

# Updated consensus guidelines for the diagnosis and management of patients with HCL and HCL variant

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**Hairy cell leukemia (HCL) and HCL variant (HCLv) are distinct, rare, and chronic splenic B-cell lymphomas/leukemias that partially overlap in clinicopathologic presentation but differ in genetic basis, prognosis, and management. HCL is caused by the *BRAF*-V600E kinase-activating mutation in >95% of the patients, usually has excellent responses to chemotherapy with purine analogues, and is also amenable to *BRAF* inhibitor-based targeted treatments. In contrast, HCLv lacks *BRAF*V600E**

**mutation, requires combined therapy with purine analogues in addition to rituximab, and generally shows less durable responses. Here, an international team of hematologists, experts on these rare diseases, was convened by the Hairy Cell Leukemia Foundation to update the previous guidelines (published in 2017) by providing a summary of current methods to diagnose and manage patients with HCL and HCLv as well as a prospective on newer targeted therapies to further improve outcomes.**

## Introduction

Hairy cell leukemia is an uncommon hematological malignancy initially described by 2 independent investigators as “leukemic reticuloendotheliosis”<sup>1,2</sup> and subsequently recognized as the 2 distinct mature B-cell malignancies, classical hairy cell leukemia (HCL) and HCL variant (HCLv).<sup>3</sup> Over the past 40 years,

substantial clinical research has improved the survival and relapse-free survival (RFS) in patients with HCL. Purine analogue-based therapy with cladribine or pentostatin has made it possible for many patients to live nearly normal life spans.<sup>4</sup> Treatment of relapsed or refractory HCL with purine analogue-based regimens can achieve durable remissions, and the use of novel agents and combinations could be even more

effective.<sup>5-10</sup> Achieving a complete remission (CR) after chemotherapy predicts a longer duration of response,<sup>4</sup> and targeted new therapies and monoclonal antibodies have secured impressive durable remissions, with a high percentage of patients having undetectable measurable residual disease (uMRD) upon evaluation with standard immunohistochemistry and flow cytometry sensitive to ~1% tumor involvement, or more sensitive polymerase chain reaction and flow cytometry methods that can detect 0.01% to 0.1% tumor involvement.<sup>4,10-12</sup> Although multiple country- or continent-specific guidelines on HCL exist,<sup>13-16</sup> international guidelines reflecting the consensus of experts from all around the world were first published in 2017<sup>12</sup> and are updated in this article.

## HCL

### Clinical presentation and assessment

The clinical features and diagnosis of HCL were reviewed in detail in the 2017 consensus guidelines.<sup>12</sup> Diagnosis can be incidental, and symptomatic patients usually present with fatigue, splenomegaly, cytopenia, or infections. Lymphadenopathy is rare. Presentation of HCL at other sites, including bone and skin, has also been described.<sup>17</sup> Most patients have monocytopenia. Examination of peripheral blood and bone marrow is important to evaluate the morphology and immunophenotype of malignant lymphocytes, perform molecular studies, and estimate the degree of marrow involvement and hematopoietic reserve. Bone marrow aspirate could be difficult to obtain because of HCL-induced reticulin fibrosis. The extent of bone marrow involvement is variable, and accurate estimation requires immunohistochemical staining for B-cells (eg, CD20) or more specifically for HCL cells using BRAFV600E mutation-specific antibodies. The characteristic immunophenotype can be evaluated in blood or bone marrow, and the detection of a clonal B-cell population coexpressing CD19, CD20, CD11c, CD25, CD103, CD123, and Annexin-1 is considered diagnostic of HCL.<sup>18,19</sup> HCL cells are usually positive for CD200 and negative for CD27<sup>20</sup> and can coexpress multiple immunoglobulin isotypes.<sup>21</sup>

More than 95% of the patients with HCL have the activating *BRAF* mutation V600E, and detection of this mutation is useful in confirming the diagnosis of HCL and determining treatment options.<sup>22,23</sup> *BRAF* V600E can be detected by immunohistochemistry using mutation-specific antibodies, polymerase chain reaction, or next-generation sequencing; <5% of the patients with HCL who do not have *BRAF* V600E may have other activating deletions, translocations, or mutations of *BRAF*<sup>17,23-25</sup> or activating mutations in *MAP2K1* (coding for MEK1, a kinase phosphorylated by *BRAF*) and could have inferior outcomes.<sup>23-26</sup> Most of the HCL cases express somatically hypermutated immunoglobulin heavy chain variable region gene (*IGHV*),<sup>27</sup> but a minor subset with somatically unmutated *IGHV* (10% of the cases) has been identified in 1 study to be associated with inferior outcome after cladribine monotherapy.<sup>28</sup>

### Treatment

Treatment of HCL is currently not curative. Therapy is indicated when patients are symptomatic (eg, because of splenomegaly or constitutional symptoms) or have significant and worsening cytopenia attributable to their HCL diagnosis (typically hemoglobin <10 g/dL, neutrophil count <1 × 10<sup>9</sup>/L, or platelet count

<100 × 10<sup>9</sup>/L).<sup>12</sup> Asymptomatic patients without significant cytopenia should be monitored, and because HCL usually has a low proliferation rate,<sup>17</sup> monitoring can often be continued for an extended period of time. Patients being monitored should start therapy before developing severe cytopenia because purine analogue-containing therapy is myelosuppressive. Although HCL is a rare disease, there have been 2 randomized controlled trials demonstrating that pentostatin is more effective than interferon alfa<sup>29</sup> and suggesting that rituximab added to cladribine improves progression-free survival (PFS).<sup>30</sup> In contrast, most data used to treat patients are derived from studies that have been conducted on smaller numbers of patients through nonrandomized trials or observational studies.

