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Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hairy Cell Leukemia

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To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/clinicians.aspx](#).

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

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

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Updates in Version 3.2019 of the NCCN Guidelines for Hairy Cell Leukemia from Version 2.2019 include:

[MS-1](#)

- The discussion section was updated to reflect the changes in the algorithm.
-

Updates in Version 2.2019 of the NCCN Guidelines for Hairy Cell Leukemia from Version 1.2019 include:

[HCL-2](#)

- Relapsed/Refractory Therapy
 - Progression: "Moxetumomab pasudotox" was added as a category 2A recommendation.

[HCL-D](#)

- A new page, "Special Considerations for the Use of Moxetumomab Pasudotox" was added.
-

Updates in Version 1.2019 of the NCCN Guidelines for Hairy Cell Leukemia from Version 2.2018 include:

[HCL-2](#)

- Relapsed/Refractory Therapy
 - "< Complete response": "Vemurafenib" was added.
- Footnote k for vemurafenib was revised from "Should be non-responsive to purine analog therapy" to "Studied for primary refractory disease and early relapse (1–2 y) after first course of purine analog."

[HCL-C](#)

- Anti-infective Prophylaxis
 - 1st bullet was revised: "Consider herpes virus prophylaxis with acyclovir or equivalent for a minimum of 2 3 months and until ~~GD4~~ ≥ 200 cells/mm $CD4^+$ T-cell counts ≥ 200 cells/ μ L."
 - 2nd bullet was revised: "Consider PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent for a minimum of 2 3 months and AND until ~~GD4~~ ≥ 200 cells/mm $CD4^+$ T-cell counts ≥ 200 cells/ μ L."
- Rare Complications for Monoclonal Antibody Therapy
 - 1st bullet, 2nd sentence was revised from "Expert consultation with dermatology is recommended" to "Consultation with a dermatologist is recommended for management of these complications."
- A new section for "Blood products" was added with the following bullet: "Recommend irradiated blood products, if available for patients who have received nucleotide analogs to avoid transfusion-associated GVHD."

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
- IHC or molecular studies for *BRAF* V600E mutation

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: *IGHV4-34* rearrangement^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 testing^f if treatment contemplated
- Pregnancy testing in women of child-bearing age (if systemic therapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Discussion of fertility issues and sperm banking

See Initial
Treatment (HCL-2)

^aThis guideline applies to classic hairy cell leukemia (cHCL), not hairy cell variant (HCLv). There are no sufficient data on treatment of HCLv.

