National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hairy Cell Leukemia

Version 2.2021 — March 11, 2021

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NCCN Guidelines Version 2.2021
Hairy Cell Leukemia

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***William G. Wierda, MD, PhD/Chair † ‡**
The University of Texas
MD Anderson Cancer Center

***John C. Byrd, MD/Vice-Chair ‡ Þ ξ**
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Jeremy S. Abramson, MD, MMSc † ‡
Massachusetts General Hospital Cancer Center

Syed F. Bilgrami, MD ‡
Yale Cancer Center/ Smilow Cancer Hospital

Greg Bociek, MD, MSc † ξ
Fred & Pamela Buffett Cancer Center

Danielle Brander, MD ‡
Duke Cancer Institute

Jennifer Brown, MD, PhD ‡
Dana-Farber/Brigham and Women's Cancer Center

Asher A. Chanan-Khan, MD † ‡
Mayo Clinic Cancer Center

Julio C. Chavez, MD ‡ †
Moffitt Cancer Center

***Steve E. Coutre, MD ‡**
Stanford Cancer Institute

Randall S. Davis, MD ‡
O'Neal Comprehensive Cancer Center at UAB

Herbert Eradat, MD, MS ‡
UCLA Jonsson Comprehensive Cancer Center

Christopher D. Fletcher, MD ‡
University of Wisconsin Carbone Cancer Center

Armin Ghobadi, MD ‡ Þ ξ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Brian Hill, MD, PhD ‡
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Manali Kamdar, MD ‡
University of Colorado Cancer Center

Lawrence D. Kaplan, MD ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Nadia Khan, MD †
Fox Chase Cancer Center

Thomas J. Kipps, MD, PhD ‡
UC San Diego Moores Cancer Center

Shuo Ma, MD, PhD †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Anthony Mato, MD ‡
Memorial Sloan Kettering Cancer Center

Claudio Mosse, MD, PhD ≠
Vanderbilt-Ingram Cancer Center

Stephen Schuster, MD † ‡
Abramson Cancer Center at the University of Pennsylvania

Mazyar Shadman, MD, MPH † ‡
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Tanya Siddiqi, MD ‡
City of Hope National Medical Center

***Deborah M. Stephens, DO ‡**
Huntsman Cancer Institute at the University of Utah

Suchitra Sundaram, MD † ‡
Roswell Park Comprehensive Cancer Center

Nina Wagner-Johnston, MD †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

NCCN
Mary Dwyer, MS
Hema Sundar, PhD

ξ Bone marrow transplantation
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology/Hematopathology
* Discussion Writing Committee Member

NCCN Guidelines Panel Disclosures

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NCCN Hairy Cell Leukemia Panel Members
Summary of the Guidelines Updates

Diagnosis and Workup (HCL-1)
Indication for Treatment, Initial Treatment and Relapsed/Refractory Therapy (HCL-2)
Suggested Treatment Regimens (HCL-A)
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Special Considerations for the Use of Moxetumomab Pasudotox (HCL-D)

Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See NCCN Guidelines for B-Cell Lymphomas)

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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.

NCCN Guidelines Version 2.2021
Hairy Cell Leukemia

Updates in Version 2.2021 of the NCCN Guidelines for Hairy Cell Leukemia from Version 1.2021 include:

MS-1
- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2021 of the NCCN Guidelines for Hairy Cell Leukemia from Version 1.2020 include:

HCL-1
- **Workup, 8th bullet, Hepatitis C testing was added.**
- **Footnote a was revised by removing, "There are no sufficient data on treatment of HCLv."**

HCL-2
- **Evaluate for indications for treatment, "splenic discomfort" was removed.**

HCL-A
- **Initial therapy, "+ rituximab" was added to cladribine as a category 2A recommendation.**
- **Relapsed/Refractory therapy, "interferon-alfa" was clarified as "peginterferon-alfa 2a."**
- **Footnote d was added, "An FDA-approved biosimilar is an appropriate substitute for rituximab."**
- **Footnote f was added, "Interferon alfa has been discontinued. Peginterferon alfa-2a may be substituted for other interferon preparations."**

