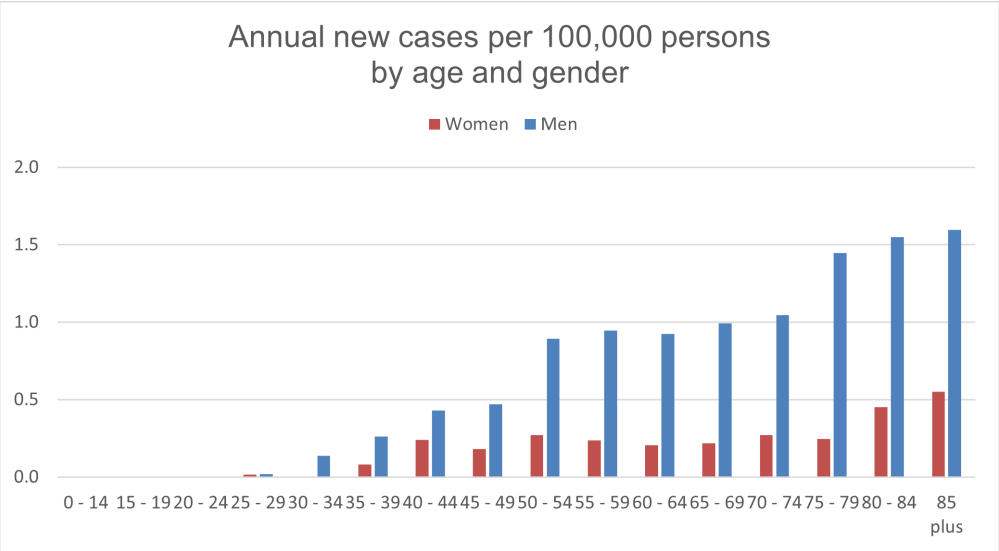
2.1 Definition and basic information

HCL is a malignant disease of B lymphocytes and is one of the indolent lymphomas. The leukemic cells are small to medium-sized and have an oval to kidney-shaped, centrally located nucleus without nucleoli. The cytoplasm shows the eponymous hair-like projections in blood and bone marrow smears [10], but these are not visible in bone marrow biopsies. HCL is primarily located in the bone marrow, spleen, and blood. Rarely, lymph nodes, liver, or skin are affected.

2.2 Epidemiology

HCL is rare with an incidence of about 0.3-0.4/100,000 persons (crude disease rate). In Germany, approximately 70 women and 220 men develop the disease annually. Incidence and distribution aore concordant with data from other countries [36]. The disease accounts for about 3% of lymphocytic leukemias in the current evaluation. The median age of onset in Germany was most recently between 62 (men) and 65 (women) years. First diagnoses before the age of 30 are very rare, men are affected significantly more often than women in all age groups, see Figure 1.

Figure 1: Annual new cases (Germany)

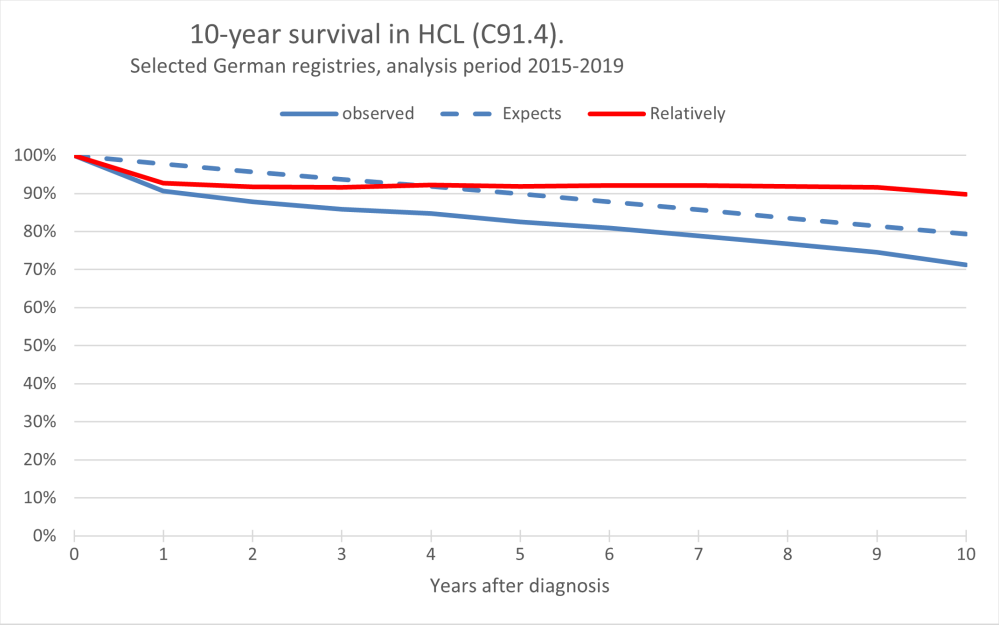


Legend:
Source: Center for Cancer Registry Data at the RKI, based on data from population-based cancer registries in Germany.

In the last decade, a trend towards a somewhat earlier age of onset of disease has been seen in the centers. This is presumably a consequence of the greater use of general screening measures by younger people, with performance of a blood count. As a result, cytopenias are diagnosed earlier, i.e. before the onset of clinical symptoms.

Survival is better than in CLL: 10 years after initial diagnosis, survival compared to the age-matched general population (relative survival) is 90% (CLL: 72%), see Figure 2.