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

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

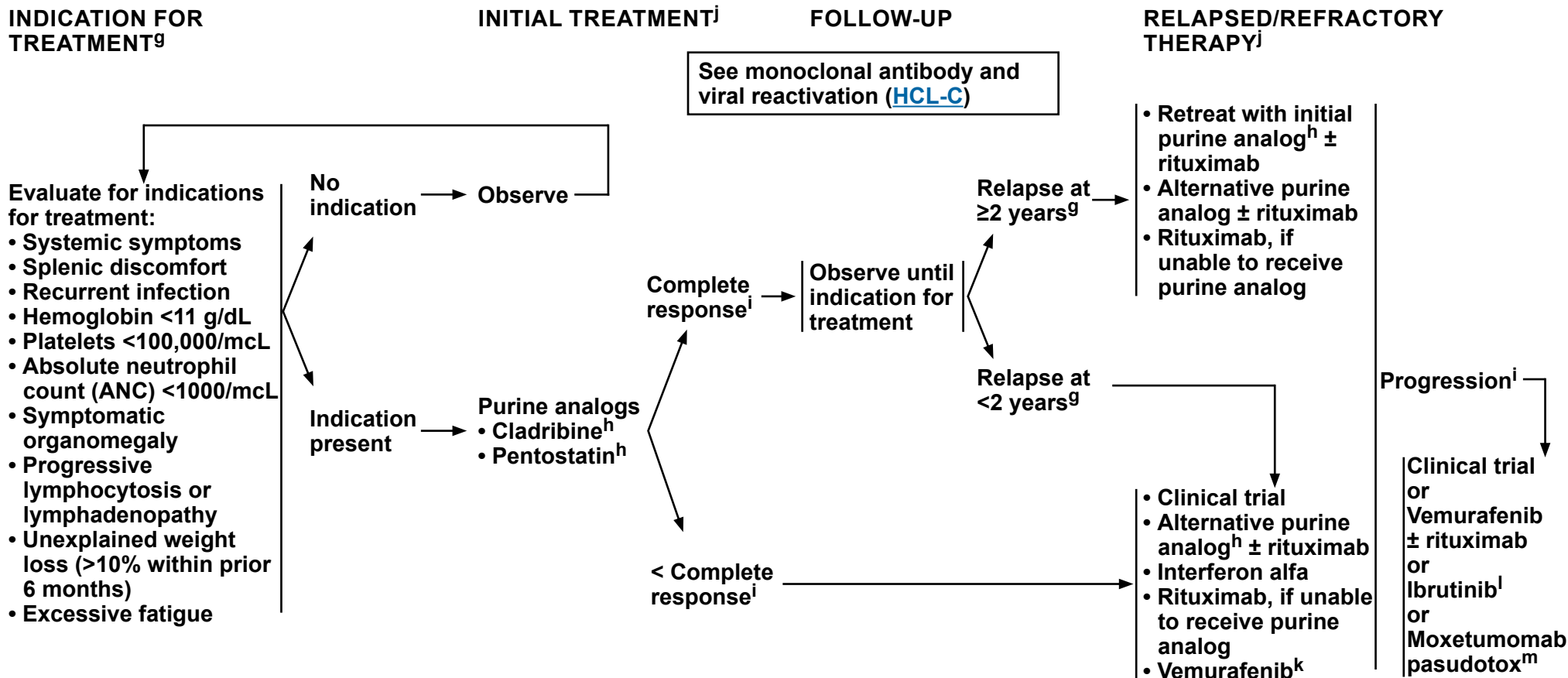
^dSee [NCCN Guidelines for B-Cell Lymphomas](#), Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

^eHCL with *IGHV4-34* rearrangement behaves more like HCLv, although it has a morphology and immunophenotype like cHCL. *IGHV4-34* HCL typically lacks *BRAF* V600E mutations, does not respond well to purine analog therapy, and has a relatively poorer prognosis compared to cHCL. There is evidence that HCLv and *IGHV4-34* HCL often show mutations in *MAPK1*.

^fHepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). 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.



^gGrever 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.

^hStandard-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.

ⁱSee HCL Response Criteria (HCL-A).

^jSee Treatment References (HCL-B).

^kStudied for primary refractory disease and early relapse (1–2 y) after first course of purine analog.

^lSee NCCN Guidelines for CLL/SLL, Special Considerations for the Use of Small-Molecule Inhibitors.

^mSee Special Considerations for the Use of Moxetumomab Pasudotox (HCL-D).

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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).

^aGrever 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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TREATMENT REFERENCES

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Moxetumomab pasudotox

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SUPPORTIVE CARE

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/ μ L.
- 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/ μ L.
- Consider broad-spectrum prophylactic antibacterial coverage during period of neutropenia.

Treatment and Viral Reactivation

- [See 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, Steven-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Consultation with a dermatologist is recommended for management of these complications.

Rituximab Rapid Infusion

- If no infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.

Growth Factors

- Neutrophil growth factor with granulocyte colony-stimulating factor (G-CSF) is indicated in cases of neutropenic fever following chemotherapy.

Blood Product Support

- Recommend irradiated blood products, if available for patients who have received nucleotide analogs to avoid transfusion-associated 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: <ul style="list-style-type: none"> • Weight • Blood pressure 	Before every infusion, check: <ul style="list-style-type: none"> • Hemoglobin levels • Platelet count • Serum creatinine
Assessment	<ul style="list-style-type: none"> • 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 check blood LDH, indirect bilirubin, and blood smear schistocytes for evidence of hemolysis.

