



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hairy Cell Leukemia

Version 1.2025 — September 26, 2024

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Trials should be designed to maximize inclusiveness and broad representative enrollment.**

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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Hairy Cell Leukemia

Updates in Version 1.2025 of the NCCN Guidelines for Hairy Cell Leukemia from Version 2.2024 include:

HCL-2

- Response to therapy
 - ▶ Complete response revised as "Full hematologic recovery consistent with complete response."
 - ▶ <Complete response revised as "Incomplete hematologic recovery."
- After incomplete hematologic recovery, added: Re-evaluate for indications for treatment
- After Relapse at <2 years revised: Relapsed/Refractory Therapy (HCL-A) -~~Less than complete response~~ *Incomplete hematologic recovery with indications for treatment present after initial treatment therapy.*

HCL-A 1 of 3

- Initial Therapy
 - ▶ Useful in Certain Circumstances revised qualifier: consider for ~~patient who are unable to tolerate~~ *patients who are not candidates* for purine analogs including ~~patients who are frail~~ *patients* and those with active infection
- Relapsed/Refractory Therapy
 - ▶ Revised qualifier: ~~Less than complete response~~ *Incomplete hematologic recovery with indications for treatment present after initial treatment therapy* OR Relapse <2 years)
 - ▶ Relapse ≥2 years, Other recommended added: Vemurafenib ± rituximab (consider for patients who are not candidates for purine analogs including patients who are frail and those with active infection)

HCL-A 2 of 3

- Footnote i revised: Peginterferon alfa-2a ~~is the only interferon available for clinical use in the United States and~~ it may be substituted for other interferon preparations.

HCL-C

- Anti-infective Prophylaxis
 - ▶ 1st bullet added: For patients who have received lymphodepleting treatment or are suspected of being immunosuppressed, monitor CD4 T-cell counts for need for prophylaxis.



DIAGNOSIS^a

ESSENTIAL:

- Bone marrow biopsy ± aspirate:
 - Presence of characteristic hairy cells upon morphologic examination of peripheral blood or bone marrow and characteristic infiltrate with increased reticulin in bone marrow biopsy samples. Dry tap is frequent.
- Adequate immunophenotyping is essential for establishing the diagnosis and for distinguishing between classical hairy cell leukemia (cHCL) and hairy cell variant (HCLv; ICC)/splenic B-cell lymphoma/leukemia with prominent nucleoli (SBLPN; WHO5)^{b,c,d}
 - Immunohistochemistry (IHC) or flow cytometry for: CD19, CD20, CD5, CD10, CD11c, CD22, CD25, CD103, CD123, cyclin D1, and CD200

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: *IGHV4-34* rearrangement^e
- IHC or molecular analysis to detect *BRAF* V600E mutation for cases that do not have cHCL immunophenotype^e

WORKUP

ESSENTIAL:

- History and physical exam with attention to node-bearing areas and the measurement of size of liver and spleen
 - Presence of enlarged spleen and/or liver; presence of peripheral lymphadenopathy (uncommon)
- Performance status
- Peripheral blood smear examination
- Complete blood count (CBC) with differential
- Comprehensive metabolic panel with particular attention to renal function
- Lactate dehydrogenase (LDH)
- Bone marrow biopsy ± aspirate
- Hepatitis B^f and C testing if treatment contemplated

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- CT of chest/abdomen/pelvis with contrast of diagnostic quality
- Pregnancy testing in patients of childbearing age (if systemic therapy planned)
- Discussion of fertility preservation^g

Initial Treatment
([HCL-2](#))

^a This guideline applies to histologically confirmed cHCL, not HCLv (ICC)/SBLPN (WHO5).

^b Typical immunophenotype for cHCL: CD5-, CD10-, CD11c+, CD20+ (bright), CD22+, CD25+, CD103+, CD123+, cyclin D1+, annexin A1+, and CD200+ (bright). Monocytopenia is characteristic.

^c HCLv (ICC)/SBLPN (WHO5) is characteristically CD25-, CD123-, annexin A1-, and negative for *BRAF* V600E mutations. This helps to distinguish HCLv (ICC)/SBLPN (WHO5) form from cHCL.

^d See [Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms in the NCCN Guidelines for B-Cell Lymphomas](#).

^e Ten percent to 20% of B-cell lymphoproliferative neoplasms with a cHCL phenotype possess *IGHV4-34* rearrangements and typically lack *BRAF* V600E mutations. These diseases behave more like HCLv (ICC)/SBLPN (WHO5) in that they do not respond well to purine analog therapy and generally have a poorer prognosis. There is evidence that HCLv (ICC)/SBLPN (WHO5) and *IGHV4-34*-mutant HCL often show mutations in *MAP2K1*.

^f Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). See [Treatment and Viral Reactivation in the NCCN Guidelines for CLL/SLL](#). Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

^g Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

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INDICATIONS FOR TREATMENT^h

Evaluate for indications for treatment:

- Systemic symptoms
 - Unexplained weight loss (>10% within prior 6 months)
 - Excessive fatigue
- Recurrent infection
- Hemoglobin <11 g/dL
- Platelets <100,000/mcL
- Absolute neutrophil count (ANC) <1000/mcL
- Symptomatic organomegaly
- Progressive lymphocytosis or lymphadenopathy

No indication

INITIAL TREATMENTⁱ

Observe

Indication present

Initial Therapy [\(HCL-A\)](#)

RESPONSE TO THERAPY

Full hematologic recovery consistent with complete response^j

Observe until indication for treatment

Incomplete hematologic recovery^j

Re-evaluate for indications for treatment

RELAPSED/REFRACTORY THERAPYⁱ

Relapse at ≥2 years^h

Relapsed/Refractory Therapy [\(HCL-A\)](#) - Relapse ≥2 years

Relapse at <2 years^h

Relapsed/Refractory Therapy [\(HCL-A\)](#) - Incomplete hematologic recovery with indications for treatment present after initial therapy OR Relapse <2 years

Progression^j

Progressive Disease After Relapsed/Refractory Therapy [\(HCL-A\)](#)

^h Grever MR, et al. Blood 2017;129:553-560.

ⁱ [Supportive Care for Patients with HCL \(HCL-C\)](#).

^j [HCL Response Criteria \(HCL-B\)](#).

Note: All recommendations are category 2A unless otherwise indicated.



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SUGGESTED TREATMENT REGIMENS^{a,b}

INITIAL THERAPY ^{c,d,e,f}	
Preferred Regimens	Useful in Certain Circumstances (consider for patients who are not candidates for purine analogs including patients who are frail and those with active infection)
<ul style="list-style-type: none"> • Purine analogs <ul style="list-style-type: none"> ▶ Cladribine ± rituximab ▶ Pentostatin 	<ul style="list-style-type: none"> • Vemurafenib[*] ± anti-CD20 monoclonal antibody (mAb)^g

RELAPSED/REFRACTORY THERAPY ^{c,e,f}			
	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Incomplete hematologic recovery with indications for treatment present after initial therapy OR Relapse <2 years	<ul style="list-style-type: none"> • Clinical trial • Dabrafenib[*] + trametinib (if not previously treated with BRAF inhibitor) • Vemurafenib^{h,*} ± rituximab (if not previously given) 	<ul style="list-style-type: none"> • Peginterferon-alfa 2aⁱ • Alternative purine analog ± rituximab 	<ul style="list-style-type: none"> • Rituximab, if unable to receive purine analog
Relapse ≥2 years	<ul style="list-style-type: none"> • Retreatment with initial purine analog + rituximab • Alternative purine analog + rituximab 	<ul style="list-style-type: none"> • Vemurafenib^{h,*} ± rituximab (consider for patients who are not candidates for purine analogs including patients who are frail and those with active infection) 	<ul style="list-style-type: none"> • Rituximab, if unable to receive purine analog

PROGRESSIVE DISEASE AFTER RELAPSED/REFRACTORY THERAPY ^{e,f}		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • Clinical trial • Dabrafenib[*] + trametinib (if not previously treated with BRAF inhibitor) • Vemurafenib[*] ± rituximab 	<ul style="list-style-type: none"> • Ibrutinib • Zanubrutinib 	(for patients with disease resistant to BRAF inhibitor therapy): <ul style="list-style-type: none"> • Venetoclax ± rituximab

* BRAF inhibitor

Footnotes on
[HCL-A 2 of 3](#)
 References on
[HCL-A 3 of 3](#)

Note: All recommendations are category 2A unless otherwise indicated.



SUGGESTED TREATMENT REGIMENS

FOOTNOTES

- ^a Treatment recommendations apply to histologically confirmed cHCL, not HCLv (ICC)/SBLPN (WHO5). See [Suggested Treatment Regimen References \(HCL-A 3 of 3\)](#).
- ^b Please refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.
- ^c Standard-dose purine analogs should not be administered to patients with active life-threatening or chronic infection. Treat active infection prior to initiating treatment with standard-dose purine analogs. If it is not possible to control infection, consider initiating treatment with low-dose pentostatin before using standard-dose purine analogs to secure a durable response.
- ^d Cladribine and pentostatin have not been compared head-to-head in clinical trials, but appear to show comparable therapeutic activity.
- ^e Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route. An FDA-approved biosimilar is an appropriate substitute for rituximab.
- ^f [Supportive Care for Patients with HCL \(HCL-C\)](#).
- ^g Anti-CD20 mAbs include: rituximab or obinutuzumab.
- ^h Studied for primary refractory disease and early relapse (1–2 y) after first course of purine analogue.
- ⁱ Peginterferon alfa-2a may be substituted for other interferon preparations.