Figure 2: -year survival rate Annual new cases (Germany)



Legend:
Source: Center for Cancer Registry Data at the RKI, based on data from population-based cancer registries in Germany.

A worsening of life expectancy is particularly evident in the first year after diagnosis, after which relative life expectancy is even above average. In other evaluations, too, patients with HCL have a life expectancy after therapy with purine analogs that corresponds approximately to the normal population [5, 25, 52].

2.3 Pathophysiology

The cellular origin and early pathogenesis of HCL are unclear. It is certain that HCL originates from mature B cells [24]. However, morphologically and phenotypically, HCL cells differ markedly from all previously known B cell populations. The clustered expression of somatically mutated immunoglobulin gene rearrangements [37] and class-switched immunoglobulin isotypes [48] in HCL are indicative of maturation of the cells of origin in germinal center reactions before or during early pathogenesis. A distinctive feature of HCL among all other B-cell malignancies is the simultaneous expression of multiple clonally related isotypes in approximately 40% of cases, sometimes even in single tumor cells [24]. Reciprocal chromosomal translocations are absent [8, 60]. This is strong evidence that the cell of origin of HCL develops only after completion of a germinal center reaction. This assumption is supported by comparative analyses of transcriptome and epigenetic profiles of HCL and normal germinal center-experienced memory B cells, which show high similarity to each other [1].

Moreover, HCL cells exhibit a similar pattern of cytokines, cytokine receptors, and adhesion molecules as activated splenic marginal zone B cells [71]. This explains the unique dissemination of HCL cells and their interaction with accessory cells and the matrix proteins of the bone marrow stroma [62].

Pathophysiologically, classic HCL and variants are distinct. Classic HCL is characterized by variable immunoglobulin heavy chain gene rearrangements (IGHV), activation of specific signal transduction pathways and the *BRAF* V600E mutation [67]. The latter is detectable in almost all patients with classic HCL. Rarely, other mutations in the BRAF gene are detected. *BRAF* mutation leads to activation of the RAS-RAF-MAPK signal transduction pathway. *BRAF*-mutated stem cells from HCL patients can induce HCL-like disease in immunodeficient mice [15]. Nevertheless, *BRAF* mutation alone is not sufficient for complete neoplastic HCL transformation, suggesting further genetic and/or epigenetic alterations. The second most common genetic aberrations in HCL are inactivating mutations of CDKN1B (approximately 16%). Furthermore, epigenetic machinery genes such as *KMT2C*, *ARID1A/ARID1B*, *EZH2*, and *KDM6A are* more frequently mutated. However, the functional context with *BRAF V600E* remains unclear [22].

BRAF wild type is present in <5% of patients with classic HCL. Molecularly, this subgroup is associated with the IGHV 4-34 genotype and an unmutated IGHV status [72], clinically with a more aggressive course and poorer response to therapy with purine analogs [24].

The HCL variant is biologically distinct. These leukemia cells have a *BRAF* wild type. They are commonly found to have the immunoglobulin heavy chain gene rearrangement IGHV4-34 and other genetic aberrations such as *MAP2K*, *KMT2C* or *TP53* mutations [22].

2.4 Risk factors

The cause of HCL is not clear. A hereditary burden is very rare, <20 families with 2 or more affected patients have been described worldwide. The genetic aberrations identified so far in these families can be attributed to different signal transduction pathways [54].

Exposure to insecticides, herbicides, organic solvents, and ionizing radiation is discussed as an exogenous risk factor [51, 64]. Workers in the agricultural sector have a higher risk of disease [49, 51].

3 Prevention and early detection

There is no evidence of effective interventions for prevention and early detection.

4 Clinical picture

4.1 Symptoms

Cytopenia and splenomegaly are characteristic of HCL. Cytopenia is due to progressive bone marrow insufficiency caused by the combination of leukemic infiltration, hematopoiesis-suppressing cytokines, reticulin fiber proliferation, and the sequelae of splenomegaly. Cytopenia may manifest as monocytopenia, bicytopenia, or tricytopenia. The pattern of cytopenia varies from individual to individual, but does not change in the majority of patients during the course of the disease.

The typical symptoms of the disease are

- general weakness and tiredness (fatigue)
- infections in neutropenia
- Paleness and reduced resilience in anemia
- Bleeding tendency in thrombocytopenia.

In about 70% of patients with HCL, pancytopenia is the leading symptom. A feeling of pressure in the left upper abdomen may be a symptom of splenomegaly. Patients with very pronounced splenomegaly have become less common in recent years, possibly due to earlier diagnosis in patients with incidentally diagnosed, moderate-grade, hematologic cytopenia.

Less common symptoms are hepatomegaly (20%), lymphadenopathy (<10%), autoimmune phenomena (vasculitis, polyarthritis, sarcoidosis, Sjögren's syndrome), skeletal manifestations (osteolysis, osteoporosis), skin involvement (infiltrates, erythema nodosum) and B symptoms. Infectious complications, including those with unusual pathogens, must be distinguished from the latter. The course of HCL is slow with an individually variable, often undulating course.

5 Diagnosis

5.2 Diagnostics

For examples of microscopic diagnostics, see eLearning Curriculum Hematology (eLCH), https://ehaematology.com/.

5.2.1 Initial diagnosis

The diagnostic algorithm is divided into basic and special tests, see Table 1. Despite the typical lymphocytopenia, hair cells are detectable in the peripheral blood of most patients [46], the relative proportion is usually below 10%, often below 1%. Standard in diagnostics is multiparametric immunophenotyping with at least 4 fluorescent dyes and a sensitivity of <1/1,000 cells.