HCL-C
- **Anti-infective Prophylaxis**
  - **4th bullet was revised, "*Hepatitis B virus (HBV) prophylaxis and monitoring is recommended for high-risk patients.* See Treatment and Viral Reactivation (See NCCN Guidelines for CLL/SLL (CSLL-C 1 of 4)."**
- **Rare Complications of Monoclonal Antibody Therapy**
  - **Bullet was revised by adding, "Re-challenge with the same monoclonal antibody in such settings is not recommended."**
- **Blood Product Support**
  - **Bullet was clarified from, "Recommend irradiated blood products, if available for patients who have received nucleotide analogs to avoid transfusion-associated graft versus-host disease (GVHD)" to "Transfuse according to institutional or published standards" and "Irradiate all blood products to avoid transfusion-associated graft-versus-host disease (GVHD)."**

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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 and hairy cell variant.[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**
- **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:

- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Pregnancy testing in women of childbearing age (if systemic therapy planned)**
- **Discussion of fertility issues and sperm banking**

→ **See Initial Treatment (HCL-2)**

[a]This guideline applies to classic hairy cell leukemia (cHCL), not HCL variant (HCLv).

[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 is characteristically CD25-, CD123-, annexin A1-, and negative for *BRAF* V600E mutations. This helps to distinguish the variant form from cHCL.

[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (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 in that they do not respond well to purine analog therapy and generally have a poorer prognosis. There is evidence that HCLv 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 (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.

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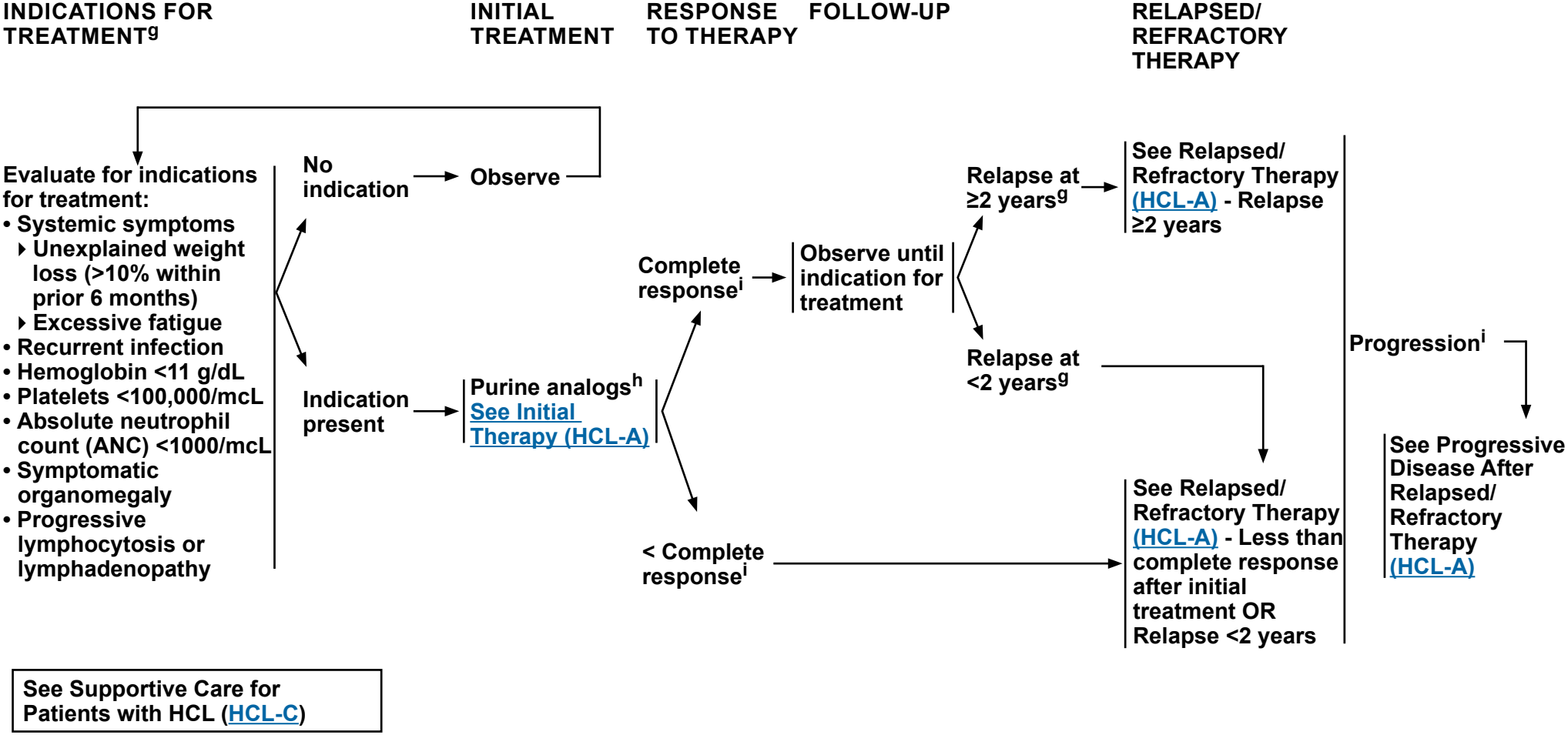
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



