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Hairy cell leukemia: update and current therapeutic approach

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Abstract

Purpose of review—In this review, we discuss the pathogenesis and standard therapeutic approach to hairy cell leukaemia (HCL) as well as newer targeted therapies under investigation showing promising end-points in treating HCL.

Recent findings—HCL is an indolent B-cell leukaemia. Historically, HCL patients have achieved excellent response to purine nucleoside analogues and single purine analogue treatment with pentostatin or cladribine is currently the standard of care for initial treatment. Most patients achieve complete remission with this form of therapy. However, long-term follow-up has demonstrated that a large number of patients eventually develop relapsed disease. Relapse disease tends to be more difficult to treat and refractory to the same purine analogues. Development of relapsing and refractory disease after initially achieving complete remission with purine analogue treatment has generated a need for alternative therapies.

Summary—Identification of the *BRAFV600E* mutation in nearly 100% of HCL patients has provided rationale for inclusion of BRAF inhibitors into the therapeutic armamentarium to treat HCL. Clinical trials are currently underway measuring efficacy of vemurafenib in achieving clinical response in relapsed/refractory HCL and also toxicity. Other novel therapies with monoclonal and immunotoxin-conjugated antibodies have also shown promising response in recent investigational studies.

Keywords

BRAFV600E; cladribine; dabrafenib; hairy cell leukaemia; *MAP2K1*; pentostatin; vemurafenib

INTRODUCTION

Hairy cell leukaemia (HCL) is unique, chronic B-cell lymphoproliferative disorder that accounts for nearly 2% of all leukaemias with approximately 900 new cases per year in the USA [1]. HCL derives its name from the distinct cellular morphology and appearance, first coined ‘hairy cells’ by Schreck and Donnelly in 1966 [2], to describe the hair-like villi and

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membrane ruffles of the characteristic HCL cells. Recent investigations into the pathogenesis of HCL have uncovered novel additional features characteristic of this disease and continue to highlight HCL as a unique entity amongst non-Hodgkin lymphomas. Moreover, improvements in the understanding of the molecular pathogenesis of HCL have identified additional novel therapeutic targets for the treatment of HCL patients. In this review, we describe the recent advances in our understanding of the diagnosis, pathophysiology and therapy of HCL.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

HCL tends to occur in elderly men more than any other demographic, as the median age of diagnosis is 52 and there is a higher incidence in men with ratio of male to female diagnosis of nearly 4 : 1 [1]. HCL is also more common in whites than any other race. The ratio of whites to nonwhites diagnosed with HCL was reported at nearly 3 : 1 [1].

The clinical hallmarks of HCL include splenomegaly, pancytopenia and the infiltration of tissues such as liver and bone marrow with classic HCL cells. The majority of patients with HCL present with fatigue, weakness and recurrent infections, symptoms secondary to cytopenia. Nearly 96% of HCL patients have splenomegaly at diagnosis [3]. Initial work up should include complete blood count with differential and peripheral smear. Most patients are pancytopenic with complete blood count revealing anaemia (haemoglobin <10 g/dl), neutropenia (absolute neutrophil count <1000/ μ l), monocytopenia (monocytes <100/ μ l) and thrombocytopenia (platelet count <100 000/ μ l) but in very rare cases, leukocytosis (white blood cells >10 000/ μ l) [3].

Diagnosis of HCL is made on the basis of the presence of atypical leukaemic cells with its 'hairy' appearance in peripheral blood and bone marrow biopsy showing a classic 'fried egg' pattern. Bone marrow aspiration is frequently unsuccessful in HCL patients because of reticulin fibrosis of the marrow. Flow cytometric analysis of peripheral blood or marrow is used to confirm the diagnosis of HCL. Immunophenotyping analysis reveals that HCL cells express CD11c, CD19, CD20, CD22, CD35, CD79a, CD103, CD123 along with tartrate-resistant acid phosphatase. HCL cells are usually negative for CD5, CD10, CD23, CD27 and CD79b. There is an established scoring system proposed by Matutes *et al.* [4] for diagnosing HCL on the basis of immunophenotype. This criterion is based on identification of four of the above surface markers (CD11c, CD25, CD103, CD123). One point is given for each positive marker. More than 98% of patients with classic HCL achieve a score of 3–4, while patients with a score of 0–2 likely have HCL variant (HCLv) or splenic marginal zone lymphoma with villous lymphocytes (SMZL), two different diseases that can mimic and are often confused for classic HCL. These two HCL-like malignancies are often mistaken as HCL due to disease features and their cellular appearance. HCLv and SMZL both present with splenomegaly (although splenomegaly of HCLv is often worse than classic HCL) and both lack nodal involvement just as in classic HCL [5]. Cellular morphology also resembles that of HCL, as they possess similar 'hairy' feature. HCLv and SMZL can be distinguished from true HCL in that these two B-cell malignancies do not contain the *BRAFV600E* mutation (as described below) [6] and fail to respond to purine analogues. Other tests that may be done at diagnosis of HCL include measurement of serum immunoglobulin levels,