Standard diagnostic procedure is bone marrow aspiration and biopsy, for characteristic morphology see chapter 2. 1. The detection of a (small) subpopulation of lymphoid cells in peripheral blood with the immunophenotype of hair cells is not sufficient for diagnosis. HCL is one of the hematologic diseases in which punctio sicca frequently occurs, in this case due to fiber formation in the bone marrow [74].

Molecular genetic testing for *BRAF* V600E mutation is recommended to confirm the diagnosis and to differentiate BRAF V600E from other indolent non-Hodgkin lymphomas and HCL. The detection of a *BRAF* V600E mutation is treatment-guiding for the option of using a BRAF inhibitor.

Table 1: Diagnostics for suspected HCL

	Method / Material	Focus
Base	Medical history	• duration of symptoms, previous blood counts • exposure to potential risk factors • familial predisposition
	Physical examination	• splenomegaly, lymphadenopathy
	Peripheral blood	• differential blood count, including reticulocytes, • automated and microscopic
	Serum	• ALAT, ASAT, AP, CRP, ferritin • LDH, vitamin B12, folic acid
	Sonography	• abdomen, determination of spleen size
Special	Peripheral blood	• flow cytometric immunophenotyping
	Bone marrow - aspirate	• panoptic staining • flow cytometric immunophenotyping (CD11c, CD19, CD20, CD22, CD25, CD103) • *BRAF* V600E
	Bone marrow - biopsy	• histology • 9mmunohistochemistry (CD20, CD11c, CD103, CD25, CD123, TBET, Annexin A1) • fiber staining

5.2.2 Course of disease

Basic and special examinations are also distinguished in the course of the disease, see Table 2. Intervals are shown in Chapter 8.

Table 2: Examinations during the course of the disease

	Material / Method	Focus
Base	Peripheral blood	differential blood count, automated
	Sonography	abdomen, determination of spleen size
Special	Peripheral blood	differential blood count, microscopic flow cytometric immunophenotyping soluble interleukin-2 receptor (sIL2R)

In the context of clinical trials, the determination of minimal residual disease (MRD) by immunophenotypic and/or molecular genetic methods is used. It allows earlier assessment of treatment response and may have prognostic relevance [9]. The methods are not yet internationally standardized [56].

5.3 Classification

Two forms of HCL are distinguished, the so-called classic HCL and the variant, see Table 3. The HCL variant (HCL-V) differs from classic HCL clinically as well as cytologically, immunologically and immunophenotypically [17, 27, 34, 47]. HCL-V is typically associated with leukocytosis ranging from 15,000 to over 400,000 /µl. Morphologically, these cells exhibit a central nucleus with dense chromatin and a prominent nucleolus, with an appearance resembling a mixture of hair cell and prolymphocyte. Immunophenotypically, the cells of HCL-V are CD25 negative, in contrast to classic HCL. Expression of CD103 may be variable. The *BRAF* V600E mutation is detectable in >95% of patients with classic HCL, not in the HCL variant [17, 67]. Patients with

the immunophenotype of classic HCL, *BRAF* V600E wild type and evidence of immunoglobulin gene rearrangement IGHV4-34 are a special form of HCL.

Table 3: Classification of HCL

	Classic hairy cell leukemia	**HCL variant**
Relative frequency (%)	95	5
Gender distribution	4-5 : 1 (M : W)	1-2 : 1 (M : W)
Age (median, years)	50 - 75	> 70
Lymphocytosis in peripheral blood (%)	≤ 10	≥ 90
Monocytes in peripheral blood	demeaned	normal
Hemoglobin	Anemia in 85 % of the patients	often normal
Thrombocytopenia	Thrombocytopenia in 80 % of the patients	often normal
	mature B cell (CD19+, CD20+, CD22+) CD11c+, CD103+, CD25+	mature B cell (CD19+, CD20+, CD22+) CD11c +/-, CD103 +/-, CD25 -
Immunohistochemistry	mature B cell CD72 (DBA. 44)+, Cyclin D1+. Annexin A1+	mature B cell CD72 (DBA. 44)+, Cyclin D1+. Annexin A1-
Genotype	*BRAF* V600E mutation	BRAF wild type

Legend:
[1] *according to CD classification - cluster of differentiation, determined in multiparametric flow cytometric immunophenotyping*

Another HCL variant has been described in Japan but is not included in this guideline.

5.4 Differential diagnosis

The differential diagnosis of cytopenia and splenomegaly is extensive. The more common conditions are summarized in Table 4.