See Supportive Care for Patients with HCL (HCL-C)

[g] Grever MR, et al. Blood 2017;129:553-560.
[h] Cladribine and pentostatin are the recommended purine analogs for hairy cell leukemia. 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.
[i] See HCL Response Criteria (HCL-B).

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SUGGESTED TREATMENT REGIMENS[a]

INITIAL THERAPY[b,c,d]

Preferred Regimens
- Purine analogs
  - Cladribine ± rituximab
  - Pentostatin

RELAPSED/REFRACTORY THERAPY[b,d]

	Preferred Regimens	Other Recommended Regimens	Useful Under Certain Circumstances
Less than complete response after initial treatment OR Relapse <2 years	• Clinical trial • Alternative purine analogue + rituximab • Vemurafenib[e]	• Peginterferon-alfa 2a[f] • Alternative purine analogue	• Rituximab, if unable to receive purine analog
Relapse ≥2 years	• Retreat with initial purine analogue + rituximab • Alternative purine analogue + rituximab	• n/a	• Rituximab, if unable to receive purine analog

PROGRESSIVE DISEASE AFTER RELAPSED/REFRACTORY THERAPY[d]

Preferred Regimens
- Clinical trial
- Moxetumomab pasudotox[g]
- Vemurafenib ± rituximab

Other Recommended Regimens
- Ibrutinib[h]

[a] See Suggested Treatment Regimen References (HCL-A 2 of 2).
[b] 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.
[c] Cladribine and pentostatin have not been compared head-to-head in clinical trials, but appear to show comparable therapeutic activity.
[d] 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.
[e] Studied for primary refractory disease and early relapse (1–2 y) after first course of purine analog.
[f] Interferon alfa has been discontinued. Peginterferon alfa-2a may be substituted for other interferon preparations.
[g] See Special Considerations for the Use of Moxetumomab Pasudotox (HCL-D).
[h] See Special Considerations for the Use of Small-Molecule Inhibitors (NCCN Guidelines for CLL/SLL).

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TREATMENT 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.

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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.

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.

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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.

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.

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.

Vemurafenib ± rituximab

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

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.

Tiacci E, De Carolis L, Zaja F, et al. The chemotherapy-free combination of vemurafenib and rituximab produces deep and durable responses in relapsed or refractory hairy cell leukemia (HCL) patients [abstract]. Blood 2017;130:Abstract 409.