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, complete blood counts, and renal function until resolution.^a

TABLE 2: CLS GRADING AND MANAGEMENT GUIDANCE^a

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

^aSee Prescribing information for moxetumomab pasudotox at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761104s000lbl.pdf.

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Discussion

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 noted.

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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 blood. 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 recurrent infection, including opportunistic.³

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.⁴

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 PubMed search resulted in 31 citations and their potential relevance was examined. 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

Morphological 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.^{5,6} 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.^{5,6}

The large majority of HCL (80–90%) is characterized by somatic hypermutation in immunoglobulin heavy chain variable (*IGHV*) gene.^{7,8} The frequency of unmutated *IGHV* is much lower in classic HCL than in HCL-variant (17% vs 54%, $P < .001$).⁸ 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.⁹

The *BRAF* V600E mutation was reported in the majority of patients with classic HCL but not in other B cell leukemias or lymphomas.¹⁰⁻¹³ *BRAF* V600E mutation is also absent in all cases of HCL-variant and in classic HCL expressing *IGHV4-34* rearrangement.^{14,15} Thus, *BRAF* V600E mutation may serve as a reliable molecular marker to distinguish classic from HCL-variant and other B-cell leukemias or lymphomas.

In addition to *BRAF* V600E mutation, targeted sequencing identified recurrent mutations in several other genes (eg. *CDKN1B* in classic HCL; *MAP2K1* and *CCND3* in HCL-variant).¹⁶ A high frequency of *MAP2K1* mutations were reported in HCL-variant and in classic HCL with *IGHV4-34* rearrangement.¹⁷ *MAPK1* mutation analysis may be useful to distinguish HCL-variant from classic HCL in *BRAF* mutation-negative cases.

In comparison to classic HCL, HCL-variant tends to be associated with more aggressive disease course and may not respond to standard HCL therapies.^{15,18} The 2008 WHO classification determined that classic HCL should be considered as a distinct clinical entity, separate from HCL-variant.^{5,6} Therefore, it is necessary to distinguish HCL-variant from classic HCL. Immunophenotype is the primary methodology used to distinguish classic HCL from HCL-variant, though the role of molecular analysis is rapidly expanding.

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).¹⁵ In contrast, HCL-variant is characteristically CD25-, CD123-, annexin A1- and negative for *BRAF* V600E mutation.¹⁵ IHC or molecular studies for *BRAF* V600E mutation is useful for the distinction of classic HCL from HCL-variant and other splenic B-cell lymphomas.^{15,19,20}

HCL expressing *IGHV4-34* rearrangement has a less favorable prognosis and does not respond well to purine analog-based therapy.²¹ 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 CBC with differential, measurements of serum lactate dehydrogenase (LDH) levels and a comprehensive metabolic panel. In particular, 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.

Initial Treatment

Purine analogs (pentostatin²²⁻²⁸ and cladribine²⁷⁻³⁵) have shown significant monotherapy activity, resulting in durable remissions in patients with previously untreated HCL. Pentostatin and cladribine have not been compared head to head, but appear to show comparable therapeutic activity.

In a phase III intergroup study that randomized 319 patients with previously untreated HCL to pentostatin versus interferon alpha, pentostatin resulted in significantly higher complete remission (CR) rate (76% vs. 11%; $P < .0001$) and longer median relapse-free survival (RFS; not reached vs. 20 months; $< .0001$) compared with interferon alpha. The median follow up was 57 months.²³ After a median follow-up of 9 years, the estimated 5-year and 10-year overall survival (OS) rate for patients initially treated with pentostatin was 89% and 80%, respectively.²⁴ 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%). In a study of 358 patients with untreated HCL, cladribine resulted in a CR rate of 91% with a median response duration of 52 months and an OS rate of 96% at 48 months.³⁰ Extended follow-up confirmed the durability of responses with cladribine.³¹ After 7 years of follow-up, of the 207 evaluable patients, 95% achieved CR and 5% achieved partial remission (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%).

