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Hairy Cell Leukemia, Version 2.2018

Clinical Practice Guidelines in Oncology

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Overview

Hairy cell leukemia (HCL) is a rare type of indolent B-cell leukemia comprising approximately 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] Additionally, patients may also present with recurrent opportunistic infections.[3]

Abstract

Hairy cell leukemia (HCL) is a rare type of indolent B-cell leukemia, characterized by symptoms of fatigue and weakness, organomegaly, pancytopenia, and recurrent opportunistic infections. Classic HCL should be considered a distinct clinical entity separate from HCLvariant (HCLv), which is associated with a more aggressive disease course and may not respond to standard HCL therapies. Somatic hypermutation in the *IGHV* gene is present in most patients with HCL. The *BRAF* V600E mutation has been reported in most patients with classic HCL but not in those with other B-cell leukemias or lymphomas. Therefore, it is necessary to distinguish HCLv from classic HCL. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnosis and management of classic HCL.

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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 noted.

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

Please Note

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Disclosures for the NCCN Hairy Cell Leukemia Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

IIndividual disclosures for the NCCN Hairy Cell Leukemia Panel members can be found on page 1427. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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 a 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.[4,5] 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 to avoid an erroneous diagnosis of aplastic anemia.[4,5]

Most HCL cases (80%–90%) are characterized by somatic hypermutation in the *IGHV* gene.[6,7] The frequency of unmutated *IGHV* is much lower in classic HCL than in HCL-variant (HCLv) (17% vs 54%; $P<.001$).[7] Unmutated *IGHV* may serve as a prognostic factor for poorer outcomes with conventional therapies because it has been associated with primary refractoriness to purine analogue monotherapy and a more rapid disease progression.[8] The *BRAF* V600E mutation has been reported in most patients with classic HCL but not in those with other B-cell leukemias or lymphomas.[9–12] *BRAF* V600E is also absent in all cases of HCLv and classic HCL expressing *IGHV4-34* rearrangement.[13,14] Thus, *BRAF* V600E mutation may potentially serve as a reliable molecular marker to

Text cont. on page 1421.

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

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

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

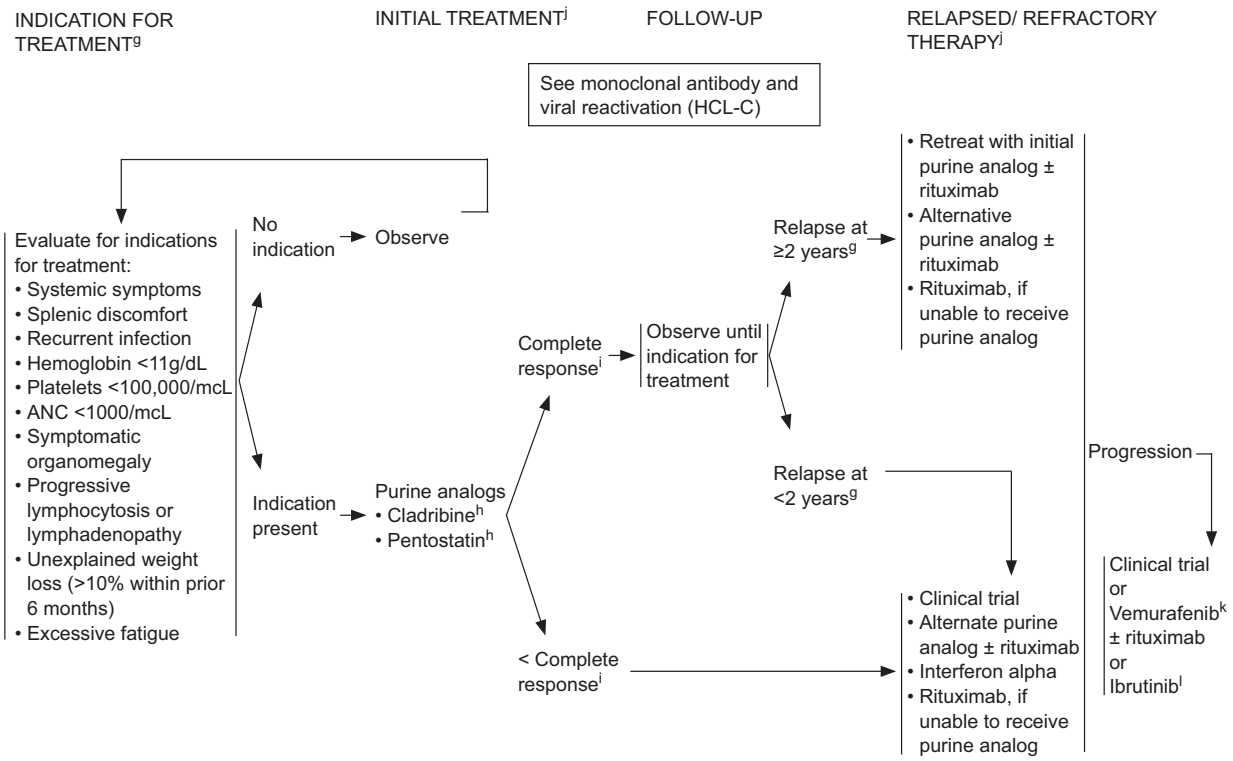
[c]Typical immunophenotype for cHCL: CD5-, CD10-, CD11c+, CD20+ (bright), CD22+, CD25+, CD103+, CD123+, cyclin D1+, annexin A1+, CD200+ (bright). Monocytopenia is characteristic.