Clinical judgment needs to be exercised in planning treatment for patients with HCL who are at a higher risk of treatment-related complications. The optimal management of patients with HCL complicated by active infections or severe cytopenia can be challenging because standard purine analogue therapy is both immunosuppressive and myelosuppressive. Favorable outcomes have been reported in patients with active infections for regimens including low-dose pentostatin<sup>31</sup> or *BRAF* inhibitors (with or without rituximab), which are less myelosuppressive than pentostatin.<sup>32-34</sup> Purine analogues are renally excreted; therefore, patients with renal impairment require dose adjustments or consideration of alternative therapies.

Definitions of response depth and relapse after treatment are provided in Table 1.<sup>12</sup> Bone marrow biopsy is useful to distinguish CR from partial remission (PR) and guide patient management, although in practice it is not universally performed (especially in older, unfit, or frail patients). The clinical value of assessing MRD testing remains uncertain and is being actively studied, as recently reviewed.<sup>11,37,38</sup> We suggest testing for MRD in both bone marrow and blood after treatment to gather data.

Since HCL is a rare disease, further improvements in therapy will likely require multi-institutional studies with collaborative sharing of data and research planning, supported by the Hair Cell Leukemia Foundation (HCLF). Whenever feasible, we recommend enrollment in a prospective clinical study for any patient in any disease setting. Patients should also be encouraged to provide consent for enrollment in registries, databases, and tissue banks to provide important clinical data and material required for improving disease management. Although the current goal of therapy is to achieve durable CR, the hope is that newer targeted therapies and cellular therapies could lead to a potentially curative treatment for HCL.

### Initial treatment of HCL

**Purine analogue monotherapy** Treatment of HCL with the purine analogue pentostatin or cladribine is highly effective, with CR rates of 70% to 90% and median response durations exceeding 10 years and up to 16 years in some studies (Figure 1).<sup>29,35,39-50</sup> Outcomes were similar after either subcutaneous or IV cladribine administration.<sup>50-52</sup> Both pentostatin and cladribine cause myelosuppression<sup>29,42,53</sup> and long-term T-lymphopenia, with time to recovery of normal CD4<sup>+</sup> T-cell counts of up to 4 years.<sup>54,55</sup> The depth and duration of myelosuppression can be more easily managed with pentostatin compared with cladribine because cladribine is usually administered over a shorter time interval (typically 5

**Table 1. Assessment of response in HCL**

| Response type                     | Definition                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CR                                | <ul style="list-style-type: none"> <li>Peripheral blood counts (without transfusions or growth factors): hemoglobin &gt;11 g/dL, platelets &gt;100 × 10<sup>9</sup>/L, and absolute neutrophil count &gt;1.5 × 10<sup>9</sup>/L*</li> <li>Absence of morphologic evidence of HCL on both the peripheral blood smear and the bone marrow biopsy†</li> <li>Resolution of splenomegaly on physical examination</li> </ul> |
| CR ± MRD‡                         | In patients who achieve CR, MRD can be assessed by IHC on the bone marrow biopsy and/or by flow cytometry or molecular techniques in the bone marrow aspirate and/or blood to separate CR with or without MRD in the marrow and/or blood.                                                                                                                                                                              |
| PR                                | <ul style="list-style-type: none"> <li>Peripheral blood counts as in CR*</li> <li>An improvement of ≥50% in bone marrow infiltration by HCL assessed in the bone marrow biopsy using IHC</li> <li>An improvement of ≥50% in splenomegaly</li> </ul>                                                                                                                                                                    |
| NR                                | No CR, PR, or PD                                                                                                                                                                                                                                                                                                                                                                                                       |
| PD                                | A decline of ≥25% in blood count(s) (not because of iatrogenic myelosuppression) and/or ≥25% increase in splenomegaly and/or worsening of HCL-related symptoms                                                                                                                                                                                                                                                         |
| Relapse after response (CR or PR) | HCL-induced reappearance of cytopenia(s) below the thresholds defined above for CR and PR§.                                                                                                                                                                                                                                                                                                                            |

Response to treatment with cladribine, which is usually delivered in a 5-day course, should be assessed 4 to 6 months later because bone marrow recovery and HCL cell clearance can be slow. Following treatment with pentostatin (which is delivered every 2 weeks for up to 12 doses), response should be assessed when blood counts reach the criteria for CR.

