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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hairy Cell Leukemia

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[Summary of the Guidelines Updates](#)

[Diagnosis and Workup \(HCL-1\)](#)

[Indication for Treatment, Initial Treatment and Relapsed/Refractory \(HCL-2\)](#)

[Treatment References \(HCL-A\)](#)

[Supportive Care \(HCL-B\)](#)

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

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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 specified.

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

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Updates in Version 2.2017 of the NCCN Guidelines for Hairy Cell Leukemia from Version 1.2017 include:

[HCL-2](#)

- Progression after relapsed/refractory therapy
 - ▶ "± rituximab" was added to "vemurafenib"
 - ▶ "Ibrutinib" was added as an option

Updates in Version 1.2017 of the NCCN Guidelines for Hairy Cell Leukemia from Version 3.2016 include:

[HCL-1](#)

- Workup, bullet was revised, "Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)."

[HCL-B 2 of 2](#)

- The "Monoclonal Antibody Therapy and Viral Reactivation" information was removed and the guideline is directed to the NCCN Guidelines for B-Cell Lymphomas for the detailed information.

DIAGNOSIS^a

ESSENTIAL:

- Presence of characteristic hairy cells upon morphologic examination of peripheral blood and characteristic infiltrate with increased reticulin in bone marrow biopsy samples. Dry tap is frequent.
- IHC and flow cytometry are essential for establishing the diagnosis and for distinguishing between hairy cell leukemia and hairy cell variant.^b
- Adequate immunophenotyping to establish diagnosis^{c,d}
 - ▶ IHC panel: CD20, CD25, CD123, cyclin D1 with or without
 - ▶ Cell surface marker analysis by flow cytometry: CD3, CD5, CD10, CD11c, CD19, CD20, CD22, CD25, CD103
- IHC for mutant *BRAF*

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: IGHV mutational status
- Sequencing of *BRAF* for V600E mutation if IHC equivocal
- Annexin A1

WORKUP

ESSENTIAL:

- Physical exam: Presence of enlarged spleen and/or liver; presence of peripheral lymphadenopathy (uncommon)
- Performance status
- Peripheral blood examination
- CBC, differential, platelets
- Comprehensive metabolic panel with particular attention to renal function
- LDH
- Bone marrow biopsy ± aspirate
- Hepatitis B testing^e if rituximab contemplated
- Pregnancy testing in women of child-bearing age (if chemotherapy 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 \(HCL-2\)](#)

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

^bHairy cell variant is characteristically CD25- CD123-, annexin A1-. This helps to distinguish the variant form from classical HCL.

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

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

^eHepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. 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.

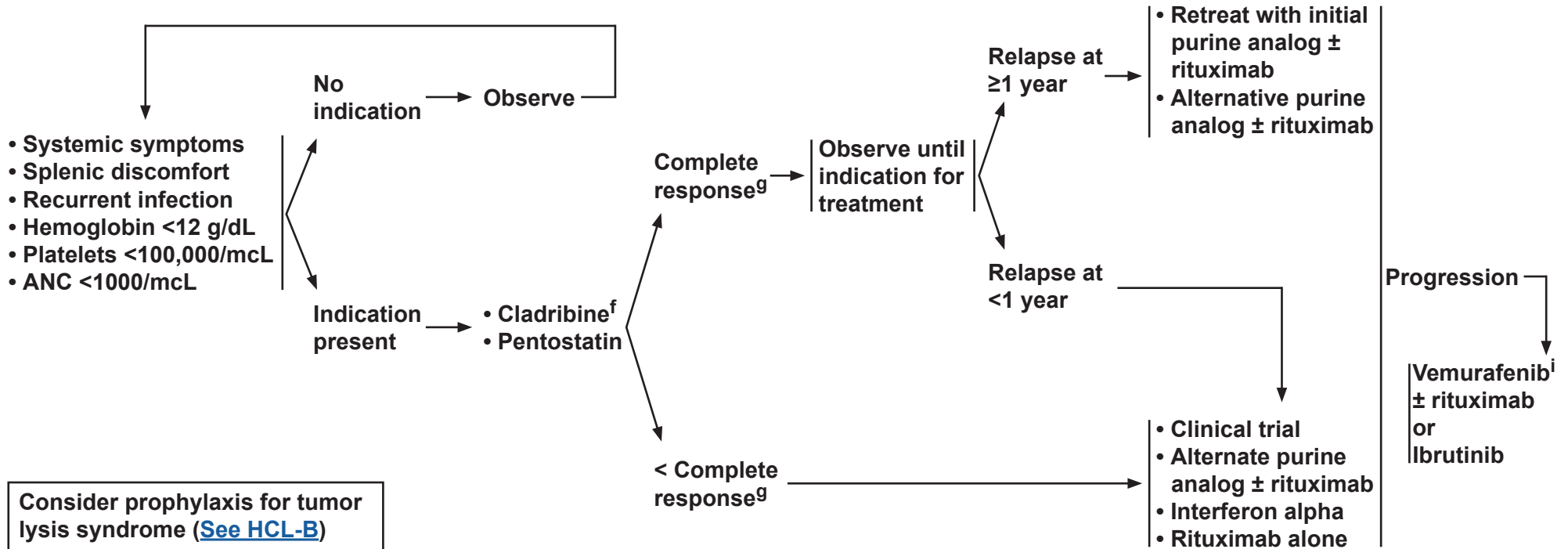
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INDICATION FOR TREATMENT