[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.

Hairy Cell Leukemia, Version 2.2018



[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]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.

[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).

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.

HCL-A

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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.

HCL-C

Cont. from page 1415.

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

In comparison to classic HCL, HCLv tends to be associated with a more aggressive disease course and may not respond to standard HCL therapies.[14,15] The 2008 WHO classification determined that classic HCL should be considered as a distinct clinical entity from HCLv.[4,5] Therefore, it is necessary to distinguish HCLv from classic HCL, with immunophenotyping being the primary methodology used, although 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).[14] In contrast, HCLv is characteristically CD25–, CD123–, annexin A1–, and *BRAF* V600E–negative.[14] IHC or molecular studies for *BRAF* V600E mutation is useful for the distinction of classic HCL from HCLv and other splenic B-cell lymphomas.[14,16,17]

HCL expressing *IGHV4-34* rearrangement has a relatively poorer prognosis and does not respond well to purine analogue therapy.[18] 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 was recently reported in HCLv and in classic HCL with *IGHV4-34* rearrangement.[19] *MAPK1* mutation analysis may be useful to distinguish HCLv from classic HCL in *BRAF*-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), size measurements of the liver and spleen, and performance status evaluation. A bone marrow biopsy with or without aspirate should be obtained. Laboratory assessments should include CBC with differential, serum lactate dehydrogenase 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 HCL treatment. 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 analogues such as pentostatin[20–26] and cladribine[25–33] 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 (1:1 fashion) to pentostatin versus interferon-alfa, 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; $P<.0001$) compared with interferon-alfa; the median follow-up was 57 months.[21] After a median follow-up of 9.3 years, estimated 5- and 10-year overall survival (OS) rates for patients initially treated with pentostatin were 89% and 80%, respectively[22]; corresponding RFS rates were 86% and 66%. Survival outcomes were not significantly different between treatment arms, although this analysis was complicated by the crossover design of the study. The most common treatment-related toxicities were neutropenia (grade 3/4; 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.[28] Extended follow-up results confirmed the durability of responses with cladribine[29]: after 7 years of follow-up, of 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 were neutropenia (grade 3/4; occurring in ≈65%–85%), febrile neutropenia (40%), thrombocytopenia (grade 3/4; 20%), and infections (10%).