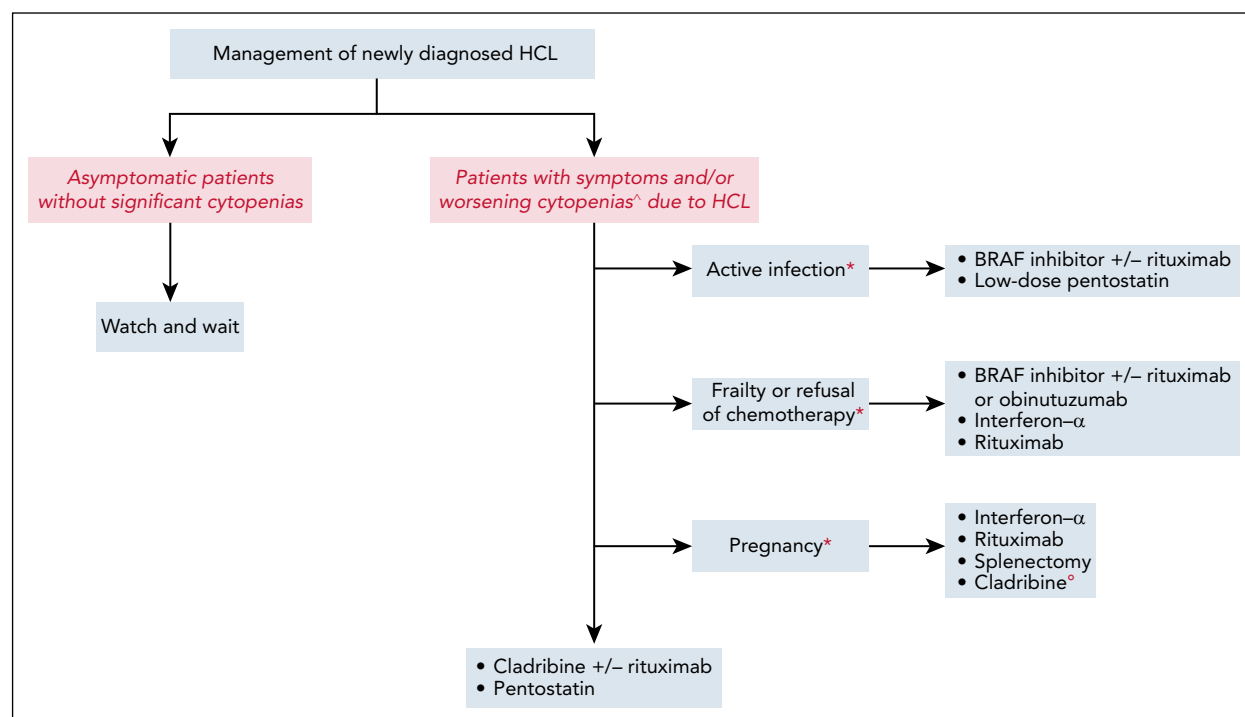
IHC, immunohistochemistry; NR, no response; PD, progressive disease.

\*In the setting of a supportive bone marrow biopsy (criterion 2), CR or PR can be declared even if the thresholds for improvement of cytopenias are not met because of causes other than HCL (eg, CR with incomplete resolution of anemia because of concomitant iron deficiency). Similarly, splenomegaly may not fully resolve after therapy because of causes other than HCL.<sup>36</sup>

†Due to the intrinsic subjectivity of, and variability in, evaluating a bone marrow or blood sample without the help of immunophenotyping, an additional criterion has been used by some investigators. This requires that the bone marrow biopsy has ≤10% HCL infiltration by IHC to confirm CR.<sup>35</sup>

‡The clinical value of MRD is uncertain, especially after first-line treatment with purine analogues, and MRD testing in HCL is currently not standardized.

§The simple reappearance in the blood and/or marrow of MRD or even of HCL cells recognizable by morphological stains may not be followed by relapse of cytopenias for several years (especially after first-line treatment); therefore, its clinical significance remains uncertain.<sup>37,38</sup>



**Figure 1. Initial treatment of hairy cell leukemia.** ^Typically Hb ≤10 g/dl and/or neutrophils <1 × 10<sup>9</sup>/L and/or platelets <100 × 10<sup>9</sup>/L. \*Irrespective of treatment setting (first versus later line of therapy). °If in the third trimester.

consecutive days, subcutaneously or IV; less commonly, once a week IV for 5 to 7 weeks<sup>56-58</sup>), whereas pentostatin is administered IV every 14 days for ~6 months to achieve an optimal response.<sup>12,29</sup> The standard pentostatin dose is 4 mg/m<sup>2</sup>, with initial dose modification for decreased performance status. Renal function is checked before each administration, and patients should receive IV fluids (1.5 L) with each dose to minimize renal toxicity. The longer duration of pentostatin therapy is less convenient but allows for changes in doses and treatment intervals to limit toxicity.

Both purine analogues can cause rashes<sup>59,60</sup> that can be exacerbated by antimicrobial prophylaxis, which should not be started at the same time. The effect on the risk of secondary malignancies in patients with HCL treated with purine analogues remains uncertain, with conflicting results from observational studies.<sup>61,62</sup> There are no randomized controlled comparisons between cladribine and pentostatin. Treatment choice can be based on patient comorbidity, active uncontrolled infection, and convenience. For patients with a compromised performance status or active uncontrolled infection, the administration of low-dose, intermittent pentostatin with careful dose titration delivered on a 14-day schedule has been effective and safe,<sup>31</sup> but chemotherapy-free options (eg, BRAF inhibitors, rituximab, obinutuzumab, and interferon alfa) should be considered in patients who are frail or those with active infections and those wishing to avoid chemotherapy. If HCL requires treatment during pregnancy, options include interferon alfa, rituximab, splenectomy, and (if in the third trimester) chemotherapy with cladribine.<sup>63</sup>

**Chemoimmunotherapy** The role of regimens combining chemotherapy (eg, cladribine, pentostatin, bendamustine, and fludarabine) and unconjugated monoclonal antibody immunotherapy (eg, rituximab and obinutuzumab) as first-line therapy has been evaluated.