Note: All recommendations are category 2A unless otherwise indicated.



REFERENCES

Purine analog monotherapy

- Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. *Blood* 2000;96:2981-2986.
- Goodman GR, Burian C, Koziol JA, Saven A. Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. *J Clin Oncol* 2003;21:891-896.
- Zinzani PL, Tani M, Marchi E, et al. Long-term follow-up of front-line treatment of hairy cell leukemia with 2-chlorodeoxyadenosine. *Haematologica* 2004;89:309-313.
- Chadha P, Rademaker AW, Mendiratta P, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience. *Blood* 2005;106:241-246.
- Robak T, Jamrozak K, Gora-Tybor J, et al. Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial. *Blood* 2007;109:3672-3675.
- Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *Br J Haematol* 2009;145:733-740.
- Zenhausen R, Schmitz SF, Solenthaler M, et al. Randomized trial of daily versus weekly administration of 2-chlorodeoxyadenosine in patients with hairy cell leukemia: a multicenter phase III trial (SAKK 32/98). *Leuk Lymphoma* 2009;50:1501-1511.
- Dearden CE, Else M, Catovsky D. Long-term results for pentostatin and cladribine treatment of hairy cell leukemia. *Leuk Lymphoma* 2011;52 Suppl 2:21-24.
- Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study. *J Clin Oncol* 1995;13:974-982.
- Tallman MS, Hakimian D, Variakojis D, et al. A single cycle of 2-chlorodeoxyadenosine results in complete remission in the majority of patients with hairy cell leukemia. *Blood* 1992;80:2203-2209.
- Kraut EH, Grever MR, Bouroncle BA. Long-term follow-up of patients with hairy cell leukemia after treatment with 2'-deoxycoformycin. *Blood* 1994;84:4061-4063.

Purine analogs with rituximab

- Else M, Osuji N, Forconi F, et al. The role of rituximab in combination with pentostatin or cladribine for the treatment of recurrent/refractory hairy cell leukemia. *Cancer* 2007;110:2240-2247.
- Else M, Dearden CE, Matutes E, et al. Rituximab with pentostatin or cladribine: an effective combination treatment for hairy cell leukemia after disease recurrence. *Leuk Lymphoma* 2011;52 Suppl 2:75-78.
- Chihara D, Kantarjian H, O'Brien S, et al. Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: update of a phase II trial. *Br J Haematol* 2016;174:760-766.
- Chihara D, Arons E, Stetler-Stevenson M, et al. Randomized phase II study of first-line cladribine with concurrent or delayed rituximab in patients with hairy cell leukemia. *J Clin Oncol* 2020;38:1527-1538.

Dabrafenib + trametinib

- Kreitman R, Moreau P, Ravandi F, et al. Dabrafenib plus trametinib in patients with relapsed/refractory BRAF V600E mutation-positive hairy cell leukemia. *Blood* 2023;141:996-1006.

Ibrutinib

- Rogers KA, Andritsos LA, Wei L, et al. Phase 2 study of ibrutinib in classic and variant hairy cell leukemia. *Blood* 2021;137:3473-3483.

Rituximab

- Lauria F, Lenoci M, Annino L, et al. Efficacy of anti-CD20 monoclonal antibodies (Mabthera) in patients with progressed hairy cell leukemia. *Haematologica* 2001;86:1046-1050.
- Nieva J, Bethel K, Saven A. Phase 2 study of rituximab in the treatment of cladribine-failed patients with hairy cell leukemia. *Blood* 2003;102:810-813.
- Thomas DA, O'Brien S, Bueso-Ramos C, et al. Rituximab in relapsed or refractory hairy cell leukemia. *Blood* 2003;102:3906-3911.
- Zenhausen R, Simcock M, Gratwohl A, et al. Rituximab in patients with hairy cell leukemia relapsing after treatment with 2-chlorodeoxyadenosine (SAKK 31/98). *Haematologica* 2008;93:1426-1428.

Vemurafenib ± obinutuzumab or rituximab

- Park JH, Winer ES, Huntington SF, et al. First line chemo-free therapy with the BRAF inhibitor vemurafenib combined with obinutuzumab is effective in patients with HCL [abstract]. *Blood* 2021;138:Abstract 43.
- Dietrich S, Pircher A, Endris V, et al. BRAF inhibition in hairy cell leukemia with low-dose vemurafenib. *Blood* 2016;127:2847-2855.
- Handa S, Lee JO, Derkach A, et al. Long-term outcomes in patients with relapsed or refractory hairy cell leukemia treated with vemurafenib monotherapy. *Blood* 2022;140:2663-2671.
- Tiacci E, Park JH, De Carolis L, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. *N Engl J Med* 2015;373:1733-1747.
- Troussard X, Montané L, Tiab M, et al. Vemurafenib in advanced patients with hairy cell leukemia (HCL): Results of the Acsé phase II trial [abstract]. *Blood* 2017;130:Abstract 156.
- Tiacci E, Carolis LD, Simonetti E, et al. Vemurafenib plus rituximab in refractory or relapsed hairy-cell leukemia. *N Engl J Med* 2021;384:1810-1823.

Venetoclax ± rituximab

- Tiacci E, De Carolis L, Santi A, Falini B. Venetoclax in relapsed or refractory hairy-cell leukemia. *N Engl J Med* 2023;388:952-954.

Zanubrutinib

- Tam C, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood Adv* 2022;64:1296-1308.
- Tam C, Trotman J, Opat S, et al. Zanubrutinib for the treatment of relapsed/refractory hairy cell leukemia. *Blood Adv* 2023;7:2884-2887.

Note: All recommendations are category 2A unless otherwise indicated.



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HCL RESPONSE CRITERIA^a

Timing of response assessment	The bone marrow examination for evaluating response in patients treated with cladribine should not be done before 4 months after therapy. In those patients being treated with pentostatin, the bone marrow can be evaluated after the blood counts have nearly normalized and the physical examination shows no splenomegaly.
Complete response (CR)	Near normalization of peripheral blood counts: hemoglobin >11 g/dL (without transfusion); platelets >100,000/mcL; ANC >1500/mcL. Regression of splenomegaly on physical examination. Absence of morphologic evidence of HCL on both the peripheral blood smear and the bone marrow examination.
CR with or without minimal residual disease (MRD)	If CR is achieved, an IHC assessment of the percentage of MRD will be useful to stratify patients based on level of CR (with or without evidence of MRD).
Partial response (PR)	A PR requires near normalization of the peripheral blood count (as in CR) with a minimum of 50% improvement in organomegaly and bone marrow biopsy infiltration with HCL.
Stable disease (SD)	Patients whose disease has not met the criteria for an objective remission after therapy are considered to have SD. Because patients with HCL are treated for specific reasons, including disease-related symptoms or decline in their hematologic parameters, SD is not an acceptable response.
Progressive disease (PD)	Patients who have an increase in symptoms related to disease, a 25% increase in organomegaly, or a 25% decline in their hematologic parameters qualify for PD. An effort must be made to differentiate a decline in blood counts related to myelosuppression effects of therapy versus PD.
HCL in relapse	Morphologic relapse is defined as the reappearance of HCL in the peripheral blood, the bone marrow biopsy, or both by morphologic stains in the absence of hematologic relapse. Hematologic relapse is defined as reappearance of cytopenia(s) below the thresholds defined above for CR and PR. Whereas no treatment is necessarily needed in case of morphologic relapse, treatment decisions for a hematologic relapse are based on several parameters (eg, hematologic parameters warranting intervention, reoccurrence of disease-related symptoms).

^a Grever MR, Abdel-Wahab O, Andritsos LA, et al. Consensus guidelines for the diagnosis and management of patients with classical hairy cell leukemia. Blood 2017;129:553-560.

Note: All recommendations are category 2A unless otherwise indicated.



SUPPORTIVE CARE FOR PATIENTS WITH HCL

Anti-infective Prophylaxis

- For patients who have received lymphodepleting treatment or are suspected of being immunosuppressed, monitor CD4 T-cell counts for need for prophylaxis.
- Consider herpes virus prophylaxis with acyclovir or equivalent for a minimum of 3 months and until CD4+ T-cell counts ≥ 200 cells/ μ L.
- Consider pneumocystis jirovecii pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent for a minimum of 3 months AND until CD4+ T-cell counts ≥ 200 cells/ μ L.
- Consider broad-spectrum prophylactic antibacterial coverage during period of neutropenia.
- Hepatitis B virus (HBV) prophylaxis and monitoring is recommended for patients at high risk. See Treatment and Viral Reactivation in the [NCCN Guidelines for CLL/SLL \(CSLL-C 1 of 5\)](#).

