National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hairy Cell Leukemia

Version 2.2018 — September 26, 2017

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Clinical Trials: NCCN believes that the best management for any cancer patient 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/physician.html.

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

HCL-1

- Footnote f was revised, "Hepatitis B testing is indicated because of the risk of reactivation *during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy)* ~~with immunotherapy + chemotherapy.~~"

MS-1

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

Updates in Version 1.2018 of the NCCN Guidelines for Hairy Cell Leukemia from Version 2.2017 include:

HCL-1

- Diagnosis, Essential
  - 1st bullet was revised, "*Bone marrow biopsy ± aspirate*: Presence of characteristic hairy cells upon morphologic examination of peripheral blood *or bone marrow* and characteristic infiltrate with..."
  - 2nd bullet was revised, "~~IHC and flow cytometry are~~ *Adequate immunophenotyping is* essential for establishing..."
    - ◊ Sub-bullet was revised, "IHC *or flow cytometry* for ~~panel~~: CD19, CD20, CD5, CD10, CD11c, CD22, CD25, CD103, CD123, cyclin D1 *and CD200*."
  - 3rd bullet was revised, "IHC *or molecular studies* for BRAF V600E mutation"
- Diagnosis, Useful Under Certain Circumstances
  - 1st bullet was clarified, "Molecular analysis to detect: IGHV*4-34 usage* ~~mutational status~~"
  - Two bullets were removed, "sequencing of BRAF for V600E mutation if IHC equivocal' and "annexin A1."
- Workup, Essential
  - 1st bullet was clarified from "Physical exam: Presence of enlarged spleen and/or liver; presence of peripheral lymphadenopathy (uncommon)" to "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)."
- Footnotes
  - Footnote b was revised, "*HCLv* is characteristically CD25-, CD123- , annexin A1- *and negative for BRAF V600E mutations*. This helps to distinguish the variant form from classical HCL."
  - Footnote c, "CD200+ (bright)" was added.
  - Footnote e was added, "HCL 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."

HCL-2

- Indication for Treatment was revised by changing hemoglobin from "<12 g/dL" to "<11g/dL" and adding "Symptomatic organomegaly, progressive lymphocytosis or lymphadenopathy, unexplained weight loss (>10% within prior 6 months), and excessive fatigue."
- After follow-up, the relapse criteria were changed from "Relapse at ≥1 year "to "Relapse at ≥2 years" and from "Relapse at <1 year" to "Relapse at <2 years."
- Relapsed/refractory therapy,
  - For "Relapse at ≥2 years" and "< Complete response," "Rituximab, if unable to receive purine analog" was added.
- Progression after relapsed/refractory therapy
  - "Clinical trial" was added.
- Footnotes
  - Footnote f was added, "Grever MR, Abdel-Wahab O, Andritsos, et al. Consensus guidelines for the diagnosis and management of patients with classical hairy cell leukemia. Blood 2017;129:553-560."
  - Footnote g was revised, "~~Cladribine~~ *Purine analogs* should not be administered to patients with active life-threatening or chronic infection. *Treat active infection prior to initiating treatment with purine analogs. If it is not possible to control infection, consider initiating treatment with low-dose pentostatin before using regular-dose purine analogs to secure a durable response.*"
  - Footnote h, the complete response criteria were replaced with a link to HCL-A with a detailed table for Response Criteria.
  - Footnote k was added, "See NCCN Guidelines for CLL/SLL, Special Considerations for the Use of Small-Molecule Inhibitors (CSLL-F 1 of 2)."

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Updates in Version 2.2018 of the NCCN Guidelines for Hairy Cell Leukemia from Version 2.2017 include:

HCL-A

- **Response criteria were added.**

HCL-C

- **Content for "Tumor Lysis Syndrome" was removed.**
- **A new section for "Anti-infective Prophylaxis" was added with the following bullets:**
  - **"Consider herpes virus prophylaxis with acyclovir or equivalent for a minimum of 2 months and until CD4 ≥200 cells/mm."**
  - **"Consider PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent for a minimum of 2 months and until CD4 ≥200 cells/mm."**
  - **"Consider broad-spectrum prophylactic antibacterial coverage during period of neutropenia."**
- **A new section for "Growth Factors" was added with the following bullet:**
  - **"Neutrophil growth factor with GCSF is indicated in cases of neutropenic fever following chemotherapy."**

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 hairy cell leukemia and hairy cell variant.[b,c,d]**
  - **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**
- **LDH**
- **Bone marrow biopsy ± aspirate**
- **Hepatitis B testing[f] if treatment contemplated**
- **Pregnancy testing in women of child-bearing age (if systemic therapy or RT 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)

[a]This guideline applies to classic hairy cell leukemia (cHCL), not hairy cell variant (HCLv). There are no sufficient data on treatment of HCLv.