#### First-line treatment of HCL with cladribine followed by rituximab

This regimen was evaluated in a clinical trial combining standard 5-day cladribine, followed 4 weeks later by 8 weekly standard doses of rituximab.<sup>64-66</sup> CR was achieved in 98% of the 108 patients. MRD (sensitivity, 0.01%) studies on bone marrow aspirate showed uMRD rate of 50% within 4 weeks of completing rituximab treatment and 78% at later time points. At a median follow-up of 7.8 years, the relapse rate was 3.6%.<sup>66</sup> In this study, detectable MRD at the first assessment after rituximab did not predict risk of relapse.<sup>66</sup> In a smaller retrospective and observational study, cladribine followed 17 to 60 days (median, 33 days) later by rituximab (n = 15 patients) was associated with improved disease-free survival compared with cladribine monotherapy (n = 14 patients).<sup>67</sup>

#### First-line treatment of HCL with cladribine and concurrent vs delayed rituximab

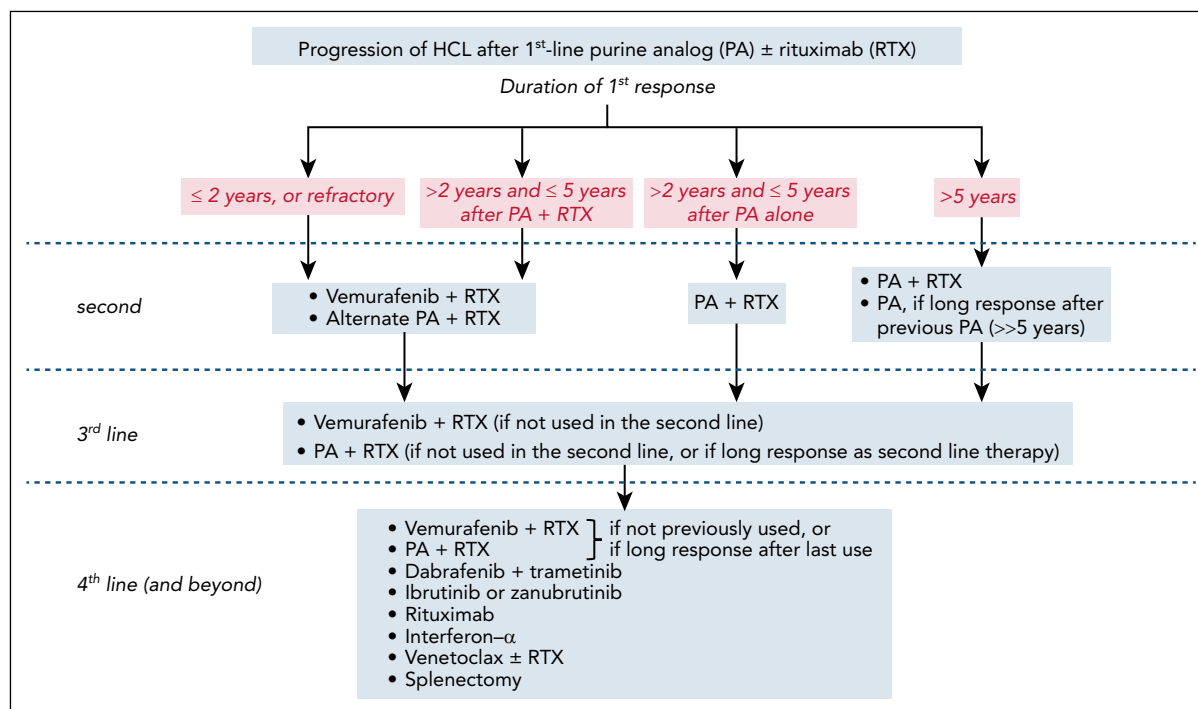
The rationale for concurrent cladribine-rituximab was preclinical data showing that rituximab increases the sensitivity of malignant lymphocytes to cladribine, suggesting that both drugs need to be given at the same time.<sup>68,69</sup> In a randomized (1:1) trial, 68 patients received either rituximab and cladribine therapy from day 1 (CDAR) or cladribine alone.<sup>30</sup> The 6-month CR rate was 100% (uMRD, 97%) for CDAR compared with 88%

(uMRD, 24%) for cladribine alone (CR,  $P = .11$ ; uMRD,  $P < .0001$ ). Patients treated with cladribine alone received rituximab therapy if they did not achieve CR or if blood MRD was positive after 6 months, and 100% achieved CR after rituximab. Compared with cladribine monotherapy, CDAR patients had a median  $50 \times 10^9/L$  transient drop in platelets by day 2, attributed to the rituximab, requiring prophylactic platelet transfusions for those with the lowest baseline platelet counts, but also had higher neutrophil and platelet counts at 4 weeks.<sup>69</sup> With a median follow-up of 6.5 years, only 1 of the 68 patients relapsed compared historically with 28% of the 90 patients relapsing after 6.5 years after CR was achieved by purine analogue monotherapy ( $P < .0001$ ).<sup>45</sup>

The available data suggest that compared with purine analogue monotherapy,<sup>29,42</sup> concomitant or sequential addition of rituximab increases uMRD CR rates and duration of response. The addition of rituximab increases the risk of adverse events, although only thrombocytopenia was increased after CDAR.<sup>13,30,64,65</sup> In addition, patients treated with chemoimmunotherapy for relapse after cladribine monotherapy had PFS and rates of relapse or death similar to those of patients treated with front-line chemoimmunotherapy.<sup>66</sup> These data suggest that initial therapy with purine analogues followed by chemoimmunotherapy for refractory and relapsing patients could have the same clinical outcome as initial chemoimmunotherapy, but continuing long-term follow-up could eventually show differences.

**Treatment of relapsed/refractory HCL** Long-term studies report a relapse risk of 30% to 40% in patients with HCL<sup>70</sup> and up to 58% in younger patients.<sup>38</sup> Most of these patients require retreatment, which is usually successful but with a generally shorter duration of response than initial therapy<sup>4,71-74</sup> and a potential for cumulative drug toxicity. Indications for treatment of relapsed HCL are the same as in initial treatment.<sup>12</sup> In patients with HCL who have refractory disease or early relapse (<2 years), the underlying diagnosis should be confirmed by repeating a bone marrow study.