INITIAL TREATMENT^h

FOLLOW-UP

RELAPSED/REFRACTORY^h



Adapted from: Grever MR. How I treat hairy cell leukemia. Blood 2010;115:21-28.

^fCladribine should not be administered to patients with active life-threatening or chronic infection.

^gComplete response defined as: recovery of blood counts (Hgb >12 g/dL, ANC >1500/mcL, platelet >100,000/mcL), absence of HCL cells by morphologic examination of bone marrow biopsy or peripheral blood samples, resolution of organomegaly by physical exam, and absence of disease symptoms. Eradication of minimal residual disease (as determined by flow cytometry, immunohistochemistry, or molecular analysis) is of unproven value at this point.

^h[See Treatment References \(HCL-A\)](#).

ⁱShould be non-responsive to purine analog therapy.

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TREATMENT REFERENCES

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Rituximab

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Ibrutinib

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SUPPORTIVE CARE

Tumor Lysis Syndrome (TLS)

- **Laboratory hallmarks of TLS:**
 - ▶ High potassium
 - ▶ High uric acid
 - ▶ High phosphorous
 - ▶ Low calcium
- **Symptoms of TLS:**
 - ▶ Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.
- **High-risk features**
 - ▶ Histologies of Burkitt lymphoma and lymphoblastic lymphoma; occasionally patients with DLBCL and CLL
 - ▶ Spontaneous TLS
 - ▶ Elevated WBC
 - ▶ Bone marrow involvement
 - ▶ Pre-existing elevated uric acid
 - ▶ Ineffectiveness of allopurinol
 - ▶ Renal disease or renal involvement by tumor
- **Treatment of TLS:**
 - ▶ TLS is best managed if anticipated and treatment is started prior to chemotherapy.
 - ▶ Centerpiece of treatment includes
 - ◇ Rigorous hydration
 - ◇ Management of hyperuricemia
 - ◇ Frequent monitoring of electrolytes and aggressive correction is essential
 - ▶ First-line and at retreatment for hyperuricemia
 - ◇ Allopurinol beginning 2–3 days prior to chemotherapy and continued for 10–14 days
 - or
 - Rasburicase is indicated for patients with any of the following risk factors:
 - presence of any high-risk feature
 - urgent need to initiate therapy in a high-bulk patient
 - situations where adequate hydration may be difficult or impossible
 - Acute renal failure
 - ◇ One dose of rasburicase is frequently adequate. Doses of 3–6 mg are usually effective.^a Redosing should be individualized.
 - ▶ If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

^aThere are data to support that fixed-dose rasburicase is very effective in adult patients.

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[Supportive Care](#)
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SUPPORTIVE CARE

Monoclonal Antibody Therapy and Viral Reactivation

- [See NCCN Guidelines for B-Cell Lymphomas](#)

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.