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.

Ibrutinib

Jones J, Andritsos L, Kreitman RJ, et al. Efficacy and safety of the bruton tyrosine kinase inhibitor ibrutinib in patients with hairy cell leukemia: stage 1 results of a phase 2 study [abstract]. Blood 2016;128:Abstract 1215.

Moxetumomab pasudotox

Kreitman RJ Dearden C, Zinzani P, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. Leukemia 2018;32:1768-1777.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HCL RESPONSE CRITERIA[a]

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.**
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.**
CR with or without minimal residual disease (MRD)	**In patients who achieved a CR, an immunohistochemical assessment of the percentage of MRD will enable patients to be separated into those with 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 who have 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 vs. 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.

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SUPPORTIVE CARE FOR PATIENTS WITH HCL

Anti-infective Prophylaxis
- Consider herpes virus prophylaxis with acyclovir or equivalent for a minimum of 3 months and until CD4+ T-cell counts ≥200 cells/μL.
- Consider pneumocystis jiroveci pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent for a minimum of 3 months AND until CD4+ T-cell counts ≥200 cells/μL.
- Consider broad-spectrum prophylactic antibacterial coverage during period of neutropenia.
- Hepatitis B virus (HBV) prophylaxis and monitoring is recommended for high-risk patients. See Treatment and Viral Reactivation in the NCCN Guidelines for CLL/SLL (CSLL-C 1 of 4).

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) 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.

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SPECIAL CONSIDERATIONS FOR THE USE OF MOXETUMOMAB PASUDOTOX

TABLE 1: MONITORING FOR CAPILLARY LEAK SYNDROME (CLS) AND HEMOLYTIC UREMIC SYNDROME (HUS)[a]

	CLS	HUS
Monitoring Parameter	**Before every infusion, check:** • Weight • Blood pressure	**Before every infusion, check:** • Hemoglobin levels • Platelet count • Serum creatinine
Assessment	• If weight has increased by 5.5 pounds (2.5 kg) or 5% or greater from Day 1 of the cycle and the patient is hypotensive, promptly check for peripheral edema, hypoalbuminemia, and respiratory symptoms, including shortness of breath and cough. • If CLS is suspected, check for a decrease in oxygen saturation and evidence of pulmonary edema and/or serosal effusions.	If HUS is suspected, promptly evaluate for evidence of hemolysis (blood smear, reticulocyte count, LDH, haptoglobin, and indirect bilirubin).

CLS
- Patients who experience grade 2 or higher CLS should receive appropriate supportive measures, including treatment with oral or intravenous corticosteroids, with monitoring of weight, albumin levels, and blood pressure until resolution.[a]

HUS
- Discontinue moxetumomab pasudotox in patients with HUS. Treat with appropriate supportive measures and fluid replacement, with monitoring of blood chemistry, CBCs, and renal function until resolution.[a]

TABLE 2: CLS GRADING AND MANAGEMENT GUIDANCE[a]

CLS Grade	Moxetumomab Pasudotox Dosing
Grade 2 *Symptomatic; medical intervention indicated*	Delay dosing until recovery of symptoms
Grade 3 *Severe symptoms; medical intervention indicated*	Discontinue moxetumomab pasudotox
Grade 4 *Life-threatening consequences; urgent intervention indicated*	

[a]See prescribing information for moxetumomab pasudotox at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761104s000lbl.pdf.

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus 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.

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Discussion

This discussion corresponds to the NCCN Guidelines for Hairy Cell Leukemia. Last updated: March 11, 2021.

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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.

Literature Search Criteria and Guidelines Update Methodology

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.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

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, showing a round, oval, or indented nucleus with a well-defined 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, the bone marrow may show hypocellularity; which is important to recognize in order to avoid an erroneous diagnosis of aplastic anemia.[2]

HCL-variant tends to be associated with a more aggressive disease course and may not respond to standard HCL therapies.[4] In the WHO classification, classic HCL is considered as a distinct clinical entity, separate from HCL-variant.[5] Therefore, it is necessary to distinguish HCL-variant from classic HCL.