Based on expert opinion because of limited data, our recommended therapy for patients relapsing >24 months after initial purine analogue monotherapy is purine analogue combined with rituximab, with an expected CR rate of ~70% and a 5-year survival rate of 94% (Figure 2).<sup>73,74</sup> For patients who are frail, older, or have comorbidities, as well as those with a long (>10 years) first response to purine analogue monotherapy, retreatment with only chemotherapy is a reasonable alternative option. Based on expert opinion and because of limited data, we also recommend that for patients with a response to initial chemotherapy of <24 months or with a response <60 months to initial chemoimmunotherapy, it is reasonable to retreat with a combination of an alternate purine analogue (pentostatin, cladribine, or fludarabine) and rituximab,<sup>75</sup> or bendamustine and rituximab.<sup>76,77</sup> An alternative approach is to consider nonchemotherapy treatments, including interferon alfa, rituximab, and off-label targeted agents as described in the next section. We also recommend these targeted therapeutic strategies, which are less myelotoxic and immunosuppressive, in patients with relapsed HCL and major comorbidities (eg, serious infections or frailty), irrespective of the duration of first response.



**Figure 2. Treatment of relapsed/refractory hairy cell leukemia.**

## Off-label targeted treatments

### BRAF inhibitors and combinations

#### Vemurafenib

Oral BRAF inhibitors target the gain-of-function *BRAF* V600E mutation present in the cells of >95% of the patients with HCL.<sup>23</sup> Vemurafenib was the first BRAF inhibitor to be studied in relapsed/refractory HCL in 2 phase 2 trials jointly reported by Italian and American investigators.<sup>78,79</sup> In both studies, vemurafenib was given at the dose of 960 mg twice daily (the same dose used in patients with *BRAF*-mutated solid tumors) for a fixed duration (median, 16-18 weeks). The Italian trial (28 patients) had an overall response rate (ORR) of 96% with a CR rate of 35%, whereas the American trial (26 patients) had an ORR of 100% with a CR rate of 42%. In the Italian trial, with a median follow-up of 23 months from the end of treatment, the median RFS was 19 months among patients who achieved CR and 6 months among patients with PR.<sup>78</sup> In a follow-up report of the American trial after a median follow-up of 40 months and an increase in the patient cohort to 36 patients, the best ORR was 86%, the CR rate was 33%, and the median RFS was 19 months.<sup>79</sup> Among the relapsed patients, response rates with vemurafenib retreatment were 50% to 67%, with 50% to 86% of the patients achieving complete hematological recovery, but with inferior depth and duration of response compared with initial therapy.<sup>78,79</sup>

Vemurafenib can be used in combination with other active agents and earlier in the disease course. In a phase 2 trial, 30 patients with relapsed/refractory HCL received vemurafenib (960 mg twice daily for 8 weeks) and rituximab (8 doses) and had a CR rate of 87%, with 60% uMRD.<sup>5</sup> At a median follow-up of 37 months, PFS was 78%. Similar results were obtained in a real-world study of this regimen in 54 patients with relapsed/refractory HCL.<sup>80</sup> In another phase 2 trial, 30 patients with

newly diagnosed HCL received vemurafenib (960 mg twice daily for 16 weeks) plus obinutuzumab (5 doses), with 27 patients completing all therapy.<sup>10</sup> The CR rate was 90%, with 96% of the patients having uMRD CR. At a median follow-up of 34.9 months, no patients had relapsed.

The optimal vemurafenib regimen and role of addition of rituximab have not been studied in randomized clinical trials. Retrospective observational studies of vemurafenib monotherapy at doses ranging from 240 to 1920 mg/d suggest shorter treatment-free survival for doses <480 mg twice daily.<sup>81,82</sup> In the studies combining vemurafenib and rituximab for treatment of relapsed/refractory HCL, lower vemurafenib dose intensity was associated with treatment failure.<sup>5,80</sup> Determining the most effective and least toxic regimen for vemurafenib, alone or with rituximab, will require a randomized trial.

Many patients with HCL requiring therapy have serious comorbidities, including infections, cytopenia, and frailty, and could benefit from regimens with a low risk of additional myelotoxicity and immunosuppression, as first-line or subsequent treatment. Vemurafenib monotherapy (usually at lower doses of 480-960 mg/d) and the combination of rituximab plus vemurafenib (at standard or lower doses) have been successfully used in patients with HCL complicated by serious infections.<sup>33,34,83-85</sup> Vemurafenib does not deplete T cells or B cells and is therefore unlikely to impair patient responses to vaccines against severe acute respiratory syndrome coronavirus 2 in patients with HCL.<sup>86</sup>

Although vemurafenib is not approved for HCL by regulatory drug agencies, it is frequently used off label in many countries. Therapy with vemurafenib plus rituximab is recommended for patients refractory to purine analogues or those with early

relapse after purine analogues ( $\leq 2$  years or  $\leq 5$  years if the purine analogue had been combined with rituximab) or those with  $\geq 2$  relapses. Furthermore, vemurafenib, alone or with rituximab, is also recommended for patients with serious infections.