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/06/2013.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

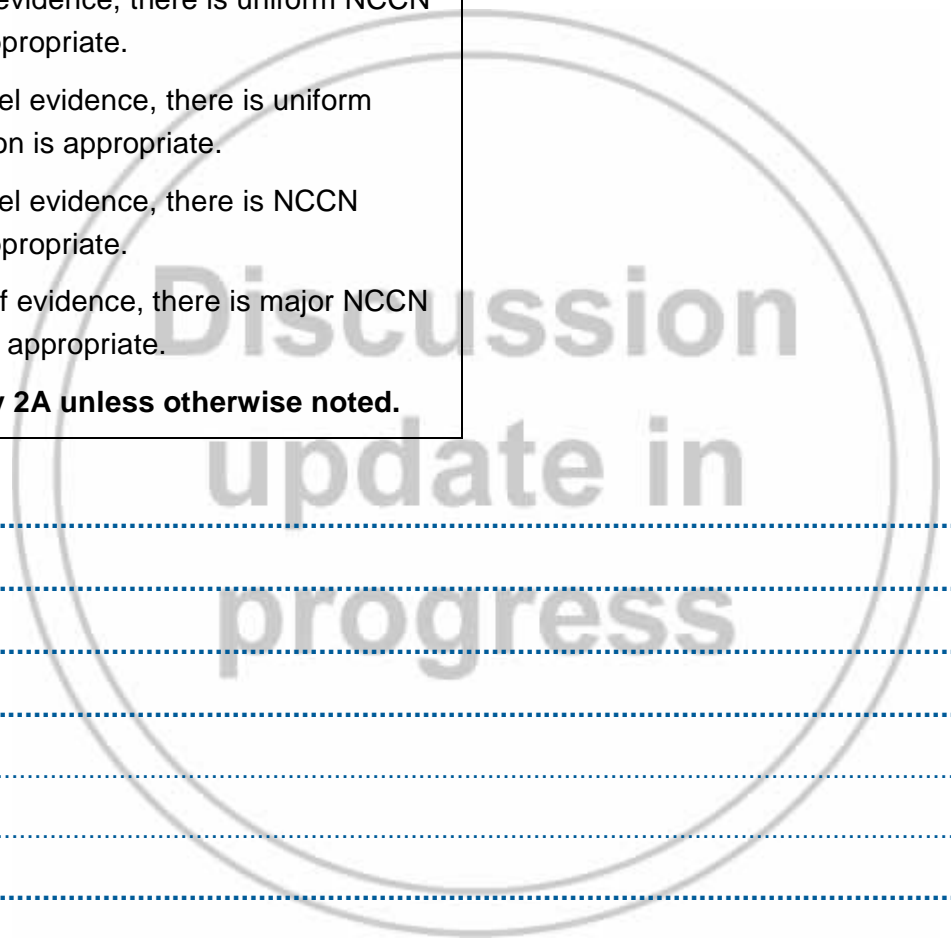
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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 pancytopenia.^{1,2} In addition, patients may present with hepatomegaly and/or lymphadenopathy. Patients may also present with recurrent opportunistic infections.^{1,2}

Diagnosis

Morphological evaluation of peripheral blood smears and bone marrow biopsy, as well as adequate immunophenotyping by immunohistochemistry (IHC) and/or flow cytometry are essential to establish the diagnosis of HCL. 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.^{3,4} 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.^{3,4} As mentioned above, immunophenotyping is essential in establishing the diagnosis. It is also necessary in distinguishing the variant form of HCL from classic HCL, as HCL variant tends to be associated with a more aggressive disease course and may not respond to standard HCL therapies.^{4,5} In the 2008 WHO classification, HCL variant is considered a separate entity that is biologically distinct from classic HCL.⁴ The IHC panel for immunophenotyping should

include the following markers: CD20, CD25, CD123, and cyclin D1. Annexin A1 may be useful under certain circumstances. In addition, the following markers should be included for analysis by flow cytometry: CD3, CD5, CD10, CD11c, CD19, CD20, CD22, CD25, and CD103. The typical immunophenotype for classic HCL shows CD5-, CD10- CD11c+(bright), CD20+(bright), CD22+(bright), CD25+(bright), CD103+, CD123+ (bright), cyclin D1+, and Annexin A1+.^{1,2,6,7} In contrast, HCL variant is uniformly CD25- and Annexin A1-.^{1,2,6}