Rare Complications of Monoclonal Antibody Therapy

- Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Consultation with a dermatologist is recommended for management of these complications. Re-challenge with the same monoclonal antibody in such settings is not recommended.

Rituximab Rapid Infusion and Subcutaneous Administration

- If no severe infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.
- Rituximab and hyaluronidase human injection for subcutaneous use is a reasonable alternative for patients who have received at least one full dose of intravenous rituximab.

Growth Factors

- Neutrophil growth factor (eg, filgrastim^a) is indicated for patients with neutropenic fever following systemic therapy.

Blood Product Support

- Transfuse according to institutional or published standards.
- Irradiate all blood products to avoid transfusion-associated graft-versus-host disease (GVHD).

For other immunosuppressive situations, see [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).

^a An FDA-approved biosimilar is an appropriate substitute for filgrastim.

Note: All recommendations are category 2A unless otherwise indicated.



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Hairy Cell Leukemia

ABBREVIATIONS

ANC	absolute neutrophil count
CBC	complete blood count
cHCL	classical hairy cell leukemia
CR	complete response
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCL	hairy cell leukemia
HCLv	hairy cell leukemia variant
ICC	International Consensus Classification
IHC	immunohistochemistry
IVF	in vitro fertilization
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MRD	minimal residual disease
PD	progressive disease
PJP	pneumocystis jirovecii pneumonia
PR	partial response
SBLPN	splenic B-cell lymphoma/leukemia with prominent nucleoli
SD	stable disease



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NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Note: All recommendations are category 2A unless otherwise indicated.



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Discussion

This discussion corresponds to the NCCN Guidelines for Hairy Cell Leukemia. Last updated: April 22, 2024.

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Overview

Hairy cell leukemia (HCL) is a rare type of indolent B-cell leukemia comprising about 2% of all lymphoid leukemias.¹ Leukemic cells typically infiltrate the bone marrow and spleen, and may also be found in the liver, lymph nodes, and rarely in the skin. Small numbers of circulating hairy cells may be present. Clinically, HCL is characterized by symptoms of fatigue and weakness, and most patients will present with splenomegaly (symptomatic or asymptomatic) and/or hepatomegaly, pancytopenia, and uncommonly peripheral lymphadenopathy.² In addition, patients may also present with infection, including opportunistic infection.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines® for Hairy Cell Leukemia, an electronic search of the PubMed database was performed to obtain key literature in Hairy Cell Leukemia published since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.³

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles selected by the panel for review during the Guidelines update as well as articles from additional sources deemed

as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnosis

Morphologic evaluation of peripheral blood smear, bone marrow biopsy with or without aspirate, and adequate immunophenotyping by immunohistochemistry (IHC) or flow cytometry are essential to establish the diagnosis of HCL.² Leukemic cells in HCL are small to medium in size, and show a round, oval, or indented nucleus with a well-defined



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nuclear border. The presence of a cytoplasm with prominent hair-like projections of the cytoplasmic membrane is characteristic of HCL.² Examination of bone marrow biopsy samples shows hairy cell infiltrates with increased reticulin fibrosis, which frequently results in a “dry” tap. In some patients with HCL, bone marrow may show hypocellularity. This is important to recognize to avoid an erroneous diagnosis of aplastic anemia.²

In the 2017 WHO classification, classic HCL (cHCL) is considered as a distinct clinical entity, separate from HCL variant (HCLv).⁴ In the updated 2022 WHO classification (WHO5), HCLv has been renamed splenic B-cell lymphoma/leukemia with prominent nucleoli (SBLPN).⁵ The 2022 International Consensus Classification (ICC) continues to list HCLv as a subtype of splenic B-cell lymphoma/leukemia, unclassifiable.⁶ HCLv (ICC)/SBLPN (WHO5) tends to be associated with a more aggressive disease course and may not respond to standard HCL therapies.⁷ Therefore, it is necessary to distinguish HCLv (ICC)/SBLPN (WHO5) from cHCL.

Somatic hypermutation in the *IGHV* gene is present in the large majority of patients with HCL (80%–90%)^{8,9} The frequency of unmutated *IGHV* is much lower in cHCL than in HCLv (ICC)/SBLPN (WHO5) (17% vs. 54%; $P < .001$).⁹ About 40% of all patients diagnosed with HCLv (ICC)/SBLPN (WHO5) also express an unmutated *IGHV4-34*, which typically results in higher disease burden at initial diagnosis, poor response to single-agent therapy, and shorter overall survival (OS).^{10,11} Unmutated *IGHV* may serve as a prognostic marker for poorer outcomes with conventional therapies since it is associated with primary refractoriness to purine analog monotherapy, more rapid disease progression, and poor survival.¹²

The *BRAF* V600E kinase-activating mutation was identified in the majority of patients with cHCL and is now regarded as the main source

of pathogenesis.¹³⁻¹⁸ Additionally, targeted sequencing has also identified recurrent mutations in several other genes (eg, *CDKN1B* in cHCL; *MAP2K1* and *CCND3* in HCLv).¹⁹⁻²¹ Unlike cHCL, HCLv (ICC)/SBLPN (WHO5) and B-cell lymphoproliferative neoplasms with a cHCL phenotype expressing *IGHV4-34* rearrangement lack *BRAF* V600E mutation.^{11,16,22} A high frequency of *MAP2K1* mutations were reported in HCLv (approximately 30% express a mutated *MAP2K1* gene) and in cHCL with *IGHV4-34* rearrangement.²³

Immunophenotyping is the primary methodology used to distinguish cHCL and HCLv (ICC)/SBLPN (WHO5), though the role of molecular analysis is rapidly expanding. *BRAF* V600E mutation serves as a reliable molecular marker to distinguish cHCL from HCLv (ICC)/SBLPN (WHO5) and other B-cell leukemias or lymphomas, and *MAPK1* mutation analysis may be useful to distinguish HCLv (ICC)/SBLPN (WHO5) from cHCL in the absence of *BRAF* V600E mutation.^{11,16,23}

IHC or flow cytometry panel for immunophenotyping should include CD5, CD10, CD11c, CD19, CD20, CD22, CD25, CD103, CD123, cyclin D1, and CD200. The typical immunophenotype for cHCL shows CD5-, CD10-, CD11c+, CD20+(bright), CD22+, CD25+, CD103+, CD123+, cyclin D1+, annexin A1+, and CD200+ (bright).¹⁶ In contrast, HCLv (ICC)/SBLPN (WHO5) is characteristically CD25-, CD123-, annexin A1-, and negative for *BRAF* V600E mutation.¹⁶

IHC or molecular studies for *BRAF* V600E mutation are useful for the distinction of cHCL from HCLv (ICC)/SBLPN (WHO5) and other splenic B-cell lymphomas.^{16,17,24} HCL expressing *IGHV4-34* rearrangement has a less favorable prognosis than cHCL and does not respond well to purine analog-based therapy.²⁵ Molecular analysis to identify the *IGHV4-34* rearrangement may be useful to distinguish cHCL from HCL with *IGHV4-34* rearrangement.



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Workup

The initial workup should include a thorough physical examination with attention to node-bearing areas (although presence of peripheral lymphadenopathy is uncommon), measurement of size of liver and spleen, and evaluation of performance status. A bone marrow biopsy, with or without aspirate, should be obtained. Laboratory assessments should include complete blood count (CBC) with differential, measurements of serum lactate dehydrogenase (LDH) levels, and a comprehensive metabolic panel. Close evaluation of renal function is advised considering the renal route of drug excretion used in the treatment of HCL. Hepatitis B virus (HBV) testing is recommended due to the increased risk of viral reactivation associated with the use of immunotherapy and chemotherapy. CT scans (with contrast of diagnostic quality) of the chest, abdomen, and/or pelvis may be useful under certain circumstances.

Treatment Guidelines

The current NCCN Guidelines apply to patients with cHCL. Regimens are stratified into three categories (based on the evidence, efficacy, toxicity, preexisting comorbidities, and in some instances access to certain agents): preferred regimens, other recommended regimens, and useful under certain circumstances.

At the present time, there are no established treatment options for the optimal frontline or subsequent treatment of patients with HCLv (ICC)/SBLPN (WHO5). However, cladribine + rituximab²⁶⁻²⁸ and ibrutinib²⁹⁻³¹ have been shown to be effective in small cohorts of patients with HCLv (ICC)/SBLPN (WHO5). Participation in a clinical trial and referral to a medical center with expertise in the management of HCL is recommended.

Initial Treatment

Clinical judgment is required in the decision to initiate therapy, since not all newly diagnosed patients with HCL will require immediate treatment. Asymptomatic disease is best managed by close observation ("watch and wait" approach), until indications develop.