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

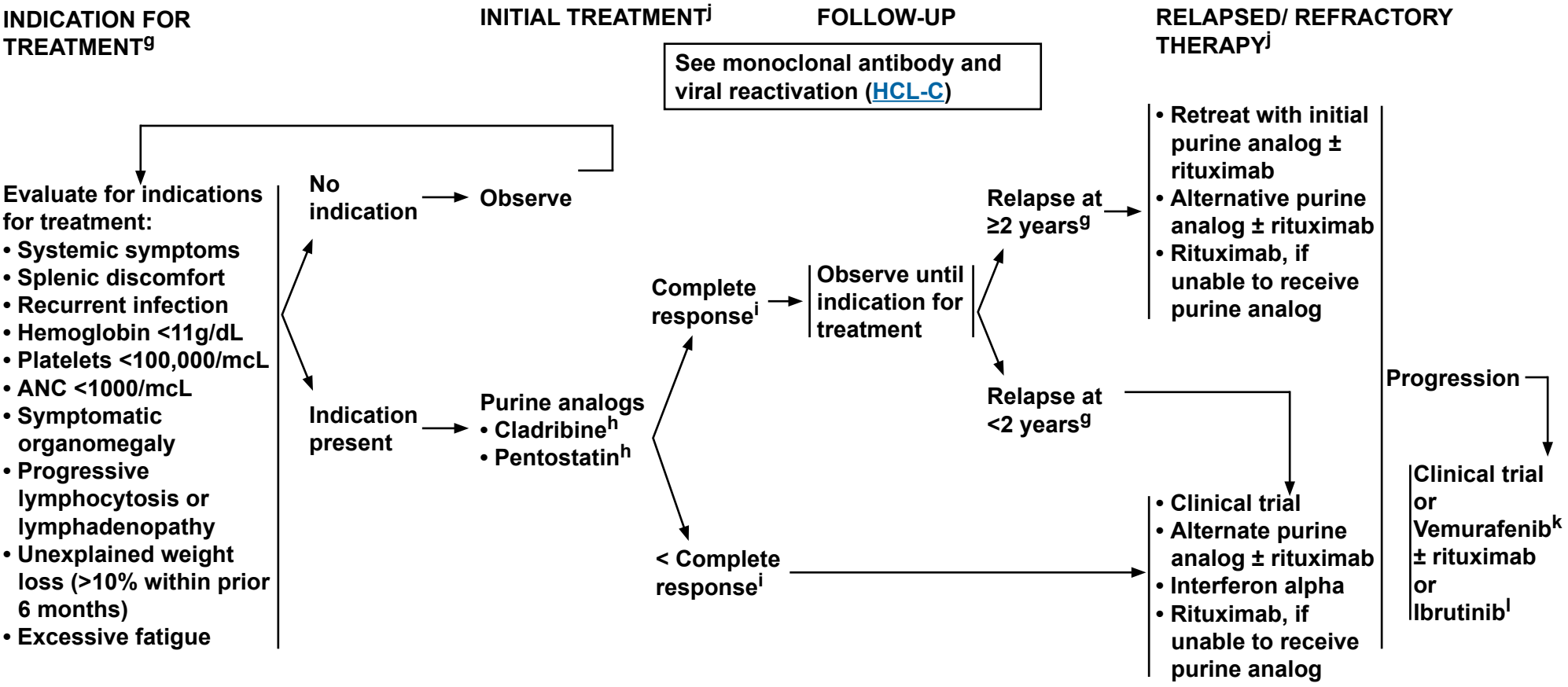
[c]HCLv is characteristically CD25-, CD123-, annexin A1- and negative for BRAF V600E mutations. This helps to distinguish the variant form from classical HCL.

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

[e]HCL 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*.

[f]Hepatitis 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.

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



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

[h]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 Response Criteria (HCL-A).

[j]See Treatment References (HCL-B).

[k]Should be non-responsive to purine analog therapy.

[l]See NCCN Guidelines for CLL/SLL, Special Considerations for the Use of Small-Molecule Inhibitors (CSLL-F 1 of 2).