Consistent with the postulation that HCL originates from post-germinal center B-cells, the large majority of HCL cases (80–90%) show immunoglobulin heavy chain variable (*IGHV*) genes with somatic hypermutation.^{1,8,9} Unmutated *IGHV* status in HCL has been associated with primary refractoriness to single-agent therapy with a purine nucleoside analog, and more rapid disease progression.⁹ Thus, unmutated *IGHV* may serve as a prognostic factor for poorer outcomes with conventional therapies. The V600E mutation of the *BRAF* gene was recently identified in patients with HCL.¹⁰ During the last year, several published reports have consistently demonstrated the presence of *BRAF* V600E mutation in all tested cases of HCL, while the mutation was absent in other cases of B-cell leukemias or lymphomas.¹⁰⁻¹³ Interestingly, recent studies reported the absence of *BRAF* V600E mutation in HCL variant cases,^{6,14} and in a small group of classic HCL cases; in the latter, about half of the *BRAF* wildtype cases also showed *VH4-34* rearrangement of the *IGHV* gene.¹⁴ Although further studies are needed, the *BRAF* V600E mutation may potentially serve as a reliable molecular marker that distinguishes HCL from other B-cell lymphoproliferative disorders. Moreover, the presence of this mutation may have implications for the use of new targeted therapies for HCL. Under certain circumstances, molecular analysis to determine *IGHV* gene mutational status and to detect *BRAF* V600E mutation may be useful.

Workup

The initial workup for newly diagnosed HCL should include a thorough physical examination with attention to palpable enlargement of the spleen, liver, and/or lymph nodes (although presence of peripheral lymphadenopathy is uncommon), and evaluation of performance status. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel. In particular, close evaluation of renal function is advised considering the renal route of excretion of drugs (e.g., pentostatin) used in the treatment of HCL. In addition, measurements of serum lactate dehydrogenase (LDH) levels should be obtained. A bone marrow biopsy, with or without aspirates, should be obtained. Hepatitis B virus (HBV) testing is recommended due to increased risks of viral reactivation when immunotherapy regimens containing rituximab are being considered for treatment. Under certain circumstances, CT scans (with contrast of diagnostic quality) of the chest, abdomen and/or pelvis may be useful.

Treatment Options

During the last several decades, the treatment strategy for patients with HCL has evolved from the use of interferon to single-agent purine analogs to the incorporation of targeted immunotherapy with rituximab. Interferon alpha was the first therapeutic agent to show activity in the treatment of HCL (as both induction and maintenance therapy) and long-term results from this agent suggested that durable disease control can be achieved.¹⁵⁻¹⁷ With the introduction of purine analogs such as pentostatin and cladribine, the initial treatment for HCL largely shifted to the use of these agents. As a single agent, pentostatin has been shown to induce a response in nearly all patients with HCL, with high complete response (CR) rates of 75-90%.¹⁸⁻²⁴ This is in contrast to the lower CR rates (about 15%) reported with interferon alpha.^{16,17,21}

In the randomized phase III intergroup study that evaluated pentostatin versus interferon alpha in patients with previously untreated HCL (N=313 evaluable), pentostatin resulted in significantly higher CR rates (76% vs. 11%; $P<0.0001$) and longer median relapse-free survival (not reached vs. 20 months; $P<0.0001$; after a median follow up of 57 months) compared with interferon alpha.²¹ Survival outcomes were not significantly different between treatment arms, although this analysis was complicated by the cross-over design of the study. Results from long-term follow up of studies with pentostatin reported 10-year disease-free survival (DFS) rates of about 65% to 70%, and 10-year overall survival (OS) rates of 80% to 90%; the median DFS was about 16 years.^{18,20,23} These favorable outcomes were observed even in studies in which the majority of patients were previously treated,²³ or cross-over to pentostatin was permitted after failure with initial interferon treatment.^{20,21} The most common toxicities reported in the randomized phase III study with pentostatin were grade 3-4 neutropenia (20%) and infections (any grade; 53%) including those requiring intravenous antibiotics (27%).²¹ In the retrospective study in a large number of patients treated with pentostatin (N=238), the most common toxicities were grade 3-4 thrombocytopenia (15%), grade 3-4 neutropenia (8%), febrile neutropenia (17%), and documented infections (6%); it should be noted that in this analysis, data from patients with pre-existing cytopenias were excluded for the first 2 months of treatment.²³