Different routes of administration (subcutaneous versus intravenous) and dosing schedules (weekly versus daily schedule) of cladribine have been evaluated. 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.³⁶⁻⁴⁰ In a prospective study, reduced dose subcutaneous cladribine (total dose of 0.5 mg/kg given as 0.1mg/kg/d x 5 days) had similar efficacy but lower toxicity than standard dose subcutaneous cladribine (total dose of 0.7 mg/kg; given as 0.1mg/kg/d x 7 days).³⁹ 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.⁴⁰ After median follow-up of 33.5 months, subcutaneous cladribine was associated with a more favorable 3-year event-free survival 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.

Weekly infusion of cladribine was also shown to have similar safety and efficacy to daily continuous infusion.⁴¹⁻⁴⁴ 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.⁴⁴ There were no significant differences in the toxicity profile between the 2 treatment arms after 10 weeks (grade 3 or 4 neutropenia, 90% vs. 80%; acute infection, 44% vs. 40%; and erythrocyte support, 22% vs. 30%).

Long-term clinical trial follow-up data suggests that treatment with interferon alpha (induction and maintenance therapy) results in durable disease control.⁴⁵⁻⁴⁷ However, with the advent of purine analogs, the role of interferon alpha as initial treatment for HCL is very limited. Interferon alpha may be useful for the management of relapsed or refractory disease.

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. 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%.⁴⁸ After a

median follow up of 60 months, the 5-year failure-free survival (FFS) and OS rate was 94.8% and 96.8%, respectively.

Relapsed/refractory Disease or Progressive Disease

Pentostatin and cladribine are also effective for the treatment of relapsed HCL.^{24,26,27} 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 93% and 85%, respectively. The corresponding RFS rate was 84% and 69%, respectively.²⁴ 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.^{31,34} 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.³¹ 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.^{48,49} In a phase II study that included 14 patients with relapsed HCL, cladribine followed by rituximab resulted in a CR rate of 100%.⁴⁸ After a median follow up of 60 months, the 5-year FFS and OS rate were 100%. In a retrospective study of 18 patients with previously treated HCL relapsing after purine analog monotherapy (median 2 prior therapies), rituximab in combination with pentostatin or cladribine resulted in a CR rate of 89%.⁴⁹ CR was maintained in all patients after a median follow up of 36 months and the estimated 3-year recurrence rate was 7%.

Rituximab monotherapy has modest activity in HCL that has relapsed after initial treatment with purine analog.⁵⁰⁻⁵³ In a small cohort of 10 patients with HCL progressing on prior therapy with cladribine or pentostatin, rituximab monotherapy resulted in an ORR of 50% with CR in only 10% of patients.⁵⁰ In another study of 24 patients with relapsed HCL after prior therapy with cladribine, rituximab induced an ORR of only 25% with CR in 13%.⁵¹ In a smaller study of 15 patients with relapsed or primary refractory HCL after treatment with purine analogs, 8 weekly doses of rituximab (rather than the standard 4 weekly doses) resulted in ORR and CR rate of 80% and 53%, respectively.⁵² In another phase II study of 25 patients with less heavily pretreated HCL relapsing after cladribine, the ORR and CR rate with rituximab was 80% and 32%, respectively.⁵³

More recently, tyrosine kinase inhibitors such as vemurafenib (BRAF V600E kinase inhibitor) and ibrutinib (Bruton's tyrosine kinase inhibitor) demonstrated activity in relapsed or refractory HCL.

Vemurafenib (960 mg twice daily) monotherapy 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.⁵⁴ 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, the progression-free survival (PFS) and OS rates was 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.⁵⁵ 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.

In another phase II trial of 31 patients with relapsed/refractory HCL after treatment with purine analogs (25 evaluable patients), vemurafenib in combination with rituximab resulted in a CR rate of 100%, which is higher than that observed with vemurafenib alone and the PFS rate was 100% after a median of 14 months of treatment.⁵⁶ In addition, minimal residual disease (MRD; measured by allele-specific polymerase chain reaction [PCR]) was undetectable (10^{-4} sensitivity) in the bone marrow in 65% of patients.