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HCL RESPONSE CRITERIA[a]

Complete response	**Near normalization of peripheral blood counts: hemoglobin >11 g/dL (without transfusion); platelets >100,000/mcL; absolute neutrophil count >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 iminimal 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	**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	**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	**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, 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

Purine analog monotherapy

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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.

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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

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Rituximab

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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.

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

SUPPORTIVE CARE

Anti-infective Prophylaxis

- Consider herpes virus prophylaxis with acyclovir or equivalent for a minimum of 2 months and until CD4 ≥200 cells/mm.
- Consider PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent for a minimum of 2 months and until CD4 ≥200 cells/mm.
- 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 with 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. Expert consultation with dermatology is recommended.

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 GCSF is indicated in cases of neutropenic fever following chemotherapy.

For other immunosuppressive situations, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

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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 and lymph nodes. 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 opportunistic infections.[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 between published between May 2016 and April 2017. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only 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 36 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting 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 on the NCCN website.

Diagnosis

Morphological evaluation of peripheral blood smears, 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 is characteristic of HCL.[5,6] Examination of bone marrow biopsy samples shows hairy cell infiltrates with increased reticulin fibers, which frequently results in a "dry" tap. In some patients with HCL, the bone marrow may show hypocellularity; this 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 gene (*IGHV*).[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 factor for poorer outcomes with conventional therapies since it has been associated with primary refractoriness to purine analog monotherapy, and more rapid disease progression.[9] The *BRAF* V600E mutation has been reported in majority of patients with classic HCL but not in other B-cell leukemias or lymphomas.[10-13] *BRAF* V600E mutation in also absent in all cases of HCL-variant and in classic HCL expressing *IGHV4-34* rearrangement.[14,15] Thus, *BRAF* V600E mutation may potentially serve as a reliable molecular marker to

distinguish HCL from HCL-variant and other B-cell leukemias or lymphomas.

In comparison to classic HCL, HCL-variant tends to be associated with a more aggressive disease course and may not respond to standard HCL therapies.[15,16] 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. Immunophenotyping 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.[15,17,18]

HCL expressing *IGHV4-34* rearrangement has a relatively poorer prognosis and does not respond well to purine analog therapy.[19] Molecular analysis to determine *IGHV4-34* rearrangement may be useful to distinguish classic HCL from HCL with *IGHV4-34* rearrangement. A high frequency of *MAP2K1* mutations were recently reported in HCL-variant and in classic HCL with *IGHV4-34* rearrangement.[20] *MAPK1* mutation analysis may be useful to distinguish HCL-variant from classic HCL in *BRAF* mutation-negative cases.

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/or chemotherapy. CT scans (with contrast of diagnostic quality) of the chest, abdomen and/or pelvis may be useful under certain circumstances.

Treatment Options

Initial Treatment

Purine analogs such as pentostatin[21-27] and cladribine[26-34] 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 clinical activity.

In a phase III intergroup study that randomized 319 previously untreated patients in 1:1 fashion to pentostatin vs interferon alpha, pentostatin resulted in significantly higher complete response (CR) rates (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.[22] After a median follow-up of 9.3 years, the estimated 5-year and 10-year

overall survival (OS) rates for patients initially treated with pentostatin were 89% and 80% respectively.[23] The corresponding RFS rates were 86% and 66%. Survival outcomes were not significantly different between treatment arms, although this analysis was complicated by the cross-over design of the study. 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.[29] Extended follow-up results confirmed the durability of responses with cladribine.[30] After 7 years of follow-up, of the 207 evaluable patients, 95% achieved a CR and 5% achieved a 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 infections (10%).

Different routes of administration (subcutaneous vs. intravenous) and dosing schedules (weekly vs. daily schedule) of cladribine have also been evaluated. Subcutaneous and intravenous injection of cladribine resulted in similar response rates, however, subcutaneous cladribine was associated with lower rate of viral infections and mucositis despite having a higher rate of neutropenia.[35-39] 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).[38] After a median follow-up of 36 months, the CR rates were 63.6% and 73.2%, respectively for reduced dose and standard dose cladribine with no difference in RFS and OS rates. In a retrospective analysis that compared the efficacy and safety of subcutaneous and intravenous injection of cladribine in 49 patients with HCL (18 patients were treated with intravenous cladribine and 31 patients were treated with subcutaneous cladribine), the CR rates were 94% and 97%, respectively, for intravenous and subcutaneous cladribine.[39] 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.[40-43] In a randomized study that evaluated the efficacy and safety of daily vs. 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.[43] 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 follow-up data from previous clinical studies suggests that treatment with interferon alpha (induction and maintenance therapy) results in durable disease control.[44-46] 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%.[47] After a median follow up of 60 months, the 5-year failure-free survival (FFS) and OS rates were 94.8% and 96.8%, respectively.