Indications for treatment initiation may include symptomatic disease with excessive fatigue, physical discomfort due to splenomegaly or hepatomegaly, unexplained weight loss (>10% within prior 6 months), cytopenias (hemoglobin <11 g/dL, platelets <100,000/mcL, and/or absolute neutrophil count <1000/mcL), progressive lymphocytosis, or lymphadenopathy.²

Purine Analogs ± Rituximab

Cladribine and pentostatin have not been compared head to head in randomized controlled trials but appear to have significant monotherapy activity, resulting in durable remissions in patients with previously untreated HCL.³²⁻⁴⁷

In a study of 358 patients with untreated HCL, cladribine resulted in a complete response (CR) rate of 91% with a median response duration of 52 months and an OS rate of 96% at 48 months.³⁵ Extended follow-up confirmed the durability of responses with cladribine.³⁸ After 7 years of follow-up, of the 207 evaluable patients, 95% achieved CR and 5% achieved partial response (PR), with median response duration of 98 months for all patients with responding disease. The most common toxicities with cladribine were grade 3–4 neutropenia (occurring in about 65%–85% of patients), febrile neutropenia (40%), grade 3–4 thrombocytopenia (20%), and infection (10%).

In a phase III intergroup study (319 patients with previously untreated HCL randomized to pentostatin versus interferon alpha; median follow-up was 57 months), pentostatin resulted in significantly higher CR rate (76%



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vs. 11%; $P < .0001$) and longer median relapse-free survival (RFS; not reached vs. 20 months; $P < .0001$) compared with interferon alpha.³³ After a median follow-up of 9 years, the estimated 5-year and 10-year OS rates for patients initially treated with pentostatin were 89% and 80%, respectively.³⁶ The corresponding RFS rates were 86% and 66%, respectively. Survival outcomes were not significantly different between treatment arms, although this analysis was complicated by the crossover study design. The most common toxicities were grade 3–4 neutropenia (20%) and infections (any grade; 53%), including those requiring intravenous antibiotics (27%).

Standard-dose purine analogs should not be administered to patients with active life-threatening or chronic infection. Active infection should be treated prior to initiating treatment with standard-dose purine analogs. If it is not possible to control infection, initiating treatment with reduced-dose pentostatin should be considered to secure a durable response before using standard-dose purine analogs.⁴⁸

Rituximab (anti-CD20 monoclonal antibody [mAb]) in combination with purine analogs has also been shown to be effective in previously untreated HCL; however, it has not been evaluated extensively in this patient population.²⁷ In a phase II study that included 59 patients with previously untreated patients with HCL, cladribine followed by rituximab resulted in a CR rate of 100%.²⁷ After a median follow-up of 60 months, the 5-year failure-free survival (FFS) and OS rates were 95% and 97%, respectively.

Initial treatment with purine analog monotherapy (cladribine or pentostatin) or cladribine + rituximab are included as preferred treatment options for untreated HCL in patients with an indication for treatment.

Routes of Administration of Purine Analogs

Subcutaneous and intravenous administration of cladribine resulted in similar response rates; however, subcutaneous cladribine was associated with a lower rate of viral infections and mucositis despite having a higher rate of neutropenia.⁴⁹⁻⁵³

In a prospective study, reduced-dose subcutaneous cladribine (total dose of 0.5 mg/kg given as 0.1 mg/kg/day x 5 days) had similar efficacy but lower toxicity than standard-dose subcutaneous cladribine (total dose of 0.7 mg/kg; given as 0.1 mg/kg/day x 7 days).⁵¹ After a median follow-up of 36 months, the CR rate was 64% and 73%, respectively, for reduced-dose and standard-dose cladribine with no difference in RFS and OS rates.

In a retrospective analysis that compared the efficacy and safety of subcutaneous and intravenous injection of cladribine in 49 patients with HCL (18 patients were treated with intravenous cladribine and 31 patients were treated with subcutaneous cladribine), the CR rates were 94% and 97%, respectively, for intravenous and subcutaneous cladribine.⁵² After a median follow-up of 34 months, subcutaneous cladribine was associated with a more favorable 3-year event-free survival (EFS) rate (60% and 96%, respectively; $P = .104$) and better (although non-significant) 3-year OS rate (81% and 100%, respectively; $P = .277$). Neutropenia (grade 3 or 4; 67% vs. 87%), mucositis (grades 1 or 2; 67% vs. 32%), and viral infections (78% vs. 34%) were the most frequent complications in the two treatment groups, respectively.

A study that evaluated the long-term outcomes of patients treated with subcutaneous cladribine in three prospective multicenter clinical trials showed that subcutaneous cladribine (0.14 mg/kg/day x 5 days) was associated with excellent long-term survival.⁵³ After a median follow-up of 13 years, the median OS was not reached and the estimated 10-year and 20-year OS rates were 80% and 67%, respectively.



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Dosing Schedules of Purine Analogs

Weekly infusion of cladribine was also shown to have similar safety and efficacy to daily continuous infusion.⁵⁴⁻⁵⁷

In a randomized study that evaluated the efficacy and safety of daily versus weekly infusion of cladribine (100 patients were randomized to receive cladribine at standard daily dosing [0.14 mg/kg/day for 5 days] or once weekly dosing [0.14 mg/kg/day once a week for 5 weeks]), the overall response rate (ORR) after 10 weeks was 78% for patients who received daily dosing and 68% for those who received once weekly dosing.⁵⁷ There were no significant differences in the toxicity profile between the two treatment arms after 10 weeks (grade 3 or 4 neutropenia, 90% vs. 80%; acute infection, 44% vs. 40%; and erythrocyte support, 22% vs. 30%).

Vemurafenib ± Anti-CD20 mAb

Vemurafenib (a *BRAF* V600E inhibitor with demonstrated activity in relapsed/refractory HCL) was also evaluated in patients with treatment-naïve HCL, either alone or in combination with anti-CD20 mAb (obinutuzumab or rituximab).⁵⁸⁻⁶¹

A 2016 study assessed vemurafenib monotherapy in patients with treatment-naïve HCL (21 patients were treated with vemurafenib outside of trials with individual dosing regimens; 240–1920 mg/day; median treatment duration, 90 days).⁵⁸ Blood count improvements were observed in all patients with a CR rate of 40% (6/15 of evaluable patients) and the median EFS was 17 months. Similar response patterns were achieved upon retreatment with vemurafenib (n = 6). Typical side effects at low dosing regimens included development of acute myeloid lymphoma (AML) subtype M6 in 1 patient, and potential disease acceleration triggered by vemurafenib.⁵⁸

In a phase II multicenter trial of 30 patients with newly diagnosed HCL, 27 patients completed 4 months of study treatment with vemurafenib + obinutuzumab and the CR rate was 96% at 4 months. At 10 months, with no further treatment, the CR rate increased to 100%.⁵⁹ The most common adverse events were rash (61%; grade 1–2 14%, grade 3 46%), arthralgia (46%; grade 1–2 36%, grade 3 11%), fatigue (29%, all grade 1), alopecia (25%, all grade 1), and pruritis (21%, grade 1–2).⁵⁹

In another study, the combination of vemurafenib + rituximab was evaluated as a treatment option for treatment-naïve HCL in patients with severe neutropenia, infection, and purine analogue intolerance, or as a treatment option for purine analogue-resistant HCL. The combination therapy was tolerable with no severe adverse events, and all patients' disease responded with rapid blood count recovery. However, median progression-free survival (PFS) and OS were not reached at a median follow-up of 18 months.⁶⁰

The guidelines recommend consideration of vemurafenib ± anti-CD20 mAb (obinutuzumab or rituximab) as an option for initial treatment for patients who are unable to tolerate purine analogs including frail patients and those with active infection.

Response Assessment

CR is defined as normalization of blood counts (hemoglobin >11 g/dL without transfusion, absolute neutrophil count >1,500/mcL, platelets >100,000/mcL), absence of HCL cells by morphologic examination of bone marrow biopsy and peripheral blood sample, regression of splenomegaly by physical examination, and absence of disease symptoms.² Available evidence suggests that achievement of CR is associated with longer duration of remission.^{44,45} Observation until there is an indication for additional treatment is recommended for patients who achieve a CR after initial treatment with purine analog.



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Few studies have evaluated the clinical relevance of minimal residual disease (MRD) status in patients with disease responding to therapy.^{27,29,59,61-66}

In a phase II study that evaluated cladribine followed by rituximab in patients with previously untreated or relapsed HCL, undetectable MRD (uMRD) status was achieved in 94% of patients at the end of treatment but MRD positivity during follow-up did not necessarily result in clinically relevant risk for relapse.²⁷

Other studies have shown that uMRD in peripheral blood at 6 months after initial treatment with purine analogs is associated with a low likelihood of disease relapse.^{64,65} In the phase II study that evaluated cladribine in combination with concurrent versus delayed rituximab in 68 patients with previously untreated HCL, the probability of achieving CR with uMRD was higher with the use of concurrent rituximab.⁶⁶ After a median follow-up of 96 months, the uMRD status (94% vs. 12%), CR (100% vs. 88%), and MRD-free CR rates (97% vs. 24%; $P < .0001$) were substantially higher with the use of concurrent rituximab versus delayed rituximab. In the 2021 phase II trial that assessed the safety and efficacy of vemurafenib plus concurrent and sequential rituximab, MRD negativity and no previous BRAF inhibitor treatment correlated with longer RFS in patients with relapsed/refractory HCL.⁶¹ Vemurafenib + obinutuzumab also resulted in a uMRD of 96% in patients with newly diagnosed HCL and all patients remained in remission, with a median follow-up of 17 months.⁵⁹ While no relapse was observed at a median follow-up of 17 months, a longer follow-up is needed to assess durability of remission and relationship between MRD status and rate of relapse.