The large majority of HCL (80%–90%) cases are characterized by somatic hypermutation in the immunoglobulin heavy chain variable (*IGHV*) gene.[6,7] The frequency of unmutated *IGHV* is much lower in classic HCL than in HCL-variant (17% vs. 54%; $P < .001$).[7] Unmutated *IGHV* may serve as a prognostic marker for poorer outcomes with conventional therapies since it was associated with primary refractoriness to purine analog monotherapy and more rapid disease progression.[8]

The *BRAF* V600E mutation was reported in the majority of patients with classic HCL.[9-11] Targeted sequencing has also identified recurrent mutations in several other genes (eg, *CDKN1B* in classic HCL; *MAP2K1* and *CCND3* in HCL-variant).[12,13] *BRAF* V600E mutation was absent in 10% to 20% of B-cell lymphoproliferative neoplasms with a classic HCL phenotype expressing *IGHV4-34* rearrangement and also in all cases of HCL-variant.[14-16] A high frequency of *MAP2K1* mutations were reported in HCL-variant and in classic HCL with *IGHV4-34* rearrangement.[17]

Immunophenotyping is the primary methodology used to distinguish classic HCL from HCL-variant, though the role of molecular analysis is rapidly expanding. *BRAF* V600E mutation may serve as a reliable molecular marker to distinguish classic HCL from HCL-variant and other B-cell leukemias or lymphomas, and *MAPK1* mutation analysis may be useful to distinguish HCL-variant from classic HCL in *BRAF* mutation-negative cases.[15-17]

IHC or flow cytometry panel for immunophenotyping should include CD19, CD20, CD5, CD10, CD11c, CD22, CD25, CD103, CD123, cyclin D1, and CD200. The typical immunophenotype for classic HCL shows CD5-, CD10-, CD11c+, CD20+(bright), CD22+, CD25+, CD103+, CD123+, cyclin D1+, annexin A1+, and CD200+ (bright).[16] In contrast, HCL-variant 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 classic HCL from HCL-variant and other splenic B-cell lymphomas.[16,18,19] HCL expressing *IGHV4-34* rearrangement has a less favorable prognosis than classic HCL and does not respond well to purine analog-based therapy.[20] Molecular analysis to identify the *IGHV4-34* rearrangement may be useful to distinguish classic HCL from HCL with *IGHV4-34* rearrangement.

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 excretion of drugs 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.

Biosimilars

A biosimilar is a biological product that is highly similar to the FDA-approved reference biological product with the exception of minor differences in clinically inactive components and no clinically meaningful differences in safety, purity, or potency.[21]

Pharmacokinetic (drug exposure) and pharmacodynamic (response) studies in the appropriate patient population are essential to demonstrate the efficacy and safety of the biosimilar.[22] Biosimilars require only one clinical trial to demonstrate equivalent safety and efficacy in the most sensitive indication for the reference biological product. If the mechanism of action, pharmacokinetics, and pharmacodynamics are similar, the biosimilar may be approved for all of the same indications as the reference biological product and can be substituted for the reference biological product.[22]

Extrapolation of clinical and safety data from one indication to other approved indications is a key concept in the development of biosimilars that potentially provides substantial cost savings in oncology care, as biosimilars are typically more affordable than their reference products. Extrapolation should only be considered for indications where the mechanism of action is identical to that studied in the pivotal trial.

Alternating between the biosimilar and the reference product is acceptable without the intervention of a health care provider only if a biosimilar is designated as interchangeable since such a substitution will not result in higher toxicity or diminished efficacy.[21] However, alternating between the biosimilar and reference product is not recommended, if the biosimilar is not designated as interchangeable.