Cladribine is another purine analog with significant activity in HCL. As a single agent, cladribine has also been reported to induce high CR rates of 80% to 98%.^{18,19,25-31} Long-term follow up data showed a median DFS or remission duration of over 8 years, and a 12-year OS rate of about 80% to 90%.^{25-27,31} Different routes of administration (subcutaneous bolus versus intravenous continuous infusion) and dosing schedules (e.g., daily versus weekly) of cladribine have been

evaluated, which showed similar activity and toxicity profiles.³²⁻³⁵ The most common toxicities with cladribine were grade 3-4 neutropenia (occurring in the large majority of patients; about 65–85%), febrile neutropenia (about 40%), grade 3-4 thrombocytopenia (about 20%) and infections (about 10%).²⁹⁻³¹

Overall, outcomes with single-agent pentostatin or cladribine appear comparable, with both agents demonstrating durable remissions in patients with HCL.^{18,36} Moreover, both agents have been shown to induce second or subsequent CRs in a large proportion of patients who received retreatment with the same agent at relapse following initial therapy; these subsequent responses were generally durable, albeit shorter with successive treatments.^{18,26,29} Results from long-term follow up with purine analogs reported that about 35% to 40% of patients eventually relapse after first-line treatment.^{18,25,26,36} In the long-term follow up data from the Scripps Research Institute in patients treated with cladribine (N=207 evaluable with long-term data), the CR rate with initial therapy was 95%; the median response duration for all responders was 98 months (range, 8–172 months).²⁶ Relapse occurred in 37% of initial responders, with a median time to relapse of 42 months (range, 8–118 months). Among the patients with relapsed disease who received retreatment with cladribine (n=59), the CR rate was 75%; the median duration of second response was 35 months.²⁶ Subsequently, 20 of these responders (33%) experienced a second relapse and 10 patients were retreated again with cladribine. The CR rate was 60% in these patients, with median response duration of 20 months.²⁶ Thus, for patients who relapse after an initial durable remission to purine analog therapy, retreatment with the same agent may yield a reasonable duration of disease control. Treatment with an alternative purine analog has been shown to induce similar rates of second remissions in patients who experience relapse.^{23,36}

Given the observation that retreatment with purine analogs resulted in shorter remission durations with each successive treatment, other agents have been investigated in the management of patients with HCL relapsing after purine analog therapies. One such agent is rituximab, a chimeric anti-CD20 monoclonal antibody with substantial activity in B-cell lymphomas and leukemias. CD20 is typically highly expressed in HCL cases, and therefore represents a potential target for therapy. Several studies have evaluated the role of single-agent rituximab in patients with HCL that relapsed after purine analog treatments.³⁷⁻⁴⁰ In an early study in a small number of patients (N=10), rituximab given at standard doses (375 mg/m² weekly for 4 weeks) resulted in an ORR of 50% with CR in only 10% of patients.³⁷ Patients had received a median of 2 prior treatments (range, 2–3) prior to rituximab. In a phase II study in patients with relapsed HCL after cladribine (N=24), rituximab induced an ORR of only 25% with CR in 13%.³⁸ These patients had also received a median of 2 prior therapies (range, 1–4), although none were considered refractory to their prior treatments. In another phase II study in less heavily pretreated patients with HCL relapsing after cladribine (N=25; median 1 prior therapy), the ORR and CR rate with rituximab was 80% and 32%, respectively.⁴⁰ In a smaller study that used 8 weekly doses of rituximab (rather than the standard 4 weekly doses) in patients with relapsed HCL (N=15; more than 1 prior therapy in 53%), the ORR and CR rate was 80% and 53%, respectively.³⁹ Among responding patients, 5 (42%) experienced disease relapse at a median 18 months from start of treatment.