In summary, the prognostic significance of uMRD after the end of first-line therapy remains uncertain at this time. In contrast, a number of studies in patients with relapsed HCL have demonstrated that CR with uMRD improves the duration of response, further suggesting the utility of

this approach. Thus, it has been suggested that MRD monitoring as a component of response assessment should be incorporated in all clinical trials for relapsed HCL.⁶⁷ Moreover, future cooperative multicenter studies will be essential to establish the value of MRD testing after the end of first-line therapy.⁶⁷ MRD assessment is not recommended (outside of clinical trials) as part of response evaluation.

Relapsed/Refractory or Progressive Disease

Dabrafenib + Trametinib

An open-label, phase 2 study assessed dabrafenib + trametinib (*BRAF* V600E inhibitors) combination therapy in 55 patients with *BRAF* V600E mutation–positive HCL refractory to first-line treatment with a purine analog or disease relapse after two or more prior lines of treatment.⁶⁸ The investigator-assessed ORR was 89%; CR was achieved in 66% of patients and PR in 24%. The 24-month PFS and OS rates were 94% and 95%, respectively. The most common treatment-related adverse events (TEAEs) were pyrexia (58%), chills (47%), and hyperglycemia (40%). These results are consistent with previous observations in other indications. Thus, dabrafenib + trametinib represents a rituximab-free treatment option for patients with relapsed/refractory *BRAF* V600E mutation–positive HCL.⁶⁸

Vemurafenib ± Rituximab

Vemurafenib monotherapy (960 mg twice daily) was evaluated in two separate phase II multicenter studies in patients with HCL refractory to purine analogs or those with relapsed disease after treatment with a purine analog.⁶⁹ In the Italian phase II multicenter trial ($n = 28$), the ORR was 96% (35% CR) after a median of 8 weeks of therapy, and the median RFS was longer for patients whose disease achieved CR versus PR (19 months and 6 months, respectively). The median follow-up was 23 months. In a U.S. phase II multicenter trial (26 out of the planned 36 patients), the ORR was 100% (42% CR) after a median of 12 weeks of



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therapy and the 1-year PFS and OS rates were 73% and 91%, respectively. Grade 1 or 2 rash and arthralgia or arthritis were the most common adverse events leading to dose reductions of vemurafenib. Long-term follow-up of 36 enrolled patients confirmed these findings as well as the efficacy of retreatment with vemurafenib at relapse.⁷⁰ After a median follow-up of 24 months, the ORR was 86% (33% CR and 53% PR). Among 18 patients with disease relapse, 13 received retreatment with vemurafenib resulting in a PR rate of 85% with complete hematologic recovery.

Vemurafenib + rituximab also induced durable responses with uMRD in most patients with relapsed/refractory HCL and the CR rates were higher than that observed with vemurafenib monotherapy.^{61,71} In a phase II study of 30 patients with relapsed/refractory HCL, vemurafenib in combination with concurrent and sequential rituximab resulted in a CR rate of 87%.⁶¹ After a median follow-up of 37 months, the PFS rate was 78%. The RFS at 34 months was 85% for patients achieving a CR.⁶¹

In a phase II trial of 31 patients with relapsed/refractory HCL after treatment with purine analogs (25 evaluable patients), the CR rate was 96% and the PFS rate was 83% after a median of 30 months of treatment with vemurafenib + rituximab.⁷¹ In addition, MRD as measured by allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) was undetectable (10^{-4} sensitivity) in the bone marrow in 65% of patients. The median PFS was significantly longer ($P = .001$) in patients with CR and uMRD (100% at a median of 31 months) than in patients with CR and detectable MRD (44% at a median of 25 months).

A single-center, phase II, academic trial assessed the safety and efficacy of vemurafenib (960 mg, twice daily for 8 weeks) in combination with simultaneous and sequential rituximab (375 mg/m², 8 doses over 18 weeks) in refractory or relapsed HCL and mutated *BRAF* V600E in patients with indications for treatment ($n = 30$).⁶¹ Vemurafenib in

combination with rituximab resulted in a CR rate of 87% ($P = .005$). uMRD was observed in 65% (17 out of 26) of patients with a CR. At a median follow-up of 37 months, the PFS rate was 78% for the overall study population. The RFS rate was 85% for the 26 patients with CR, at median follow-up of 34 months.⁶¹ MRD as measured by PCR for *BRAF* V600E mutation was undetectable in the bone marrow aspirate and peripheral blood in 65% of patients with CR (17 of 26).

Purine Analog ± Rituximab

Pentostatin and cladribine are also effective for the treatment of relapsed/refractory HCL.^{36,39,72} In the long-term follow-up of the phase III randomized study that evaluated pentostatin and interferon alpha, among the 87 patients who crossed over to pentostatin after progression on initial interferon treatment, the 5-year and 10-year OS rates were 93% and 85%, respectively.³⁶ The corresponding RFS rates were 84% and 69%, respectively.

Retreatment with the same purine analog may yield a reasonable duration of disease control in patients with relapsed HCL after an initial durable remission to purine analog therapy.^{38,41,46} In the long-term follow-up of a study that evaluated cladribine as initial treatment, relapse occurred in 37% of patients with an initial responding disease, with a median time to relapse of 42 months.³⁸ Among the patients with relapsed disease who received retreatment with cladribine, the CR rate after first relapse was 75% (median response duration of 35 months) and the CR rate after subsequent relapse was 60% (median response duration of 20 months).

Given the observation that retreatment with purine analogs resulted in shorter remission durations with each successive treatment, the use of rituximab in combination with purine analogs was evaluated in patients with relapsed/refractory HCL.^{27,66,73} In a retrospective study of 18 patients with previously treated HCL relapsing after purine analog monotherapy



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(median two prior therapies), rituximab in combination with pentostatin or cladribine resulted in a CR rate of 89%.⁷³ CR was maintained in all patients after a median follow-up of 36 months and the estimated 3-year recurrence rate was 7%. In a phase II study that included 14 patients with relapsed HCL, cladribine followed by rituximab resulted in a CR rate of 100%. After a median follow-up of 60 months, the 5-year FFS and OS rates were each 100%.

Moxetumomab Pasudotox

Moxetumomab pasudotox (CD22-directed recombinant immunotoxin) was initially approved for the treatment of relapsed or refractory HCL after at least two prior lines of therapy in September 2018.^{74,75} However, the manufacturer decided to permanently discontinue moxetumomab pasudotox in the United States in July 2023 due to very low clinical uptake since FDA approval, possibly due to the specialized complexity of administration, toxicity prophylaxis, and safety monitoring needs for patients. Accordingly, moxetumomab pasudotox is no longer recommended in the NCCN Guidelines for the treatment of relapsed or refractory HCL.

Ibrutinib

Ibrutinib is a covalent Bruton tyrosine kinase (BTK) inhibitor approved for the treatment of patients with CLL/SLL. In a phase II, multicenter, open-label study of 37 patients with relapsed HCL (cHCL, n = 28; HCLv [ICC]/SBLPN [WHO5]), ibrutinib was evaluated at two dose levels (420 mg once daily, n = 24; and 840 mg once daily, n = 13).²⁹ The ORR (CR and PR) was 24% at 32 weeks (improved to 36% at 48 weeks). Additionally, three patients with CR had uMRD. The ORRs were not significantly different between cHCL and HCLv (ICC)/SBLPN (WHO5) (54% and 56% respectively).²⁹ At a median follow-up of 3.5 years, the estimated 36-month PFS and OS rates were 73% and 85%, respectively.

Diarrhea (59%), fatigue (54%), myalgia (54%), and nausea (51%) were the most common grade 1–2 nonhematologic adverse events.²⁹ Anemia (5%), thrombocytopenia (22%), and neutropenia (22%) were the most common grade ≥3 hematologic adverse events. Hypertension (11%), atrial flutter (3%), and heart failure (3%) were the most common grade ≥3 cardiovascular adverse events. There was no grade ≥3 atrial fibrillation or bleeding and no significant differences in the safety profile between the two dose levels. The benefit and risk of ibrutinib should be evaluated in patients requiring anti-platelet or anticoagulant therapies.