Table 4: Differential diagnosis for suspected HCL

Differential diagnosis		Pancytopenia	Splenomegaly	slow progression
	Stage IV indolent non-Hodgkin's lymphoma:			
	• Splenic marginal zone lymphoma (with villous lymphocytes)	possible	frequent	frequent
	• others: follicular lymphoma, lymphocytic lymphoma, chronic lymphocytic leukemia (CLL), Waldenström's disease, etc.	possible	possible	frequent
Acute leukemia		possible	possible	rare
Myelodysplastic syndrome		frequent	rare	frequent
Primary / secondary myelofibrosis		possible	frequent	frequent
Aplastic anemia		frequent	Rare	frequent
Paroxysmal nocturnal hemoglobinuria (PNH)		possible	No	possible
Hemophagocytic lymphohistiocytosis (HLH)		frequent	frequent	rare
Hemolytic anemia / Evans syndrome		frequent	frequent	possible
Felty syndrome		rare	frequent	frequent
Vitamin B12 deficiency		possible	no	no
Folic acid deficiency		possible	no	frequent
Liver cirrhosis with portal hypertension		possible	frequent	frequent
Budd - Chiari - Syndrome		possible	frequent	Rare
Portal vein thrombosis		possible	frequent	possible
Gaucher's disease		possible	frequent	frequent

5.5 Prognostic factors

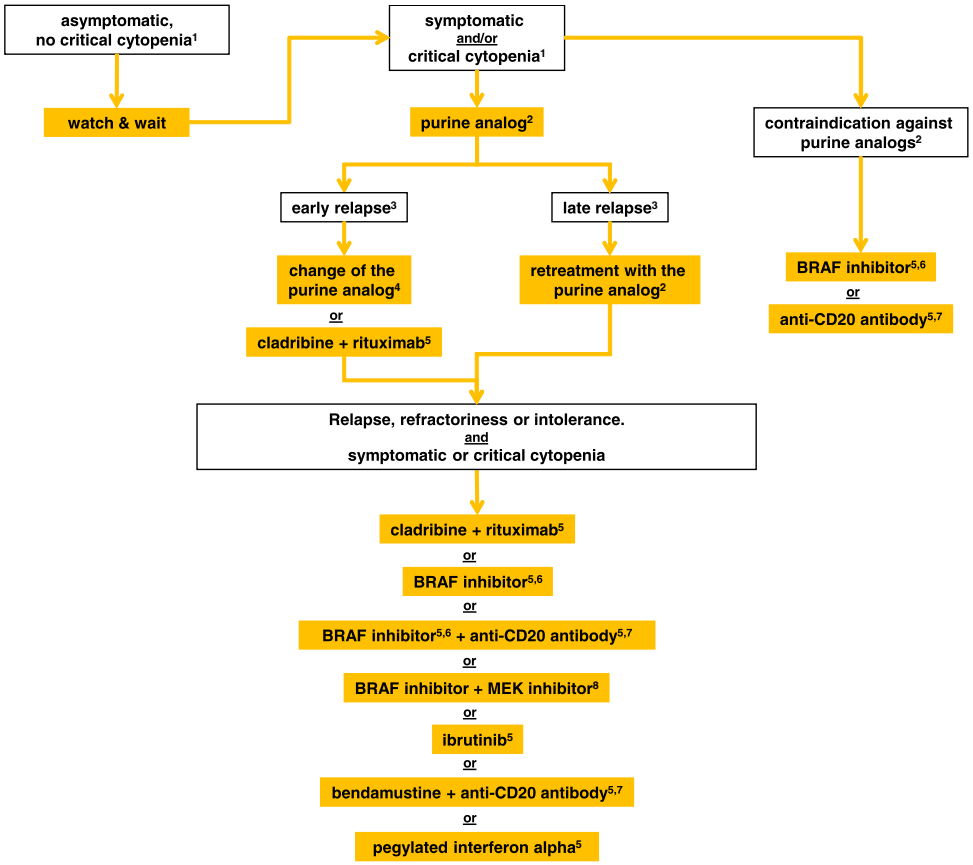
Prognosis has improved markedly since 1980 [12, 21, 53]. About 70% of patients with HCL have a normal life expectancy. The response to systemic therapy with purine analogs is crucial. Patients with complete hematologic remission have significantly longer progression-free survival than patients with partial hematologic remission [17, 27, 73].

6 Therapy

6.1 Therapy structure

The difference between classic HCL and variant is mainly in the response to therapy and prognosis. A therapy algorithm is shown in Figure 3 [17, 27, 50, 58].

Figure 3: Therapy – Algorithm



Legend:
curative therapy; therapy in non-curative intent;
[1] see chapter 6. 1. 1.
[2] Cladribine or pentostatin
[3] Recurrence requiring treatment within 3 years
[4] from cladribine to pentostatin or from pentostatin to cladribine, respectively.
[5] is not approved for this indication
[6] most experience is available for vemurafenib
[7] most experience is available for rituximab
[6] most experience is available for dabrafenib in combination with trametinib

6.1.1 Classic HCL

Classic hairy cell leukemia is a well-treatable disease. Initiation of therapy is indicated in symptomatic disease or in marked cytopenia. In asymptomatic patients, regular blood counts should be performed at least every three months after initial diagnosis to assess disease dynamics. After one year, the examination intervals can be extended if the findings are stable.

Criteria for the decision to start therapy are

- HCL-associated symptomatology (e.g., fatigue, B symptomatology, recurrent infections) and/or
- neutrophil granulocytes < 1,000/µl and/or
- platelets <100,000/µl and/or
- hemoglobin <11g/dl

In patients with severe symptoms, the initiation of therapy may be indicated, even if the laboratory values have not (yet) decreased below the threshold values. In the long, chronic course of HCL, laboratory values may fluctuate. In case of unexpected values, short-term controls are useful: "One value is no value".

Relative contraindications to initiation of therapy with purine analogs are uncontrolled infections. There is usually sufficient time for empiric or targeted antibiotic therapy in HCL patients until the infection is resolved or at least under control. It is not uncommon for marked neutropenia or thrombocytopenia to regress somewhat after successful antibiotic therapy, creating a better basis for the use of purine analogs. If possible, therapy with purine analogs should be started only after complete regression of the infection.