As shown from the studies mentioned above, rituximab given as single-agent therapy appears to have modest activity, at best, in patients with relapsed HCL. Recent studies have evaluated rituximab in combination (concurrent or sequential) with purine analogs in both relapsed/refractory and previously untreated HCL.⁴¹⁻⁴⁴ In a

retrospective study in patients with pretreated HCL relapsing after single-agent purine analog treatments (N=18; median 2 prior therapies, range 1–6), rituximab combined with pentostatin or cladribine resulted in a CR rate of 89%.⁴¹ CR was maintained in all patients after a median follow up of 36 months. The estimated 3-year recurrence rate was 7% with this combination approach.⁴¹ In a recent phase II study, cladribine followed (sequentially) by rituximab (8 weekly doses) was evaluated in previously untreated patients with HCL (N=36; including HCL variant, n=5).⁴⁴ All patients achieved a CR with this regimen. After a median follow up of 25 months, the duration of CR has not yet been reached. Disease relapse occurred in 1 patient with HCL variant.⁴⁴ Among the patients with classic HCL who were assessed for minimal residual disease (MRD) at the end of treatment, MRD negativity was demonstrated in 79% of patients based on multiparameter flow cytometry and in 70% by consensus primer PCR assay.⁴⁴ Grade 3-4 infections occurred in 33% of patients (resolved in all). The regimen was otherwise well tolerated, with no other grade 3-4 non-hematologic toxicities reported.⁴⁴ In a small retrospective analysis of data from patients with relapsed/refractory HCL treated with a different purine analog (fludarabine) combined with rituximab (N=15), response was achieved in all patients (although categorization of CR versus PR was not available).⁴⁵ Fourteen patients (93%) remained progression free at a median follow up of 35 months; 1 patient died from progressive disease. The 5-year progression-free survival rate and OS rate was 89% and 83%, respectively.⁴⁵ Further prospective studies are needed to confirm these promising outcomes with fludarabine combined with rituximab.

Investigational agents for the treatment of HCL include recombinant immunotoxin (e.g., BL22 and HA22, a protein comprising anti-CD22 antibody fragment fused to a bacterial exotoxin), which has shown promising response rates (about 70-85% ORR; 45% CR) in phase I/II

studies.^{46,47} As briefly mentioned above, targeting of the *BRAF* mutation may also hold promise for future investigation in HCL therapy. Vemurafenib is an orally administered inhibitor of mutated forms of the BRAF kinase, including V600E-mutated BRAF kinase, and is currently approved for the treatment of patients with metastatic or unresectable melanoma harboring the *BRAF* V600E mutation.⁴⁸ In 2 recent case reports, treatment with vemurafenib resulted in a CR in patients with HCL who were refractory to or relapsed after conventional therapies (including with purine analogs).^{49,50}

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 debilitating fatigue, physical discomfort due to splenomegaly, and/or cytopenias. Patients who are asymptomatic may be best managed by close observation (“watch and wait” approach) until indications develop.

The current NCCN Guidelines apply to cases of classic HCL, and not the HCL variant; at the present time, sufficient data are not available to determine the optimal management of HCL variant cases.

Initial Therapy and Follow Up

For patients with indications for treatment, the NCCN Guidelines panel recommends first-line therapy with either of the purine analogs cladribine or pentostatin. Data from randomized controlled trials are not available to compare the efficacy of one purine analog to the other, and both agents have been extensively evaluated in clinical studies in HCL. In general, cladribine should be avoided in patients with an active life-threatening infection or recurrent (chronic) infections.

Patients who achieve a CR with initial purine analog therapy should be observed until indications for additional treatment (disease relapse). CR is defined as normalization of blood counts (e.g., hemoglobin >12 g/dL, 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, resolution of organomegaly by physical examination, and absence of disease symptoms.³ The role of MRD status in responding patients remain uncertain at this time. Patients with less than a CR to initial therapy should be managed similarly to patients who relapse within 1 year after a CR (see “Second-line therapy” below).

Second-line Therapy

Treatment options for patients with relapsed/refractory HCL depend upon the quality and duration of remission to initial therapy.³ As mentioned in the discussion above, patients who achieve a durable CR to initial therapy may benefit from retreatment with the same agent. For patients with a durable CR (i.e., those who relapse after 1 year or later from initial response), second-line treatment options include retreatment with the same purine analog with or without rituximab, or treatment with an alternative purine analog with or without rituximab. For patients with a CR who relapse within 1 year of initial response, or for patients with less than a CR to initial therapy, second-line treatment options include participation in a clinical trial (if available), an alternative purine analog with or without rituximab, rituximab alone or interferon alpha.

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Discussion
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