Zanubrutinib

A pooled safety analysis evaluated zanubrutinib-associated TEAEs and treatment-limiting toxicities in patients with relapsed/refractory or treatment-naïve hematologic malignancies, including HCL (779 patients from 6 studies; median treatment duration was 26 months).⁷⁶ Common nonhematologic TEAEs included upper respiratory tract infection (URI, 39%), rash (27%), bruising (25%), musculoskeletal pain (24%), diarrhea (23%), cough (21%), pneumonia (21%), urinary tract infection (UTI), and fatigue (15% each). Atrial fibrillation and major hemorrhage were observed in 3% and 4% of patients, respectively. Atrial fibrillation, hypertension, and diarrhea occurred at lower rates than those reported historically for ibrutinib. Serious TEAEs included pneumonia (11%), sepsis (2%), and pyrexia (2%). Thirty-nine patients (4%) had fatal TEAEs, including pneumonia (n = 9), sepsis (n = 4), unspecified cause (n = 4), and multiple organ dysfunction syndrome (n = 5). This analysis demonstrates that zanubrutinib is generally well tolerated with a safety profile consistent with known BTK inhibitor toxicities.⁷⁶

A phase I/II open-label study evaluated zanubrutinib monotherapy in 12 patients with relapsed/refractory HCL.⁷⁷ The ORR was 58% (17% CR). The median PFS and OS were not reached. At 36 months, PFS and OS rates were 80% and 82%, respectively. The PFS rate at 48 months was



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100% for all patients with disease responding to therapy. Eleven (92%) patients had baseline cytopenias. Eight (67%) patients experienced TEAEs of infections (including grade 3 pneumonia and grade 3 cerebral aspergillosis). Five (42%) patients experienced minor hemorrhage events. Other TEAEs included hypertension (8%), basal cell carcinoma (17%), grade 3 or 4 neutropenia (42%), thrombocytopenia (25%), and grade 3 anemia (8%). Thus, zanubrutinib results in clinically significant and durable responses in relapsed/refractory HCL with a safety profile consistent with its known safety profile in other indications.⁷⁷

Venetoclax ± Rituximab

A 2023 study evaluated venetoclax ± rituximab for the treatment of patients with relapsed/refractory HCL.⁷⁸ Out of 6 patients who received venetoclax, 2 showed CR with MRD, 1 showed PR, and 3 had a minor response, no response, or progressive disease. The main toxic effect of this drug involved worsening of baseline neutropenia, which was sometimes complicated by infections or febrile neutropenia. Addition of rituximab to the treatment regimen of 3 patients improved both the response as well as MRD compared to venetoclax alone.⁷⁸ Another study assessing venetoclax monotherapy for the treatment of refractory HCL in a male patient observed CR within 5 weeks of treatment initiation with a reduction in spleen size and number of leukemic cells in bone marrow over a period of 36 months and with no hematologic toxic effects.⁷⁹

Treatment Options for Relapsed/Refractory Disease

Treatment options for relapsed HCL depend upon the quality and duration of remission with initial therapy.

Clinical trial (if available), or dabrafenib + trametinib (if not previously treated with BRAF inhibitors)⁶⁸ or vemurafenib ± rituximab (if not previously given)^{58,61,69,70,80} are preferred treatment options for patients with primary refractory disease (less than CR to initial treatment) or disease relapse within 2 years after achieving CR to initial therapy.

Alternative purine analog ± rituximab are included as the other recommended treatment options.^{27,36,39,66,72,73} Retreatment with the same purine analog or treatment with an alternative purine analog + rituximab is the preferred option for patients with disease relapse after ≥2 years after achieving CR to initial therapy.^{27,66,73} Rituximab monotherapy has modest activity in patients with relapsed HCL after initial treatment with purine analogs, resulting in an ORR of 25% to 80% (10%–53% CR), and the median duration of response was 32 to 34 months.^{81–84} Rituximab monotherapy is included as an option for patients unable to receive purine analogs.

Long-term clinical trial follow-up data suggest that interferon alpha results in durable disease control and may be useful for the management of relapsed or refractory disease.^{85–87} The manufacturing of interferon alfa has been discontinued. Peginterferon alfa-2a may be substituted for other interferon preparations for the treatment of relapsed/refractory disease.

Treatment Options for Progressive Disease

Clinical trial (if available), vemurafenib (with or without rituximab),^{61,69,70} or dabrafenib + trametinib (if not previously treated with BRAF inhibitors)⁶⁸ are the preferred treatment options for progressive disease following second-line therapy. Ibrutinib and zanubrutinib are included as other recommended regimens.^{29,76} Venetoclax ± rituximab is included as an option for patients with disease resistant to BRAF inhibitor therapy.⁷⁸

Supportive Care

Infections

Patients with HCL are susceptible to infectious complications due to treatment with purine analogs.⁸⁸ Acyclovir or equivalent is recommended for herpes virus prophylaxis, and sulfamethoxazole trimethoprim or equivalent is recommended for pneumocystis jirovecii pneumonia (PJP)



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prophylaxis.⁸⁹ Anti-infective prophylaxis for a minimum of 3 months and until CD4+ T-cell count is ≥ 200 cells/mm³ is recommended for all patients requiring treatment. Broad-spectrum antibacterial prophylaxis should be considered for patients with neutropenia.

Available evidence suggests that the use of granulocyte colony-stimulating factors (G-CSFs) shortens the duration of severe neutropenia after treatment with cladribine; however, it has no clinically significant impact on infection-related outcomes.⁹⁰ The use of G-CSFs either as primary prophylaxis or based on the absolute neutrophil count have been shown to be effective for the management of neutropenia.⁹¹ The use of G-CSF might be considered in patients with severe neutropenic fever following chemotherapy.

Hepatitis B Virus Reactivation

HBV reactivation leading to fulminant hepatitis, hepatic failure, and death have been reported in patients receiving chemotherapy and immunosuppressive therapy.⁹² HBV prophylaxis and monitoring is recommended in patients at high risk when receiving rituximab and purine analogs. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) testing, and hepatitis B e-antigen (in patients with risk factors or previous history of hepatitis B) are recommended for all patients receiving immunotherapy and/or chemotherapy. In patients who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be obtained to determine viral load and consultation with a gastroenterologist is recommended. A negative baseline PCR, however, does not preclude the possibility of reactivation.

Monitoring hepatitis B viral load with PCR monthly during treatment and every 3 months thereafter is recommended. Entecavir is more effective than lamivudine for the prevention of HBV reactivation associated with rituximab-based chemoimmunotherapy.⁹³ Lamivudine prophylaxis should

be avoided due to the risks for the development of resistance. Prophylactic antiviral therapy is recommended for patients who are HBsAg positive. Prophylactic antiviral therapy is preferred for patients who are HBcAb positive. However, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored for serial hepatitis B viral load.

Management of Intolerance to anti-CD20 Monoclonal Antibody Therapy

Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur in patients treated with rituximab. Consultation with a dermatologist is recommended for management of these complications. Rechallenge with the same anti-CD20 mAb is not recommended in patients experiencing aforementioned severe reactions. There are some data (based on clinical experience) showing that substitution with an alternative anti-CD20 mAb is tolerated in patients experiencing severe reactions to a specific anti-CD20 mAb; however, it is unclear if such a substitution poses the same risk of recurrence.^{94,95}

Rituximab and hyaluronidase human injection for subcutaneous use is approved by the FDA for the treatment of patients with chronic lymphocytic leukemia, follicular lymphoma, and diffuse large B-cell lymphoma.⁹⁶⁻⁹⁸ Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for intravenous rituximab in patients who have received at least one full dose of intravenous rituximab without experiencing severe adverse reactions. Switching to subcutaneous rituximab is not recommended until a full intravenous dose of rituximab is successfully administered without experiencing severe adverse reactions. A rapid infusion over 90 minutes can be used if no severe infusion-related reactions were experienced with the prior cycle of rituximab.



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References

1. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin* 2016;66:443-459. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27618563>.
2. Grever MR, Abdel-Wahab O, Andritsos LA, et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. *Blood* 2017;129:553-560. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27903528>.
3. MEDLINE PubMed Production Statistics. Available at: https://www.nlm.nih.gov/bsd/medline_pubmed_production_stats.html. Accessed March 21, 2024.
4. Swerdlow SH, Harris NL, Jaffe ES, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. revised 4th ed. Lyon, France: IARC; 2017.
5. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia* 2022;36:1720-1748. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35732829>.
6. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. *Blood* 2022;140:1229-1253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35653592>.
7. Robak T. Hairy-cell leukemia variant: recent view on diagnosis, biology and treatment. *Cancer Treat Rev* 2011;37:3-10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20558005>.
8. Arons E, Sunshine J, Suntum T, Kreitman RJ. Somatic hypermutation and VH gene usage in hairy cell leukaemia. *Br J Haematol* 2006;133:504-512. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16681637>.
9. Arons E, Roth L, Sapolsky J, et al. Evidence of canonical somatic hypermutation in hairy cell leukemia. *Blood* 2011;117:4844-4851. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21368287>.
10. Arons E, Kreitman RJ. Molecular variant of hairy cell leukemia with poor prognosis. *Leuk Lymphoma* 2011;52 Suppl 2:99-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21599610>.
11. Xi L, Arons E, Navarro W, et al. Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. *Blood* 2012;119:3330-3332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22210875>.
12. Forconi F, Sozzi E, Cencini E, et al. Hairy cell leukemias with unmutated IGHV genes define the minor subset refractory to single-agent cladribine and with more aggressive behavior. *Blood* 2009;114:4696-4702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19667403>.
13. Boyd EM, Bench AJ, van 't Veer MB, et al. High resolution melting analysis for detection of BRAF exon 15 mutations in hairy cell leukaemia and other lymphoid malignancies. *Br J Haematol* 2011;155:609-612. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21910720>.
14. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med* 2011;364:2305-2315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21663470>.
15. Andrusis M, Penzel R, Weichert W, et al. Application of a BRAF V600E mutation-specific antibody for the diagnosis of hairy cell leukemia. *Am J Surg Pathol* 2012;36:1796-1800. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22531170>.
16. Shao H, Calvo KR, Gronborg M, et al. Distinguishing hairy cell leukemia variant from hairy cell leukemia: development and validation of diagnostic criteria. *Leuk Res* 2013;37:401-409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23347903>.
17. Wang XJ, Kim A, Li S. Immunohistochemical analysis using a BRAF V600E mutation specific antibody is highly sensitive and specific for the



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diagnosis of hairy cell leukemia. *Int J Clin Exp Pathol* 2014;7:4323-4328. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25120816>.