The time until starting therapy with purine analogs should be used to complete or update the vaccination status. This includes in particular the vaccinations against human herpes viruses (herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2)) and against SARS-CoV-2.

The goals of HCL therapy are symptomatic relief, hematologic remission, and normal life expectancy. Achieving complete hematologic remission is associated with longer progression-free survival, but overall survival is not affected. The impact of additional therapy to eradicate minimal residual disease on overall survival is uncertain [9, 42, 61]. The determination of minimal residual disease is not predictive for further therapy and is not a standard investigation.

6.1.1.1 First-line therapy

Standard treatment of HCL consists of purine analogs (PA). Both cladribine (2-chlorodeoxyadenosine, 2-CdA) and dexoycoformicin (pentostatin, DCF) are effective. A prospective randomized trial comparing the two agents has not yet been conducted. In Germany, 2-CdA has become more widely accepted; in Austria and Switzerland, only 2-CdA is approved as a purine analog in HCL.

For the relative contraindication of therapy with purine analogs in uncontrolled infections, we refer to Chapter 6. 1. 1.

6.1.1.1.1 Cladribine (2-chlorodeoxyadenosine, 2-CdA)

Patients with classic HCL have response rates of 95 - 98%, including complete remissions in over 75% of patients [review in 17, 27, 42, 45, 58, 70]. There are several options for the application of cladribine with comparable response rates [57, 58, 76]:

Recommended:

- Subcutaneous: daily for 5 days, dose 0.14 mg/kg body weight (bw) [4].

Alternative:

- intravenously over 2 hours: daily for 5 days, dose 0.12 mg/kg bw
- intravenously over 2 hours: weekly for 6 weeks, dose 0.12 mg/kg bw

The previously recommended continuous infusion over 24 hours is no longer recommended due to the increased risk of inflammation of the venous access and the greater burden on the patients..

The standard of care is one cycle of administration. Evaluation of remission status by bone marrow aspiration should not be performed until 4-6 months after completion of the cladribine cycle because the time to optimal hematologic remission is typically long in HCL [27]. If clinical response is inadequate in the evaluation after 4-6 months, a second course of cladribine may be considered after diagnostic reevaluation.

About 50% of patients relapse within 15 years. 20-30% of patients do not relapse in the long term.

In a randomized phase II study for first-line therapy, the concomitant administration of cladribine plus rituximab was evaluated against delayed rituximab administration after cladribine [14]. This showed an increase in the rate of patients without evidence of minimal residual disease (MRD) with concurrent cladribine/rituximab administration. It is unclear whether this effect is sustained, whether the rate of second therapies can be reduced, and whether there is an impact on overall survival - especially when compared with cladribine monotherapy.

6.1.1.1.2 Pentostatin (deoxycoformicin)

Pentostatin is a specific adenosine deaminase (ADA) inhibitor. The enzyme ADA is essential for the development of T- and B- lymphocytes, therefore inhibition of ADA has a lymphocytotoxic effect. Remission rates of > 90% are achieved by therapy with pentostatin, complete hematologic remissions in > 75% of patients [review in 17, 27, 42, 45, 58, 70].

It is administered intravenously at two- to three-weekly intervals for at least 3 months (6-9 cycles in total). In a randomized study, pentostatin was superior to interferon alpha [26].

Although all purine analogs have a similar spectrum of action, clinical studies suggest a relatively specific lymphocytotoxicity of pentostatin with little myelosuppression [32, 33].

6.1.1.1.3 Alternatives for contraindications to purine analogs

The sometimes prolonged myelosuppression associated with the administration of purine analogs may lead to increased morbidity and mortality in patients with unmanaged infections or at high risk for the severe course of infections. This discussion was also held at the onset of the COVID-19 pandemic [28].

A short-term effective option in patients with infectious complications is the use of a BRAF inhibitor. Most experience is available for vemurafenib [7]. Vemurafenib resulted in a hematologic remission rate of >95% in pretreated patients see Chapter 6. 1. 1. 2. 4. In Germany, vemurafenib was used during the COVID-19 pandemic in first-line therapy of patients with active infections and/or high risk for severe course of COVID-19 at a dose of 2 x 240 mg/day for 3 months. 8 of 12 patients achieved complete hematologic remission [personal communication]. Neutro- and thrombocytopenia regressed within 2 weeks. The median duration of remission was 12-18 months. Therapy with vemurafenib can bridge the time to therapy with purine analogs (bridging). Vemurafenib is not approved in this indication.

Other effective drugs are anti-CD20 antibodies. Most experience is available with rituximab [29, 66]. The use of rituximab can bridge the time to therapy with purine analogs. The vaccine response is suppressed by anti-CD20 antibodies, thus the risk for a severe course of COVID-19 is increased in these patients. Anti-CD20 antibodies are not approved for this indication.

Another option was interferon alpha. However, the manufacturers have withdrawn the approved preparations (Intron A®, Roferon®) from the market. Data on the early use of pegylated interferon alpha are limited to case reports [25].

6.1.1.2 Recurrence / refractoriness

6.1.1.2.1 Purine analogs

In relapse, re-treatment with purine analogs is possible, especially if the previous remission has been long-lasting (> 3 years). The rates of complete remission are 40-70% in second-line therapy and 20-50% in third-line therapy. With identical therapy, the duration of remission tends to be shorter after each cycle.