### Dabrafenib

A phase 2 trial of 12 weeks of dabrafenib for the treatment of 10 patients with relapsed/refractory HCL reported an ORR of 80%, with 30% CR rate.<sup>87</sup> Resistance to BRAF inhibition is often because of bypass MEK/extracellular signal-regulated kinase (ERK) phosphorylation downstream of mutant BRAF.<sup>17</sup> In a phase 2 trial of patients ( $n = 55$ ) with progressive HCL after at least 2 lines of therapy, dabrafenib was combined with the MEK inhibitor trametinib.<sup>6</sup> Dabrafenib and trametinib were given together until disease progression or unacceptable toxicity for a median of 38 months. ORR was 89%, with 66% CR rate (uMRD, 9%) and a 2-year PFS of 95%. Serious adverse drug effects occurred in 35% of the patients and resulted in 22% of the patients stopping the therapy. The rate of nonmelanoma skin cancer included 24% basal cell and 16% squamous cell carcinomas, although given the patient ages and number of years of follow-up, it was unclear whether these rates were study related.

BRAF and/or MEK inhibitors, followed by the addition of rituximab, have been successfully used as time-limited treatment in rare patients with relapsed/refractory HCL bearing BRAF short-in-frame deletions or MAP2K1 mutations.<sup>22,23,88</sup>

**BTK inhibitors** Ibrutinib, a first-generation oral covalent-binding inhibitor of Bruton tyrosine kinase (BTK), blocks B-cell receptor signaling in HCL cells.<sup>89</sup> A phase 2 study enrolled 37 patients with relapsed/refractory HCL/HCLv who were treated with daily ibrutinib for up to 6 years.<sup>7</sup> ORR increased over time to reach 54% with an estimated 36-month PFS of 73% and overall survival (OS) of 85%.

The second-generation inhibitor zanubrutinib was studied in 12 patients with relapsed/refractory HCL on a phase-1/2 clinical trial.<sup>90</sup> Zanubrutinib treatment for a median of 33 months achieved an ORR of 58.3%, and at 36 months, the PFS was 80%, and OS was 82%.

Although the kinetics of cytopenia resolution are slower compared to BRAF inhibitors, BTK inhibitors represent an additional treatment option in suitable patients or in cases of no access to BRAF inhibitors.

**BCL2 inhibitors** HCL cells express BCL2 and are sensitive to the BCL2 inhibitor venetoclax in vitro.<sup>9,91</sup> In total, 6 patients with relapsed/refractory HCL, whose most recent previous treatment was vemurafenib and rituximab, were treated with venetoclax for up to 12 cycles.<sup>9</sup> Of these, 3 patients responded with 2 CRs. Sequential addition of rituximab (for up to 8 cycles) in 3 of these patients improved the treatment response. An additional case report describes a patient with relapsed HCL who achieved a uMRD CR after 48 months of venetoclax therapy.<sup>8</sup> These data suggest that venetoclax, although slower in action compared with BRAF inhibitors, is active in relapsed/refractory HCL, and a clinical trial of venetoclax is ongoing in relapsed/refractory HCL/HCLv (ClinicalTrials.gov identifier: NCT06311227).

## Cellular therapies

### Chimeric antigen receptor T-cell therapy

The bright expression of the B-cell marker CD22 in HCL provides a rationale to explore anti-CD22 chimeric antigen receptor T-cell therapy in clinical trials (ClinicalTrials.gov identifiers: NCT04815356 and NCT06340737), and preliminary results have been recently published on 2 patients with relapsed/refractory HCL.<sup>92</sup>

### allo-HCT

The European Society for Blood and Marrow Transplantation (EBMT) reported outcomes of allogeneic hematopoietic cell transplant (allo-HCT) performed on 22 patients with relapsed/refractory HCL from 1996 to 2018.<sup>93</sup> Day 100 nonrelapse mortality was 14%, with the best ORR of 64% and a CR in 59%. At a median follow-up of 54.5 months, the 5-year nonrelapse mortality was 26%, PFS was 46% with no plateau, OS was 46%, and relapse rate was 41%. Given the appreciable early transplant-related mortality, the lack of plateau in the PFS curve, and the number of novel approaches now available for HCL, all other therapeutic options should be exhausted before undertaking allo-HCT in HCL.

## HCLv

### Background

HCLv is a mature B-cell neoplasm that was first differentiated from HCL in the 1980s because of the higher rate and level of lymphocytosis, morphology of circulating malignant lymphocytes (prominent nucleoli), absence of monocytopenia, and bone marrow with no or minimal reticulin fibrosis that could be aspirated.<sup>94,95</sup> Additional differences were subsequently noted in clinical presentation, disease biology, treatment response, and prognosis. HCLv was recognized as a provisional disease entity by the World Health Organization (WHO) in 2008<sup>96</sup> within the splenic B-cell lymphoma/leukemia unclassifiable category, comprising HCLv and splenic diffuse red pulp small B-cell lymphoma (SDRPL). This was retained in the revised fourth edition (2017)<sup>97</sup> and adopted by the 2022 International Consensus Classification of mature lymphoid neoplasms.<sup>98</sup> In 2022, the fifth edition of the WHO classification defined a new basket category of "splenic B-cell lymphoma/leukemia with prominent nucleoli" combining HCLv with selected cases of B-cell prolymphocytic leukemia (B-PLL) within the category of splenic B-cell lymphomas and leukemias, which also includes HCL, splenic marginal zone lymphoma (SMZL), and SDRPL.<sup>99,100</sup> We continue to use the diagnosis of HCLv as defined in the revised fourth edition of the WHO classification and the 2022 International Consensus Classification.<sup>97,101</sup>