18. Parry-Jones N, Joshi A, Forconi F, et al. Guideline for diagnosis and management of hairy cell leukaemia (HCL) and hairy cell variant (HCL-V). *Br J Haematol* 2020;191:730-737. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33053222>.

19. Dietrich S, Hullein J, Lee SC, et al. Recurrent CDKN1B (p27) mutations in hairy cell leukemia. *Blood* 2015;126:1005-1008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26065650>.

20. Durham BH, Getta B, Dietrich S, et al. Genomic analysis of hairy cell leukemia identifies novel recurrent genetic alterations. *Blood* 2017;130:1644-1648. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28801450>.

21. Maitre E, Bertrand P, Maingonnat C, et al. New generation sequencing of targeted genes in the classical and the variant form of hairy cell leukemia highlights mutations in epigenetic regulation genes. *Oncotarget* 2018;9:28866-28876. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29989027>.

22. Arcaini L, Zibellini S, Boveri E, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. *Blood* 2012;119:188-191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22072557>.

23. Waterfall JJ, Arons E, Walker RL, et al. High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias. *Nat Genet* 2014;46:8-10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24241536>.

24. Turakhia S, Lanigan C, Hamadeh F, et al. Immunohistochemistry for BRAF V600E in the differential diagnosis of hairy cell leukemia vs other splenic B-cell lymphomas. *Am J Clin Pathol* 2015;144:87-93. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26071465>.

25. Arons E, Suntum T, Stetler-Stevenson M, Kreitman RJ. VH4-34+ hairy cell leukemia, a new variant with poor prognosis despite standard therapy. *Blood* 2009;114:4687-4695. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19745070>.

26. Kreitman RJ, Wilson W, Calvo KR, et al. Cladribine with immediate rituximab for the treatment of patients with variant hairy cell leukemia. *Clin Cancer Res* 2013;19:6873-6881. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24277451>.

27. Chihara D, Kantarjian H, O'Brien S, et al. Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: update of a phase II trial. *Br J Haematol* 2016;174:760-766. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27301277>.

28. Hu Z, Sun Y, Wang W, et al. Refractory hairy cell leukemia-variant. *Am J Hematol* 2017;92:1398-1399. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27727469>.

29. Rogers KA, Andritsos LA, Wei L, et al. Phase 2 study of ibrutinib in classic and variant hairy cell leukemia. *Blood* 2021;137:3473-3483. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33754642>.

30. Bohn JP, Wanner D, Steurer M. Ibrutinib for relapsed refractory hairy cell leukemia variant. *Leuk Lymphoma* 2017;58:1224-1226. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27733095>.

31. Visentin A, Imbergamo S, Trimarco V, et al. Ibrutinib in relapsed hairy cell leukemia variant: A case report and review of the literature. *Hematol Oncol* 2020;38:823-826. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32979282>.

32. Kraut EH, Grever MR, Bouroncle BA. Long-term follow-up of patients with hairy cell leukemia after treatment with 2'-deoxycoformycin. *Blood* 1994;84:4061-4063. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7994024>.

33. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with



NCCN Guidelines Version 1.2025

Hairy Cell Leukemia

hairy cell leukemia: an intergroup study. *J Clin Oncol* 1995;13:974-982. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7707126>.

34. Cheson BD, Sorensen JM, Vena DA, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine via the Group C protocol mechanism of the National Cancer Institute: a report of 979 patients. *J Clin Oncol* 1998;16:3007-3015. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9738569>.

35. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. *Blood* 1998;92:1918-1926. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9731048>.

36. Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. *Blood* 2000;96:2981-2986. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11049974>.

37. Johnston JB, Eisenhauer E, Wainman N, et al. Long-term outcome following treatment of hairy cell leukemia with pentostatin (Nipent): a National Cancer Institute of Canada study. *Semin Oncol* 2000;27:32-36. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10877049>.

38. Goodman GR, Burian C, Koziol JA, Saven A. Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. *J Clin Oncol* 2003;21:891-896. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12610190>.

39. Maloisel F, Benboubker L, Gardembas M, et al. Long-term outcome with pentostatin treatment in hairy cell leukemia patients. A French retrospective study of 238 patients. *Leukemia* 2003;17:45-51. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12529659>.

40. Jehn U, Bartl R, Dietzfelbinger H, et al. An update: 12-year follow-up of patients with hairy cell leukemia following treatment with 2-chlorodeoxyadenosine. *Leukemia* 2004;18:1476-1481. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15229616>.

41. Chadha P, Rademaker AW, Mendiratta P, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience. *Blood* 2005;106:241-246. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15761021>.

42. Dearden CE, Else M, Catovsky D. Long-term results for pentostatin and cladribine treatment of hairy cell leukemia. *Leuk Lymphoma* 2011;52 Suppl 2:21-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21599603>.

43. Zinzani PL, Pellegrini C, Stefoni V, et al. Hairy cell leukemia: evaluation of the long-term outcome in 121 patients. *Cancer* 2010;116:4788-4792. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20597132>.

44. Rosenberg JD, Burian C, Waalen J, Saven A. Clinical characteristics and long-term outcome of young hairy cell leukemia patients treated with cladribine: a single-institution series. *Blood* 2014;123:177-183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24192579>.

45. Else M, Dearden CE, Catovsky D. Long-term follow-up after purine analogue therapy in hairy cell leukaemia. *Best Pract Res Clin Haematol* 2015;28:217-229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26614900>.

46. Madanat YF, Rybicki L, Radivoyevitch T, et al. Long-term outcomes of hairy cell leukemia treated with purine analogs: a comparison with the general population. *Clin Lymphoma Myeloma Leuk* 2017;17:857-862. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28778620>.

47. Paillassa J, Cornet E, Noel S, et al. Analysis of a cohort of 279 patients with hairy-cell leukemia (HCL): 10 years of follow-up. *Blood Cancer J* 2020;10:62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32461544>.

48. Andritsos LA, Dunavin N, Lozanski G, et al. Reduced dose pentostatin for initial management of hairy cell leukemia patients who have active infection or risk of hemorrhage is safe and effective. *Haematologica*



NCCN Guidelines Version 1.2025

Hairy Cell Leukemia

2015;100:e18-20. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25361945>.

49. Juliusson G, Heldal D, Hippe E, et al. Subcutaneous injections of 2-chlorodeoxyadenosine for symptomatic hairy cell leukemia. *J Clin Oncol* 1995;13:989-995. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/7707128>.

50. von Rohr A, Schmitz SF, Tichelli A, et al. Treatment of hairy cell leukemia with cladribine (2-chlorodeoxyadenosine) by subcutaneous bolus injection: a phase II study. *Ann Oncol* 2002;13:1641-1649. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12377655>.

51. Forconi F, Cencini E, Zaja F, et al. Analysis of toxicity and efficacy of subcutaneous cladribine at reduced or standard doses (five versus seven consecutive days) in patients with hairy cell leukemia (HCL) in the ICGHCL2004 Protocol by the Italian Cooperative Group on HCL [abstract]. *Blood* 2010;116:Abstract 701. Available at:

<http://www.bloodjournal.org/content/116/21/701.abstract>.

52. Khorshid O, Namour AE, El-Gammal MM, et al. Efficacy and safety of cladribine: subcutaneous versus intravenous administration in hairy cell leukemia patients. *Mediterr J Hematol Infect Dis* 2015;7:e2015058. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26543527>.

53. Benz R, Arn K, Andres M, et al. Prospective long-term follow-up after first-line subcutaneous cladribine in hairy cell leukemia: a SAKK trial. *Blood Adv* 2020;4:3699-3707. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32777066>.

54. Tallman MS, Hakimian D, Variakojis D, et al. A single cycle of 2-chlorodeoxyadenosine results in complete remission in the majority of patients with hairy cell leukemia. *Blood* 1992;80:2203-2209. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/1358262>.

55. Lauria F, Bocchia M, Marotta G, et al. Weekly administration of 2-chlorodeoxyadenosine in patients with hairy-cell leukemia is effective and reduces infectious complications. *Haematologica* 1999;84:22-25. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10091389>.