Patients who relapse or become resistant after initial pentostatin therapy may respond well to cladribine. Patients who relapse or become resistant after initial pentostatin therapy may also respond well to cladribine. The same is true vice versa for patients treated with pentostatin in the first line who are switched to cladribine in relapse or refractoriness.

For the combination of purine analogs with rituximab, please refer to chapter 6. 1. 1. 2. 3.

Classic HCL has poor sensitivity to cytostatic drugs, commonly used for other indolent non-Hodgkin lymphomas. Bendamustine has been successfully used in relapse of classic HCL [11, 42] and in HCL-V, see Chapter 6. 1. 2.

6.1.1.2.2 Anti-CD20 antibodies

HCL has the immunophenotype of mature B cells and in particular a very high expression of CD20. Most clinical experience on the use of anti-CD20 antibodies in therapy is available with rituximab. In phase II studies of monotherapy, remission rates of 50-80% have been achieved, with complete hematologic remissions in 20-50% of patients [review in 17, 27, 42, 45, 58, 70]. However, most remissions are not long-lasting. Rituximab is given intravenously every 1-2 weeks with 4-8 applications.

Rituximab may be an option in patients with contraindications to purine analogs, see Figure 3.

In single observations, other anti-CD20 antibodies such as obinutuzumab have also been successfully used in patients with refractory HCL [6].

6.1.1.2.3 Chemoimmunotherapy

Combined chemoimmunotherapy of purine analogs and rituximab is more effective than chemotherapy in other indolent B cell lymphomas in terms of remission rates, progression-free survival, and in some entities, overall survival. In classic HCL, the combination is used in two different forms [13, 42, 55]:

- Cladribine, combined with rituximab (start with chemotherapy, then weekly for 8 weeks). In a randomized phase II study with 68 patients, an initial cladribine-rituximab combination was compared with delayed rituximab administration after ≥ 6 months in the presence of minimal residual disease (MRD) [14]. The rate of complete remissions in the 34 patients in the combination arm was 100%, and all patients were also MRD-free in peripheral blood. The combination was associated with more severe neutropenia and thrombocytopenia.
- Cladribine followed by rituximab (start ~1 month after chemotherapy, weekly for 8 weeks).

In the largest study with 73 patients (59 initial diagnosis, 14 relapse), 100% achieved complete hematologic remission. No minimal residual disease was detectable in 94%.

- Pentostatin combined with rituximab
  The combination of pentostatin with rituximab also results in high remission rates, but the data base is narrower [17].

In the treatment of patients with early relapse, the combination of purine analogs with rituximab is a highly effective option. Rituximab can be given concurrently or at short intervals (1-3 months) after cladribine. In the randomized phase II study, the rate of patients without evidence of MRD was higher with concurrent than with delayed administration [14].

6.1.1.2.4 BRAF inhibitors

The detection of the *BRAF* V600E mutation in almost all patients with classic HCL offers a new target for molecular targeted therapy [19, 67]. In the two largest phase II trials of vemurafenib in patients in relapse after purine analogs or in refractoriness, 96-100% achieved a hematologic remission [19, 67]. Rates of complete remission were 35-42%, and median time to relapse was 12-19 months [20, 30, 68]. In patients with classic HCL, a dosage of 480 mg/day seems sufficient (2 x 240 mg); a higher dose may not improve outcome [20]. The optimal dosage is currently unclear.

The duration of therapy is on average 3 months. An advantage of BRAF inhibitors is the rapid response to therapy without transient worsening of HCL-associated cytopenia. A decrease in critical cytopenia may occur after only a few days or weeks.

Upon resumption of therapy, patients respond again even at low doses [30]. The optimal therapeutic regimen for vemurafenib in monotherapy is open. In patients with only short-term remission after time-limited vemurafenib therapy without the subsequent option of salvage therapy with purine analogs, e.g. due to repeated infectious complications, continuous administration of BRAF inhibitors until progression may also be an appropriate therapeutic option if well tolerated [44].

Vemurafenib is administered orally. It is usually well tolerated. Main side effects are hyperproliferative skin changes including squamous cell carcinoma and keratoacanthoma, as well as allergic skin reactions. Compared to the use of vemurafenib in melanoma (1920 mg/day), hyperproliferative skin changes seem to be less frequent in HCL patients, but allergic skin reactions are frequent.

An alternative to the use of vemurafenib is dabrafenib, at a dosage of 100 mg / day (2 x 50 mg). In melanoma, vemurafenib and dabrafenib are equieffective.

The combination of BRAF inhibitors with rítuximab has also been investigated in clinical trials. In the largest study in intensively pretreated patients, 26 of 30 patients (87%) achieved complete remission, and 65% had no detectable minimal residual disease (MRD). Thrombocytopenia regressed after a median of 2 weeks, neutropenia after 4 weeks. Progression-free survival at 37 months was 78% [69].

Another option to overcome BRAF inhibitor resistance is the combination with MEK inhibitors [41, 43]. In an open-label phase II study in 55 *BRAF* V600E-positive patients with at least 2 prior therapies, the combination of dabrafenib plus trametinib achieved a remission rate of 89%. 65.5% of patients achieved remission without evidence of MRD. The progression-free survival rate at 24 months was 94.4%.

A prerequisite for the use of BRAF inhibitors is the detection of the *BRAF* V600E mutation. The analysis can be performed in peripheral blood if sufficient HCL cells are detectable. If the result is negative (*BRAF* wild type), confirmation on bone marrow preparation is required. Because of the increased risk for secondary skin malignancies, close dermatologic monitoring is required.