HCLv is a rarer disease than HCL and can be difficult to diagnose. The collection of accurate data on HCLv epidemiology over time has been complicated by the identification of SDRPL as a separate entity with some features in common with HCLv and the revisions to the disease description and nomenclature. The initial estimates of HCLv incidence of 0.03:100 000 per year ( $\sim 10\%$  of HCL)<sup>97,102,103</sup> were revised upward based on a US study published in 2016 to 0.2/100 000 per year.<sup>104</sup> The median age at diagnosis of HCLv is  $\sim 70$  years compared with 50 to 60 years for HCL.<sup>17</sup> Unlike HCL, which has a male to female ratio of 4:1,<sup>17</sup> there is no observed sex difference in the incidence of HCLv.<sup>94</sup> There are limited data on the survival of patients with HCLv. A 2012 study reported a median 5-year

survival of 57%, which was significantly shorter than the 84% for patients with SMZL.<sup>105,106</sup>

## Establishing the diagnosis

**Clinical features** Splenic B-cell lymphomas (HCL, HCLv, SDRPL, and SMZL) have overlapping clinical presentations, which include splenomegaly and its sequelae, circulating malignant B-lymphocytes with surface projections (“hairy cells”), cytopenia, infections, and constitutional symptoms. Lymphadenopathy is rare. These diseases can often be differentiated by clinical presentation, blood counts, immunophenotype of malignant cells, and genetic characteristics, but definitive diagnosis can be difficult in some patients without histological examination of splenic tissue.<sup>107,108</sup>

## Recommendations for diagnosis

**Peripheral blood** HCLv often presents with anemia, thrombocytopenia, lymphocytosis, and a normal monocyte count. The morphology of circulating malignant lymphocytes ranges from condensed nuclei and prominent nucleoli to those with dispersed chromatin and irregular nuclear contours. The number and distribution of surface projections are variable.<sup>97</sup>

**Bone marrow** Fibrosis is rare, and cells can usually be aspirated. Infiltrating malignant cells can be difficult to identify in the bone marrow biopsy without immunohistochemical staining for B cells, especially in the case of purely intrasinusoidal involvement.<sup>97</sup>

**Spleen** HCLv, HCL, and SDRPL primarily involve the red pulp of the spleen. HCLv and HCL cells diffusely infiltrate the red pulp and dilate sinusoids, forming red blood cell “lakes,” whereas the white pulp is atrophied.<sup>97</sup> HCLv can usually be differentiated from HCL by immunophenotypic and genetic analysis. In contrast, differentiation between HCLv and SDRPL may be difficult even if a splenectomy specimen is available, whereas SMZL is differentiated primarily by splenic white pulp involvement.<sup>107,109</sup> B-PLL expands white pulp nodules and infiltrates the red pulp.<sup>97</sup>

**Immunophenotype** HCLv usually have bright expression of CD20 and immunoglobulin light chain and coexpress CD11c, CD103, and DBA.44.<sup>94,97</sup> Cells usually do not express CD25, CD123, CD200, annexin A1, cyclin D1, or tartrate resistant acid phosphatase.<sup>94,97</sup>

**Genetic analysis** HCLv has a gene expression profile distinct from HCL but does not have defining genetic characteristics.<sup>110</sup> Unmutated *IGHV4-34* use and *MAP2K1* mutations are much more frequent in HCLv than in other splenic B-cell lymphomas. Although HCLv, SDRPL, and SMZL do not have *BRAF V600E*, rare patients with HCL are also negative for *BRAF V600E*,<sup>17,23-25,97</sup> so the absence of *BRAF* mutations alone is not a reliable marker of HCLv.<sup>94,111</sup>

**Chromosome analysis** Deletion of 17p13 is reported in up to 42% of patients and predicts a poorer prognosis. Other reported recurrent genetic aberrations include deletions of 18q and 7q and gains of material on chromosome 5.<sup>94,112,113</sup>

***IGHV* analysis** Patients with HCLv have a skewed *IGHV* use with a high frequency of somatically unmutated (>98% germ line homology) *VH4-34* (17%-55%), which is associated with poorer prognosis.<sup>94,105,106,114</sup> Unmutated *IGHV* and *TP53* dysfunction is more frequent in patients with HCLv cells using *IGHV4-34*.<sup>105,114</sup>

***MAP2K1* mutation** Activating mutations in the kinase domain of *MAP2K1* occur in both HCLv (~20%-40% of the patients with HCLv) and *BRAF* wild-type HCL but are rare in other hematological malignancies.<sup>23,26,94</sup>

**Differential diagnosis** The differential diagnosis of HCLv includes HCL, SDRPL, SMZL, blastoid mantle cell lymphoma, and B-PLL. HCLv can usually be differentiated from HCL because of prominent nucleoli, presence of circulating monocytes, and lack of expression of annexin-1, *BRAF V600E*, CD25, and CD123, although rare exceptions exist.<sup>23,115</sup> Distinguishing HCLv from SDRPL and SMZL can be more difficult. HCLv, SMZL, and SDRPL can have overlapping immunophenotypes, although CD103 expression is relatively rare in SMZL and SDRPL.<sup>102,107,108,111</sup> The circulating malignant lymphocytes in SDRPL and SMZL can have smaller or no nucleoli and a more polar distribution of cytoplasmic villous projections, but morphology can be variable. HCLv is more likely to have prominent nucleoli, a *MAP2K1* mutation, or an unmutated *IGHV4-34* compared with SMZL or SDRPL.<sup>94,111,116</sup> The expression of CD103 is more likely in HCLv compared with B-PLL. In patients with an immunophenotype intermediate between HCLv and HCL and in the absence of *BRAF V600E*, a definitive diagnosis can be difficult to reach unless the whole constellation of all other clinicopathological features is considered, including the presence/absence of monocytes, prominent nucleoli, unmutated *IGHV4-34*, and other genetic lesions of *BRAF*.<sup>17,23-25,115</sup> Splenectomy is useful for the diagnosis of SMZL, which primarily involves the white pulp, but may not be sufficient to discriminate HCLv from SDRPL, both of which predominantly involve the red pulp.<sup>107,109</sup>

## Treatment

The standard of care for initial treatment of progressive HCLv is cladribine and rituximab.<sup>113,117</sup> Therapy is not curative, and patients can be initially observed if treatment is not yet indicated.