In a phase II study of 28 patients with relapsed HCL (17 patients with classic HCL), ibrutinib resulted in an ORR of 46%.⁵⁷ 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 5 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.

Moxetumomab pasudotox (CD22-directed recombinant immunotoxin) was recently approved for the treatment of relapsed or refractory HCL after at least 2 prior therapies. In a single-arm, open-label study (N=80), treatment of patients with relapsed or refractory HCL with moxetumomab pasudotox resulted in an ORR of 75% (41% CR and 34% PR).⁵⁸ Among 33 patients in CR, undetectable MRD (as measured by IHC) was achieved in 27 patients (85%). Peripheral edema (39%), nausea (35%), fatigue (34%), and headache (33%) were the most frequent adverse events. 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. Hemolytic uremia syndrome and capillary leak syndrome were managed with close monitoring of vital signs and laboratory values (including blood pressure, body weight, blood creatinine, and schistocytes in peripheral blood smear) and supportive medical care including adequate hydration.

Treatment Guidelines

The current NCCN Guidelines apply to patients with classic HCL. At the present time, there is insufficient data to determine the optimal management 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 judgement is required in the decision to initiate therapy, since not all newly diagnosed patients with HCL will require immediate treatment. 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

Asymptomatic disease is best managed by close observation (“watch and wait” approach), until indications develop. First-line therapy with a purine analog (cladribine or pentostatin) is recommended for patients with an indication for treatment. Both agents have shown significant activity, resulting in durable remissions in patients with previously untreated HCL. However, data from randomized controlled trials are not

available to compare the efficacy of one purine analog to the other. In light of the high response rates of purine analog monotherapy, the role of rituximab in management of patients with untreated HCL is unclear and is generally not recommended as initial treatment.

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.²

Response Assessment and Additional Therapy

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.^{27,35} The clinical relevance of MRD status in patients with disease responding to therapy remains uncertain at this time. 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.⁴⁸ However, MRD-positivity during follow up did not necessarily result in clinically relevant risk for relapse.

Observation until there is an indication for additional treatment is recommended for patients who achieve a CR after initial treatment with purine analog. Clinical trial, alternate purine analog ± rituximab, interferon alpha, rituximab monotherapy (if unable to receive purine analog) or vemurafenib are included as options for patients with less than a CR to initial treatment with purine analogs.

Second-line Therapy for Disease Relapse or Progressive Disease

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

Patients with disease relapse after ≥2 years after achieving CR to initial therapy with purine analog may benefit from retreatment with the same purine analog or treatment with an alternative purine analog with or without rituximab. Rituximab monotherapy is included an option for patients unable to receive purine analog.

Clinical trial (if available) is recommended for patients with disease relapse within 2 years after achieving CR to initial therapy and for those with progressive disease following second-line therapy.

Treatment with an alternate purine analog ± rituximab, interferon alpha, rituximab monotherapy (if unable to receive purine analog) or vemurafenib are included as options for patients with disease relapse within 2 years after achieving CR to initial therapy.

Ibrutinib, vemurafenib (with or without rituximab) or moxetumomab pasudotox are appropriate options for progressive disease following second-line therapy.

Supportive Care

Infections

Patients with HCL are susceptible to infectious complications due to treatment with purine analogs.⁵⁹ Acyclovir or equivalent is recommended for herpes virus prophylaxis and sulfamethoxazole trimethoprim or equivalent is recommended for pneumocystis jiroveci pneumonia (PJP) prophylaxis.⁶⁰ 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.

Available evidence suggests that the use of granulocyte-colony stimulating factors (GCSF) shortens the duration of severe neutropenia after treatment with cladribine; however, it has no clinically significant impact on infection related outcomes.⁶¹ The use of GCSF might be considered in patients with severe neutropenic fever following chemotherapy. Broad-spectrum antibacterial prophylaxis should be considered for patients with neutropenia.

Hepatitis B virus Reactivation

HBV reactivation leading to fulminant hepatitis, hepatic failure and death have been reported in patients receiving chemotherapy and immunosuppressive therapy.⁶² 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) is 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.⁶³ 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.

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