6.1.1.2.5 Interferon alpha (IFN alpha)

Interferon alpha was the common and only available therapy in the 1980s, and provided the first successful drug treatment for HCL. Response rates were 75-80%, with <20% of patients achieving complete remission [2, 3, 17, 27, 42, 45, 58, 70]. Interferon is applied subcutaneously. The effect of interferon occurs slowly, sometimes only after a transient deterioration of blood count parameters in the first 2-3 months. In a randomized trial, pentostatin was shown to be superior to IFN alpha in remission rates and time to relapse. Regarding overall survival, there are no differences [26]. Characteristic side effects are fatigue, flu symptoms, depression, and enhancement of autoimmune phenomena.

Due to market withdrawals of the interferon alpha preparations approved for HCL therapy (Intron A®, Roferon®), no preparation is currently available. Patients who had been treated with interferon alpha for many years as maintenance therapy had to discontinue this treatment. Thus far, there has been no increased relapse rate in patients in complete hematological remission. In case of relapse, switching to one of the other therapeutic options discussed in this chapter 6. 1. 1. 2. is recommended.

A further development of interferon alpha is its application in pegylated form. Due to its longer half-life, pegylated interferon allows longer application intervals. Approvals for the EU exist only for the treatment of chronic hepatitis B and C. The only interferon alpha approved for the treatment of hematologic hepatitis C is pegylated interferon alpha. The only drug approved for the treatment of a hematologic disorder is ropeginterferon alpha-2b (Besremi®), indicated for the treatment of adult patients with polycythaemia vera without symptomatic splenomegaly. Experience in HCL is limited to anecdotal reports.

6.1.1.2.6 Moxetumumab Pasudotox

Drug immunoconjugates consist of monoclonal antibodies and toxins, and are now approved for use in various hematologic diseases and in solid tumors. In HCL, the immunoconjugate moxetumomab pasudotox was tested. It consists of an anti-CD22 antibody and a fragment of Pseudomonas exotoxin. In 80 patients with relapsed/refractory HCL (77 classic HCL, 3 variant HCL), 80% achieved hematologic remission, 41% achieved complete hematologic remission, and 36% achieved durable complete remission for >180 days [39, 40]. Most common side effects were nausea, edema, headache, and fever. Most common side effects in CTCAE grade 3/4 were lymphocytopenia (20%), hypophosphatemia (10%), anemia (10%), hypertension (7.5%), thrombocytopenia (6%), febrile neutropenia (5%), and hemolytic uremic syndrome (5%). These data led to FDA approval in September 2018 and for the EU in spring 2021. In August, the pharmaceutical company withdrew approval for commercial reasons, making moxetumomab pasudotox unavailable in the EU.

6.1.1.2.7 bruton tyrosine kinase inhibitors (BTKi)

Ibrutinib is a highly effective therapeutic option for chronic lymphocytic leukemia, but also for other indolent B-NHL such as Waldenström's disease. Ibrutinib is an inhibitor of Bruton's tyro-

sine kinase (BTK). This kinase plays a central role in B lymphocyte development, differentiation, signal transduction and survival. BTK is highly expressed in HCL. In the first publication of an ongoing phase II study started in 2013, 37 patients with relapsed HCL (28 classic HCL, 9 variant HCL) have been evaluated to date [35, 59]. After 32 weeks, 24% of patients achieved remission, and after 48 weeks, 36% of patients achieved remission. The progression-free survival rate at 3 years was 73%, and the overall survival rate was 85%. Most common side effects were diarrhea, fatigue, myalgia, and nausea. Atrial fibrillation was documented in 16% of patients, and sinus bradycardia in another 16%. Published data on the use of other BTK inhibitors such as acalabrutinib or zanubrutinib in HCL are not yet available.

6.1.1.2.8 Splenectomy

Splenectomy was the first effective therapy for HCL and resulted in hematologic remissions in up to 70% of patients [74, 75]. However, the recurrence rate is >90%. In patients with classic HCL, splenectomy is no longer part of the standard therapy, but it may be considered in individual cases of refractory patients and symptomatic splenomegaly. Prophylactic vaccinations are recommended prior to splenectomy.

6.1.1.3 Supportive measures for purine analogs

Both cladribine and pentostatin are eliminated renally, thus special attention should be paid to monitoring renal function. Appropriate dose adaptation can avoid overdose and any resulting protracted cytopenia.

Patients with HCL have an increased risk of infections at initial manifestation and after therapy with purine analogs. 50-60% of patients develop neutropenia $<0.5x10^9$/L after cladribine therapy [18]. Myelosuppression is less common after pentostatin therapy [32, 33]. The risk of therapy-associated infections is approximately 20-30% [38, 63].

Routinely, continuous Pneumocystis jirovecii pneumonia prophylaxis (PjP) with administration of cotrimoxazole / trimethoprim (2-3x/week) is no longer recommended because this infectious complication occurs very rarely in HCL patients. On the other hand, since HCL patients often experience distressing side effects, especially cutaneous, the indication should be restricted. One decision parameter for the use of PjP prophylaxis can be a drop in T-helper cells (CD4+) to <200/µl.

Due to the increased risk of reactivation of herpes simplex virus (HSV) infections, prophylaxis e.g. with aciclovir (3x200 mg/day) is recommended. In patients with HCL, vaccination with the inactivated vaccine Shingrix® is recommended.