56. Robak T, Jamrozik K, Gora-Tybor J, et al. Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial. *Blood* 2007;109:3672-3675. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17209059>.

57. Zenhausern R, Schmitz SF, Solenthaler M, et al. Randomized trial of daily versus weekly administration of 2-chlorodeoxyadenosine in patients with hairy cell leukemia: a multicenter phase III trial (SAKK 32/98). *Leuk Lymphoma* 2009;50:1501-1511. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19672771>.

58. Dietrich S, Pircher A, Endris V, et al. BRAF inhibition in hairy cell leukemia with low-dose vemurafenib. *Blood* 2016;127:2847-2855. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26941398>.

59. Park JH, Winer ES, Huntington SF, et al. First line chemo-free therapy with the BRAF inhibitor vemurafenib combined with obinutuzumab is effective in patients with HCL [abstract]. *Blood* 2021;138:Abstract 43. Available at:

<https://doi.org/10.1182/blood-2021-151074>.

60. Moore JE, Delibert K, Baran AM, et al. Targeted therapy for treatment of patients with classical hairy cell leukemia. *Leuk Res* 2021;102:106522. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33582427>.

61. Tiacchi E, De Carolis L, Simonetti E, et al. Vemurafenib plus rituximab in refractory or relapsed hairy-cell leukemia. *N Engl J Med* 2021;384:1810-1823. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33979489>.

62. Sigal DS, Sharpe R, Burian C, Saven A. Very long-term eradication of minimal residual disease in patients with hairy cell leukemia after a single course of cladribine. *Blood* 2010;115:1893-1896. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20056789>.

63. Lopez Rubio M, Da Silva C, Loscertales J, et al. Hairy cell leukemia treated initially with purine analogs: a retrospective study of 107 patients from the Spanish Cooperative Group on Chronic Lymphocytic Leukemia (GELLC). *Leuk Lymphoma* 2014;55:1007-1012. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23885799>.



NCCN Guidelines Version 1.2025

Hairy Cell Leukemia

64. Garnache Ottou F, Chandesris MO, Lhermitte L, et al. Peripheral blood 8 colour flow cytometry monitoring of hairy cell leukaemia allows detection of high-risk patients. *Br J Haematol* 2014;166:50-59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24661013>.

65. Ortiz-Maldonado V, Villamor N, Baumann T, et al. Is there a role for minimal residual disease monitoring in the management of patients with hairy-cell leukaemia? *Br J Haematol* 2018;183:127-129. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28832940>.

66. Chihara D, Arons E, Stetler-Stevenson M, et al. Randomized phase II study of first-line cladribine with concurrent or delayed rituximab in patients with hairy cell leukemia. *J Clin Oncol* 2020;38:1527-1538. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32109194>.

67. Ravandi F, Kreitman RJ, Tiacci E, et al. Consensus opinion from an international group of experts on measurable residual disease in hairy cell leukemia. *Blood Cancer J* 2022;12:165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36509740>.

68. Kreitman RJ, Moreau P, Ravandi F, et al. Dabrafenib plus trametinib in patients with relapsed/refractory BRAF V600E mutation-positive hairy cell leukemia. *Blood* 2023;141:996-1006. Available at: <https://doi.org/10.1182/blood.2021013658>.

69. Tiacci E, Park JH, De Carolis L, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. *N Engl J Med* 2015;373:1733-1747. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26352686>.

70. Park JH, Lee J-O, Stone RM, et al. Acquired resistance to BRAF inhibition in HCL is rare and retreatment with vemurafenib at relapse can induce high response rates: final results of a phase II trial of vemurafenib in relapsed HCL. *Blood* 2018;132:392-392. Available at: http://www.bloodjournal.org/content/132/Suppl_1/392.abstract.

71. Tiacci E, De Carolis L, Simonetti E, et al. The BRAF inhibitor vemurafenib plus rituximab produces a high rate of deep and durable responses in relapsed/refractory hairy cell leukemia: updated results of a

phase-2 trial. *Hematol Oncol* 2019;37:110-111. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/hon.72_2629.

72. Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *Br J Haematol* 2009;145:733-740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19344416>.

73. Else M, Dearden CE, Matutes E, et al. Rituximab with pentostatin or cladribine: an effective combination treatment for hairy cell leukemia after disease recurrence. *Leuk Lymphoma* 2011;52 Suppl 2:75-78. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21504288>.

74. Kreitman RJ, Dearden C, Zinzani PL, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. *Leukemia* 2018;32:1768-1777. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30030507>.

75. Kreitman RJ, Dearden C, Zinzani PL, et al. Moxetumomab pasudotox in heavily pre-treated patients with relapsed/refractory hairy cell leukemia (HCL): long-term follow-up from the pivotal trial. *J Hematol Oncol* 2021;14:35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33627164>.

76. Tam CS, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood Adv* 2022;6:1296-1308. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34724705>.

77. Tam CS, Trotman J, Opat S, et al. Zanubrutinib for the treatment of relapsed/refractory hairy cell leukemia. *Blood Adv* 2023;7:2884-2887. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36753605>.

78. Tiacci E, De Carolis L, Santi A, Falini B. Venetoclax in relapsed or refractory hairy-cell leukemia. *N Engl J Med* 2023;388:952-954. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36884329>.

79. Forconi F, Ashton-Key M, Meakin N. BCL2 Inhibition in Refractory Hairy-Cell Leukemia. *N Engl J Med* 2023;388:2010-2012. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37224205>.



NCCN Guidelines Version 1.2025

Hairy Cell Leukemia

80. Handa S, Lee J-O, Derkach A, et al. Long-term outcomes in patients with relapsed or refractory hairy cell leukemia treated with vemurafenib monotherapy. *Blood* 2022;140:2663-2671. Available at: <https://doi.org/10.1182/blood.2022016183>.

81. Lauria F, Lenoci M, Annino L, et al. Efficacy of anti-CD20 monoclonal antibodies (Mabthera) in patients with progressed hairy cell leukemia. *Haematologica* 2001;86:1046-1050. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11602410>.

82. Nieva J, Bethel K, Saven A. Phase 2 study of rituximab in the treatment of cladribine-failed patients with hairy cell leukemia. *Blood* 2003;102:810-813. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12663446>.

83. Thomas DA, O'Brien S, Bueso-Ramos C, et al. Rituximab in relapsed or refractory hairy cell leukemia. *Blood* 2003;102:3906-3911. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12816862>.

84. Zenhausern R, Simcock M, Gratwohl A, et al. Rituximab in patients with hairy cell leukemia relapsing after treatment with 2-chlorodeoxyadenosine (SAKK 31/98). *Haematologica* 2008;93:1426-1428. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18603561>.

85. Federico M, Frassoldati A, Lamparelli T, et al. Long-term results of alpha interferon as initial therapy and splenectomy as consolidation therapy in patients with hairy cell leukemia. Final report from the Italian Cooperative Group for HCL. *Ann Oncol* 1994;5:725-731. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7826905>.

86. Damasio EE, Clavio M, Masoudi B, et al. Alpha-interferon as induction and maintenance therapy in hairy cell leukemia: a long-term follow-up analysis. *Eur J Haematol* 2000;64:47-52. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10680705>.

87. Benz R, Siciliano RD, Stussi G, Fehr J. Long-term follow-up of interferon-alpha induction and low-dose maintenance therapy in hairy cell leukemia. *Eur J Haematol* 2009;82:194-200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19077050>.

88. Tadmor T. Purine analog toxicity in patients with hairy cell leukemia. *Leuk Lymphoma* 2011;52 Suppl 2:38-42. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21463124>.

89. Cooley L, Dendle C, Wolf J, et al. Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014. *Intern Med J* 2014;44:1350-1363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25482745>.

90. Saven A, Burian C, Adusumalli J, Koziol JA. Filgrastim for cladribine-induced neutropenic fever in patients with hairy cell leukemia. *Blood* 1999;93:2471-2477. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10194424>.

91. Tadmor T, Levy I, Herishanu Y, et al. Primary peg-filgrastim prophylaxis versus filgrastim given "on demand" for neutropenia during therapy with cladribine for hairy cell leukemia. *Leuk Res* 2019;82:24-28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31152919>.

92. Di Bisceglie AM, Lok AS, Martin P, et al. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* 2015;61:703-711. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25412906>.

93. Huang H, Li X, Zhu J, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA* 2014;312:2521-2530. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25514302>.

94. Castillo JJ, Kanan S, Meid K, et al. Rituximab intolerance in patients with Waldenstrom macroglobulinaemia. *Br J Haematol* 2016;174:645-648. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26523929>.

95. Chen LY, Shah R, Cwynarski K, et al. Ofatumumab is a feasible alternative anti-CD20 therapy in patients intolerant of rituximab. *Br J*



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Haematol 2019;184:462-465. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29363752>.

96. Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. Lancet Haematol 2016;3:e128-138. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/26947201>.

97. Davies A, Merli F, Mihaljevic B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. Lancet Haematol 2017;4:e272-e282. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/28476440>.

98. Lugtenburg P, Avivi I, Berenschot H, et al. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study. Haematologica 2017;102:1913-1922. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/28935843>.

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