The guidelines recommend the use of an FDA-approved biosimilar as an appropriate substitute for rituximab. The approval is based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic data, clinical immunogenicity data, and other clinical data that demonstrate these are biosimilar to rituximab in terms of safety and efficacy. These biosimilars have not been approved as interchangeable biological products. Therefore, during a single course of therapy, the patient should remain on the same product that was used to initiate treatment throughout the course of the treatment.

Treatment Guidelines

The current NCCN Guidelines apply to patients with classic HCL. Regimens are stratified into three categories (based on the evidence, efficacy, toxicity, preexisting comorbidities, and in some cases 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 management of patients with HCL-variant. However, cladribine + rituximab[23-25] and ibrutinib[26-28] have been shown to be effective in small cohorts of patients with HCL-variant. Participation in a clinical trial and referral to a medical center with expertise in the management of these patients 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 <11g/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.[29-44]

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 overall survival (OS) rate of 96% at 48 months.[32] Extended follow-up confirmed the durability of responses with cladribine.[35] 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 responders. 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% vs.11%; *P* < .0001) and longer median relapse-free survival (RFS; not reached vs. 20 months; *P* < .0001) compared with interferon alpha.[30] After a median follow-up of 9 years, the estimated 5-year and 10-year OS rate for patients initially treated with pentostatin was 89% and 80%, respectively.[33] The corresponding RFS rate was 86% and 66%, respectively. Survival outcomes were not significantly different between treatment arms, although this analysis was complicated by the cross-over 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.[45]

Rituximab 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.[24,46] 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%.[24] After a median follow-up of 60 months, the 5-year failure-free survival (FFS) and OS rates were 95% and 97%, respectively. In another phase II study, 68 patients with previously untreated HCL were randomized to receive cladribine in combination with concurrent versus delayed rituximab. This study showed that the probability of achieving CR with undetectable minimal residual disease (MRD) was higher with the use of concurrent rituximab.[46] After a median follow-up of 96 months, the undetectable MRD 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.

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.[47-51]

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).[49] 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 rate was 94% and 97%, respectively, for intravenous and subcutaneous cladribine.[50] 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.[51] 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.

Dosing Schedules of Purine Analogs

Weekly infusion of cladribine was also shown to have similar safety and efficacy to daily continuous infusion.[52-55]

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.[55] 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%).

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.[41,42] Observation until there is an indication for additional treatment is recommended for patients who achieve a CR after initial treatment with purine analog.

The clinical relevance of MRD status in patients with disease responding to therapy remains uncertain at this time.[24,56-58] In a phase II study that evaluated cladribine followed by rituximab in patients with previously untreated and relapsed HCL, undetectable MRD 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.[24] In contrast, other studies have shown that undetectable MRD in peripheral blood at 6 months after initial treatment with purine analogs is associated with a low likelihood of disease relapse.[57,58]

Relapsed/Refractory or Progressive Disease

Purine Analog ± Rituximab

Pentostatin and cladribine are also effective for the treatment of relapsed/refractory HCL.[33,36,59] 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 failure of initial interferon treatment, the 5-year and 10-year OS rates were 93% and 85%, respectively.[33] The corresponding RFS rate was 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.[35,38,43] In the long-term follow-up of a study that evaluated cladribine as initial treatment, relapse occurred in 37% of initial responders, with a median time to relapse of 42 months.[35] 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.[24,46,60] In a retrospective study of 18 patients with previously treated HCL relapsing after purine analog monotherapy (median two prior therapies), rituximab in combination with pentostatin or cladribine resulted in a CR rate of 89%.[60] 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 rate were 100%.

Vemurafenib ± Rituximab

Vemurafenib monotherapy (*BRAF* V600E kinase inhibitor; 960 mg twice daily) was evaluated in two separate phase II multicenter studies in patients with HCL refractory to purine analogues or those with relapsed disease after treatment with a purine analogue.[61] 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 who 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 therapy and the 1-year progression-free survival (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.[62] 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 undetectable MRD in most patients with relapsed/refractory HCL. 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.[63] 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 undetectable MRD (100% at a median of 31 months) than in patients with CR and detectable MRD (44% at a median of 25 months).