Depending on the individual risk profile, additional antibiotic and/or antifungal prophylaxis may be useful.

The use of G-CSF did not reduce the rate of febrile neutropenia or shorten the duration of neutrophil granulocyte nadir in a retrospective study [65].

6.1.2 HCL variant (HCL-V)

The HCL variant is biologically and clinically distinct from classic HCL, see Table 3. In contrast to classic HCL, which takes a chronic indolent course, HCL-V presents aggressively with shorter survival and poorer response to conventional therapies [review in 17, 27, 42, 45, 58, 70]. Response rates to purine analogs are approximately 50%. They are significantly increased by

combination therapies such as rituximab/purine analogs, see chapter 6. 1. 1. 3. or rituximab/bendamustine [11].

Other effective therapeutic options are BTK inhibitors. However, the number of patients studied is small. Splenectomy is a therapeutic option in patients, who do not respond to purine analogs or suffer a short-term relapse.

In relapsed/refractory patients with limited therapeutic options, targeted therapy based on molecular genetic testing, e.g., for the use of a MEK inhibitor when a *MAP2K1* mutation is detected, may also be considered.

6.3 Special situations

6.3.1 COVID-19

Early in the pandemic, there have been several reports of severe, including fatal, courses of COVID-19 in patients with active HCL. Patients with prolonged neutropenia (<1,000 neutrophils/µl) and/or lymphocytopenia (CD4 cells <200/µl) are at increased risk for the severe course of COVID-19 infection, see Onkopedia Coronavirus Infection (COVID-19) in Patients with Hematological Diseases and Cancer. No data are known for an increased risk in patients in stable, hematologic remission.

All patients are advised to follow the regulatory orders for protection against COVID-19 infection. There are no contraindications to vaccination in HCL patients. However, especially under or in the first months after anti-CD20 antibody therapy, there is a risk that adequate vaccine protection will not be secured after a properly administered anti-SARS-CoV-2 vaccination.

In immunosuppressed HCL patients the following therapeutic options are available:

- Pre-exposure prophylaxis (in immunocompromised patients without response to vaccination).
    - Tixagevimab/Cilgavimab (AZD7442, Evusheld®)
- Therapy in symptomatic patients to prevent severe progression.
    - Sotrovimab (Xevudy®)
    - Tixagevimab/Cilgavimab (AZD7442, Evusheld®)
    - Molnupiravir (Lagevrio®
    - Nirmatrelvir/ritonavir (Paxlovid®)
    - Remdesivir (Veklury®)

In the case of HCL, too, the fear of infection with SARS-CoV2 may not lead to inadequate treatment of the underlying malignant disease. In case of indication for initiation of systemic therapy, see chapter 6. 1. 1, therapy should start at the earliest possible time. An alternative to the standard long-term immunosuppressive therapy with purine analogs is the temporary use of low-dose BRAF inhibitors (off-label use).

7 Rehabilitation

The majority of affected patients are in working life, have a life expectancy of decades ahead of them and face the challenge of integrating this chronic disease into their lives. Important support is provided through an intact personal environment and reliable, serious information. This support also includes the psychosocial area.

Psychooncology deals with the experience and behavior as well as the social resources of patients in connection with their cancer disease, its treatment and related problems. It includes not only those directly affected by the disease, but also relatives and the personal environment. Professional discussions with psychooncologists make it easier to come to terms with the shock of diagnosis and release the energy needed to actively deal with the disease.

Patients should be informed at an early stage about the possibilities of outpatient and inpatient rehabilitation measures as well as other claims arising from social law. With regard to the rehabilitation clinic, the patient's wishes should be taken into account (§9 SGB IX). Nevertheless, a recommendation for a clinic with an oncological focus should be made in order to ensure optimal rehabilitation success.

Another challenge is the social and financial burdens of HCL. Restructuring of the workplace, hardship regulations, tax relief, etc. can help effectively. HCL patients are entitled to a severely disabled person's card. The degree of disability is based on regulations for chronic lymphocytic leukemia. Particularly relevant in determining the degree of disability are the effects of the diseases and the current need for therapy.

8 Follow-up and aftercare

8.1 Follow-up

HCL is a chronic disease. Late relapses are possible. There is no prospectively evaluated control program. A risk-adapted approach is recommended: In the first 6 months after achieving optimal response, blood count checks every 4 weeks are reasonable, abdominal sonography to check spleen size every 3 months. In case of stable hematologic remission, the examination intervals for blood counts can be extended to 3 months or for sonography to 6 months or more. Blood count changes again suggest shorter follow-up intervals. A suitable complementary parameter is the determination of soluble interleukin-2 receptor in peripheral blood. Bone marrow biopsies are usually not required.

8.2 Aftercare

There is evidence that patients with HCL have an increased risk of second malignancies. The published data from long-term observations diverge. A significantly increased rate of hematologic neoplasms has been described. The pattern of secondary solid tumors is not substantially different from malignancies occurring in men and women aged >60 years [4, 18, 23, 31, 77]. It is also controversial whether there is an association with purine analog therapy. There is an increased risk of skin tumors with BRAF inhibitor therapy.

Patients with HCL should participate in the recognized measures of prevention and early detection of cancer offered by the health insurances.

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14 Links

https://www.haarzell-leukaemie.de/

Patients information: https://haarzell-leukaemie.de/pdf/patientenbroschuere_2019

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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.