**Chemotherapy** HCLv is considerably less responsive than HCL to treatment with purine analogue monotherapy with cladribine or pentostatin. Observational studies report low CR rates (~7%) and a short median duration of response (~15 months).<sup>113,117</sup>

**Chemoimmunotherapy** Regimens combining purine analogues with anti-CD20 monoclonal antibodies have improved treatment responses in patients with HCLv. In a phase 2 trial, cladribine (0.15 mg/kg IV daily for 5 days) and rituximab (375 mg/m<sup>2</sup> IV weekly for 8 weeks) starting on day 1 in 10 patients with HCLv (2 previously untreated) achieved a sustained CR in 9 patients. At a median follow-up of 27 months, 8 patients had uMRD (sensitivity, <0.002%).<sup>117</sup> The study regimen was then modified to treat patients with MRD with a second course of

rituximab at 6 months. An update published after enrollment of 10 additional patients (for a total of 20) with a median follow-up of 69.7 months reported 95% CR rate, 80% uMRD, 5-year PFS of 63%, and OS of 74%.<sup>113</sup> These results, which are the best prospective data reported in HCLv, point to cladribine plus rituximab as a standard of care in this disease and suggest that MRD and TP53 testing could be useful in managing patients with HCLv because achievement of uMRD and lack of TP53 dysfunction predicted longer PFS and OS.<sup>113</sup> There are limited data on the use of other chemoimmunotherapy regimens in HCLv, with reports of responses to treatment with pentostatin and rituximab and bendamustine and rituximab.<sup>76,77,118,119</sup>

**Targeted small-molecule therapy** Ibrutinib has been shown to be an effective therapy for patients with HCLv. Of the 9 patients (2 previously untreated), 1 achieved CR, 4 PR, and 3 had stable disease.<sup>7</sup> The cohort of HCL (n = 28) and patients with HCLv had an estimated 36-month PFS of 73% and OS of 85%, with no statistically significant difference in outcome detected between patients with HCL compared with HCLv in this small study.<sup>7</sup> Trametinib, which inhibits MEK1 and MEK2, has been reported to be clinically effective in a patient with HCLv harboring an activating MAP2K1 mutation.<sup>120</sup> There is also 1 report of a patient with HCLv responding well to combination therapy with ibrutinib and venetoclax.<sup>121</sup>

**Splenectomy** For some patients, splenectomy may be required for a definitive diagnosis. Patients with HCLv can have a therapeutic response to splenectomy with resolution of symptoms and recovery of cytopenia. There are limited data on the therapeutic value of splenectomy, but a recently published observational study reported that the median time to next treatment after splenectomy was not reached for 9 patients at a median follow-up of 3.9 years.<sup>107</sup>

**Cellular therapy** The only clinical data on cellular therapy in HCLv are limited to 1 report of response to allo-HCT in 2 patients.<sup>93</sup>

## Supportive care

There are limited data to guide supportive care in patients with HCL/HCLv, and management is based in part on experience with other indolent B-cell lymphomas with regional variations in approach. Patients with indolent B-cell lymphomas, including patients with HCL and HCLv, are at increased risk of serious infections, and this risk is increased by treatment with purine analogues. The risk of other complications of immune suppression, including second cancers, is less well defined.<sup>122,123</sup>

## Infection after treatment with purine analogues

Patients treated with purine analogue therapy have a high risk (20%-30%) of severe infection because of prolonged neutropenia (up to ~6 weeks after therapy) and severe lymphopenia (~6 months duration).<sup>31,83-85,124</sup> Although observational studies suggest that prophylactic granulocyte colony-stimulating factor does not decrease the overall rate of neutropenic fever in patients with HCL treated with cladribine,<sup>124,125</sup> this growth factor treatment could be appropriate in a subpopulation of patients with high risk of infection. Patients receiving purine analogues should be considered for limited-duration prophylactic antimicrobial therapy to decrease

the risk of reactivation of varicella-zoster virus, herpes simplex virus, and *Pneumocystis jirovecii*.

## Tumor lysis syndrome

Tumor lysis syndrome is very rare in HCL/HCLv, and allopurinol is contraindicated because of the high risk of adverse drug reactions.<sup>126</sup>

## Vaccination

Vaccination against the varicella-zoster virus, *Streptococcus pneumoniae*, hepatitis B virus, influenza virus, and COVID-19 should be considered for all patients. Live vaccines are contraindicated.

## Patient education

Patients should be educated about the risk of infection and the need to immediately seek medical care if symptomatic or febrile. All blood product transfusions should be irradiated to decrease the risk of transfusion-associated graft-versus-host disease.

There is a clear and important need for studies on the complications of HCL/HCLv to generate data that could improve supportive care. The recent establishment of an international HCLF database<sup>127</sup> will facilitate these studies and provide data to plan more effective management. Special topics that could further benefit supportive care include more data on management of pregnancy in patients with HCL/HCLv, maintenance of fertility, and psychosocial needs of patients and their families. In the interim, the HCLF continues to provide resources for patients and caregivers who can request expert input on the management of complex HCL/HCLv-related problems ([info@hairycellleukemia.org](mailto:info@hairycellleukemia.org)).

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## Footnotes

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