Moxetumomab Pasudotox

Moxetumomab pasudotox (CD22-directed recombinant immunotoxin) is approved for the treatment of relapsed or refractory HCL after at least two prior therapies. In a single-arm, open-label study of 80 patients with relapsed or refractory HCL, moxetumomab pasudotox resulted in an ORR of 75% (41% CR and 34% PR).[64] Among 33 patients in CR, undetectable MRD (as measured by IHC) was achieved in 27 patients (85%). Long-term follow-up data confirmed that moxetumomab pasudotox resulted in a high rate of durable responses with a manageable safety profile in patients with heavily pretreated HCL.[65] After a median follow-up of 25 months, the ORR was 75% (41% CR) and the median PFS was 42 months. The undetectable MRD status was 34% for all patients (82% for patients who achieved a CR).

Peripheral edema (39%), nausea (35%), fatigue (34%), and headache (33%) were the most frequent adverse events.[64] Decreased lymphocyte count (8%), hemolytic uremia syndrome (5%), and capillary leak syndrome (5%) were the most common grade 3 or 4 adverse events, which were

generally manageable with supportive care and treatment discontinuation. The pooled safety analysis of 165 patients with hematologic malignancies (129 patients with HCL) treated with moxetumomab pasudotox in clinical trials also demonstrated an acceptable safety profile with few treatment-related discontinuations (10%).[66] Hemolytic uremia syndrome (4%) and capillary leak syndrome (2%) were the most common adverse events associated with treatment discontinuations. Hemolytic uremia syndrome and capillary leak syndrome should be managed with close monitoring of vital signs and laboratory values (blood pressure, body weight, blood creatinine, and schistocytes in peripheral blood smear) and appropriate supportive care measures (adequate hydration and oral or intravenous corticosteroids).

Ibrutinib

In a phase II study of 28 patients with relapsed HCL (17 patients with classic HCL), ibrutinib (Bruton's tyrosine kinase inhibitor) resulted in an ORR of 46%.[26] At median follow-up of 22 months, the estimated 24-month PFS rate was 79% and the median PFS was not reached.

Lymphopenia (21%), neutropenia (18%), lung infection (18%), thrombocytopenia (14%), hypertension (11%), and hypophosphatemia (11%) were the most common grade ≥3 adverse events. Grade 1 or 2 atrial fibrillation was observed in five patients but no grade ≥3 atrial fibrillation or bleeding were reported. The benefit and risk of ibrutinib should be evaluated in patients requiring anti-platelet or anticoagulant therapies.

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), alternate purine analog + rituximab,[24,46,60] or vemurafenib monotherapy[61,62] 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. Alternate purine analog monotherapy is included as the other recommended treatment option.[33,36,59]

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.[24,46,60] 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% to 53% CR) and the median duration of response was 32 to 34 months.[67-70] 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.[71-73] 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),[61,62,74] or moxetumomab pasudotox[64,65] are the preferred treatment options for progressive disease following second-line therapy. Ibrutinib is included as other recommended regimen.[26]

Supportive Care

Infections

Patients with HCL are susceptible to infectious complications due to treatment with purine analogs.[75] Acyclovir or equivalent is recommended for herpes virus prophylaxis, and sulfamethoxazole trimethoprim or equivalent is recommended for pneumocystis jirovecii pneumonia (PJP)

prophylaxis.[76] Anti-infective prophylaxis for a minimum of 3 months and until CD4+ T-cell count is ≥200 cells/mm^3 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 use 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.[77] 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.[78] 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.[79] HBV prophylaxis and monitoring is recommended in high-risk patients 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.[80] 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. Re-challenge with the same anti-CD20 monoclonal antibody (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.[81,82]

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.[83-85] 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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