Different routes of administration (ie, subcutaneous vs intravenous) and dosing schedules (ie, weekly vs daily) of cladribine have also been evaluated. Subcutaneous and intravenous injection has resulted in similar response rates; however, subcuta-

neous cladribine was associated with a lower rate of viral infections and mucositis despite having a higher rate of neutropenia.[34–38] In a prospective study, reduced-dose subcutaneous cladribine (total dose, 0.5 mg/kg; given as 0.1 mg/kg/d x 5 days) had a similar efficacy but lower toxicity than standard-dose subcutaneous cladribine (total dose, 0.7 mg/kg; given as 0.1 mg/kg/d x 7 days).[37] After a median follow-up of 36 months, 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 intravenous and subcutaneous injection of cladribine in 49 patients with HCL (18 intravenously, 31 subcutaneously), CR rates were 94% and 97%, respectively.[38] After median follow-up of 33.5 months, subcutaneous cladribine was associated with a more favorable 3-year event-free survival rate (96% vs 60%, respectively; *P*=.104) and a better (although nonsignificant) 3-year OS rate (100% vs 81%, respectively; *P*=.277) than intravenous cladribine. Neutropenia (grade 3/4; 87% vs 67%), mucositis (grade 1/2; 32% vs 67%), and viral infections (34% vs 78%) were the most frequent complications in the 2 treatment groups, respectively.

Weekly infusion of cladribine was also shown to have similar safety and efficacy to daily continuous infusion.[39–42] In one study of 100 patients randomized to receive cladribine at standard daily dosing (0.14 mg/kg/d x 5 days) or once-weekly dosing (0.14 mg/kg/d once a week x 5 weeks), the overall response rate (ORR) after 10 weeks was 78% and 68%, respectively.[42] There were no significant differences in toxicity profile between the treatment arms after 10 weeks (grade 3/4 neutropenia, 90% vs 80%; acute infection, 44% vs 40%; and erythrocyte support, 22% vs 30%, respectively).

Long-term follow-up data from previous clinical studies suggest that treatment with interferon-alfa (induction and maintenance therapy) results in durable disease control.[43–45] However, with the advent of purine analogues, the role of interferon-alfa as initial treatment for HCL is very limited. It may, however, be useful for the management of relapsed or refractory (R/R) disease.

Rituximab in combination with purine analogues has also been shown to be effective in previously untreated HCL, but it has not been evaluated extensively in this patient population. In a phase II study that included 59 patients with previously untreated HCL, cladribine followed by rituximab resulted in a CR rate of 100%.[46] After a median follow-up of 60 months, 5-year failure-free survival (FFS) and OS rates were 94.8% and 96.8%, respectively.

R/R Therapy

Pentostatin and cladribine are also effective for the treatment of relapsed HCL.[22,24,25] In the long-term follow-up of a phase III randomized study that evaluated pentostatin and interferon-alfa, among the 87 patients who crossed over to pentostatin after failure of initial interferon treatment, 5- and 10-year OS rates 93% and 85%, respectively; corresponding RFS rates were 84% and 69%, respectively.[22] Retreatment with the same purine analogue may yield a reasonable duration of disease control in patients with relapsed HCL after an initial durable remission to purine analogue therapy.[29,32] 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.[29] Among those with relapsed disease who received retreatment with cladribine, the CR rate after both first relapse was 75% (median duration of response, 35 months) and after subsequent relapse was 60% (median response duration, 20 months).

Given the observation that retreatment with purine analogues resulted in shorter remission durations with each successive treatment, the use of rituximab in combination with purine analogues has been evaluated in patients with R/R HCL.[46,47] In a phase II study that included 14 patients with relapsed HCL, cladribine followed by rituximab resulted in a CR rate of 100%.[46] After a median follow-up of 60 months, 5-year FFS and OS rates were 100%. In a retrospective study of 18 patients with pretreated HCL relapsing after purine analogue monotherapy (median of 2 prior therapies), rituximab in combination with pentostatin or cladribine resulted in a CR rate of 89%.[47] 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 a purine analogue.[48–51] In a small cohort of 10 patients with HCL that progressed on prior therapy with cladribine or pentostatin, rituximab monotherapy resulted in an ORR of 50%, with CR in only

10% of patients.[48] In another study of 24 patients with relapsed HCL after prior therapy with cladribine, rituximab induced an ORR of only 25%, with a CR in 13% of patients.[49] In a smaller study of 15 patients with relapsed or primary refractory HCL after treatment with purine analogues, 8 weekly doses of rituximab (vs standard 4 weekly doses) resulted in ORR and CR rates of 80% and 53%, respectively.[50] In another phase II study of 25 patients with less-heavily-pretreated HCL that relapsed after cladribine, the ORR and CR rates with rituximab were 80% and 32%, respectively.[51]