Relapsed/refractory Therapy

Pentostatin and cladribine are also effective for the treatment of relapsed HCL.[23,25,26] 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 rates were 84% and 69%, respectively.[23] 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.[30,33] 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.[30] Among the patients with relapsed disease who received retreatment with cladribine, the CR rate after first relapse was 75% (median duration of response was 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 has been evaluated in patients with relapsed/refractory HCL.[47,48] In a phase II study that included 14 patients with relapsed HCL, cladribine followed by rituximab resulted in a CR rate of 100%.[47] After a median follow up of 60 months, the 5-year FFS and OS rates were 100%. In a retrospective study of 18 patients with pretreated HCL relapsing after purine analog monotherapy (median 2 prior therapies), rituximab in combination with pentostatin or cladribine resulted in a CR rate of 89%.[48] 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.[49-52] 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.[49] 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%.[50] 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) in resulted in ORR and CR rates of 80% and 53%, respectively.[51] In another phase II study of 25 patients with less heavily pretreated HCL relapsing after cladribine, the ORR and CR rates with rituximab were 80% and 32%, respectively.[52]

More recently, tyrosine kinase inhibitors such as vemurafenib (BRAF V600E kinase inhibitor)[53-55] and ibrutinib (Bruton's tyrosine kinase inhibitor)[56] have demonstrated activity in relapsed or refractory HCL.

Vemurafenib (960 mg twice daily) was evaluated in two separate phase II multicenter studies for relapsed or refractory HCL (28 patients in the Italian trial and 26 of 36 planned patients in the U.S. trial).[53] The ORR was 96% (35% CR) after a median of 8 weeks therapy in the Italian trial and 100% (42% CR) after a median of 12 weeks therapy in the U.S. trial. In the Italian trial, after a median follow-up of 23 months, the median RFS was longer for patients who achieved CR versus PR (19

months and 6 months, respectively). In the U.S. trial, at 1 year, the 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. In another phase II trial of 22 patients relapsed or refractory HCL, vemurafenib in combination with rituximab resulted in a CR rate of 86% after 4 weeks, which is higher than that observed with vemurafenib alone.[54] In addition, minimal residual disease (MRD; measured by immunophenotyping and by allele-specific polymerase chain reaction [PCR]) was undetectable in 73% of patients.

In a phase II study of 28 patients with relapsed HCL (17 patients with classical HCL), ibrutinib resulted in an ORR of 46%.[56] 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.

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, as 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/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 purine analogs (cladribine or pentostatin) is recommended for patients with indications 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 low-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 morphological examination of bone marrow biopsy or peripheral blood samples, 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 RFS.[26,34] 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.[47] However, MRD-positivity during follow up did not necessarily result in clinically relevant risk for relapse.

Observation until indications for additional treatment (disease relapse) is recommend for patients who achieve a CR with initial purine analog therapy. Clinical trial, treatment with alternate purine analog ± rituximab, interferon alpha or rituximab monotherapy (if unable to receive purine analog) are included as options for patients with less than a CR to initial therapy.

Second-line Therapy for Relapsed/refractory or Progressive Disease

Treatment options for patients with relapsed/refractory HCL depend upon the quality and duration of remission to 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 with or without rituximab. Other options include treatment with alternative purine analog with or without rituximab or rituximab monotherapy (if unable to receive purine analog). Clinical trial, treatment with alternate purine analog ± rituximab, interferon alpha or rituximab monotherapy (if unable to receive purine analog) are included as options for patients with disease relapse within 2 years after achieving CR to initial therapy.

Clinical trial, ibrutinib or vemurafenib with or without rituximab 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.[57] Acyclovir or equivalent is recommended for herpes virus prophylaxis and sulfamethoxazole trimethoprim or equivalent is recommended for pneumocystis jiroveci pneumonia (PJP) prophylaxis.[58] Antiinfective prophylaxis for a minimum of 2 months and until CD4 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 (GCSF) shortens the duration of severe neutropenia after treatment with cladribine; however, it has no clinically significant impact on infection related outcomes.[59] The use GCSF 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.[60] 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.[61] 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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