More recently, tyrosine kinase inhibitors such as vemurafenib (BRAF V600E kinase inhibitor)[52–54] and ibrutinib (Bruton tyrosine kinase)[55] have demonstrated activity in R/R HCL. Vemurafenib, 960 mg twice daily, was evaluated in 2 separate phase II multicenter studies for R/R HCL (28 patients in the Italian trial and 26/36 planned patients in the US trial).[52] The ORR was 96% (CR, 35%) after a median of 8 weeks therapy in the Italian trial and 100% (CR, 42%) after a median of 12 weeks therapy in the US 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 vs 6 months, respectively). In the US trial, at 1 year, progression-free survival (PFS) and OS rates were 73% and 91%, respectively. Grade 1/2 rash and arthralgia or arthritis were the most common adverse events leading to dose reductions. In another phase II trial of 22 patients with R/R 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.[53] In addition, minimal residual disease (MRD; measured by immunophenotyping and by allelespecific PCR) was undetectable in 73% 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%.[55] At median follow-up of 22 months, the estimated 24-month PFS rate was 79% (median PFS 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 1/2 atrial fibrillation was observed in 5 patients, but no grade ≥3 atrial fibrillation or bleeding was reported. The benefit and risk of ibrutinib should be evaluated in patients requiring antiplatelet 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 HCLv. 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, because not all patients with newly diagnosed 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 (ie, "watch and wait" approach) until indications develop. First-line therapy with purine analogues (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 analogue to the other. Due to the high response rates of purine analogue monotherapy, the role of rituximab in patients with untreated HCL is unclear and is thus generally not recommended as initial treatment.

Standard-dose purine analogues should not be administered to patients with active, life-threatening, or chronic infection. Active infection should be treated before initiating treatment with standard-dose purine analogues. 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 analogues.[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 ex-

amination, and absence of disease symptoms.[2] Available evidence suggests that achievement of a CR is associated with a longer duration of RFS.[25,33] The clinical relevance of MRD status in patients whose disease responds 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.[46] However, MRD-positivity during follow-up did not necessarily result in clinically relevant risk for relapse.

Observation until indications for additional treatment (eg, disease relapse) is recommended for patients who achieve a CR with initial purine analogue therapy. Enrollment on a clinical trial and treatment with an alternate purine analogue ± rituximab, interferon-alfa, or rituximab monotherapy (if unable to receive a purine analogue) are included as options for patients with less than a CR to initial therapy.

Second-Line Therapy for R/R or Progressive Disease

Treatment options for patients with R/R HCL depend on the quality and duration of remission to initial therapy. Patients with disease relapse ≥2 years after achieving CR to initial therapy with a purine analogue may benefit from retreatment with the same purine analogue with or without rituximab. Other options include treatment with an alternative purine analogue with or without rituximab or rituximab monotherapy (if unable to receive a purine analogue). Enrollment on a clinical trial, and treatment with an alternate purine analogue ± rituximab, interferon-alfa, or rituximab monotherapy (if unable to receive purine analogue) 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 after second-line therapy.

Supportive Care

Infections: Patients with HCL are susceptible to infectious complications due to treatment with purine analogues.[56] Acyclovir or an equivalent is recommended for herpes virus prophylaxis and sulfamethoxazole trimethoprim or an equivalent is recommended for pneumocystis jiroveci pneumonia prophylaxis.[57] Anti-infective 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.[58] The use GCSFs might be considered in patients with severe neutropenic fever after chemotherapy.

HBV Reactivation: HBV reactivation leading to fulminant hepatitis, hepatic failure, and death have been reported in patients receiving chemotherapy and immunosuppressive therapy.[59] HBV prophylaxis and monitoring is recommended in high-risk patients receiving rituximab and purine analogues. 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 HBV) 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.[60] Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. Prophylactic antiviral therapy is recommended for patients who are HBsAg+. Prophylactic antiviral therapy is preferred for patients who are HBcAb+. 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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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty potential conflict:
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Sami Malek, MD: Portola