somatic *IGHV* mutational status and *VH* gene usage. Adverse prognostic indicators once diagnosis of HCL is made include unmutated *IGHV* and expression of the *IGHV* VH-34 (*IGHV*4-34⁺) immunoglobulin rearrangement [7].

PATHOPHYSIOLOGY

HCL cells lack two classic elements typical of most chronic B-cell malignancies: HCL cells do not express reciprocal chromosomal translocations seen in most mature B-cell lymphomas and HCL patients lack clinically evident lymph node involvement (although this may be seen in late stages of the disease) [8]. Other features making HCL an atypical mature B-cell lymphoma are the frequent presence of bone marrow fibrosis and the exquisite responsiveness of the disease to therapy with single purine nucleoside analogues.

The genetic pathogenesis of HCL was obscure until the last 4 years. The discovery of the *BRAF*V600E mutation in HCL by Tacci *et al.* [9] in 2011 provided a breakthrough in our understanding of the pathogenesis of HCL. The *BRAF*V600E mutation was initially seen in all 47 of 47 HCL patients in the study by Tacci *et al.* [9]. Later studies verified that the *BRAF*V600E mutation is present in more than 97% of classic HCL cases [10–13] yet does not exist in HCLv and may also be absent in *IGHV*-34 along with HCL [6,14[■]]. Moreover, recurrent activating mutations in *MAP2K1*, the kinase immediately downstream of *BRAF*V600E, have been noted in patients with HCLv and *IGHV*4-34 and HCL [14[■]]. These data implicate activation of the MAP kinase pathway and phosphorylation of ERK as critical components of HCL pathogenesis [13], concepts that were previously not understood until the discovery of these mutations in HCL and HCLv. Rare exon 11 *BRAF* mutations have since been noted in the very small percentage (<5%) of *BRAF*V600E-wildtype classic HCL patients [15].

Similar to the genetic cause of HCL, the cellular pathogenesis of HCL also remained limited until recently. The hallmark leukaemic cell in HCL is thought to be derived from a mature B cell as HCL cells express CD19, surface immunoglobulin [16], and clonal rearrangements of immunoglobulin heavy and light chain genes [17,18], all features of mature B cells [8,19]. At the same time, HCL cells express markers not seen in normal B cell subsets including CD103 and CD11c, cell surface antigens typically expressed on intraepithelial T cells and monocytes, respectively [20,21]. In addition, HCL patients have long been known to have clinical features disparate from most mature B cell malignancies, notably the conspicuous lack of lymph node involvement and frequent splenomegaly due to extramedullary haematopoiesis [19]. Moreover, gene expression microarray studies of HCL cells have not fully identified a counterpart along the continuum of B cell development as the cell-of-origin of HCL [22]. Thus, the cell-of-origin of HCL has been long debated [23–26]. We recently identified that a proportion of long-term haematopoietic stem cells of HCL patients bear *BRAF*V600E mutations [27[■],28]. Moreover, expression of *BRAF*V600E at the level of haematopoietic stem cells resulted in a lethal, transplantable haematopoietic disorder characterized by anaemia, thrombocytopenia, splenomegaly due to extramedullary haematopoiesis, increased common lymphoid progenitors and proB cells, increased clonogenic capacity of B cells and germinal centre hyperplasia in response to alloantigen. In contrast, when *BRAF*V600E expression is restricted to pan-B lymphocyte expression, no

overt phenotype outside of the B cell lineage is seen. These data suggest that the phenotypic features of HCL are linked to dysfunctional haematopoietic stem/progenitor cells bearing the *BRAFV600E* mutation.

Given that expression of the *BRAFV600E* mutation alone *in vivo* does not result in development of morphologic HCL, the link between the molecular pathogenesis of HCL and this characteristic morphologic feature of HCL is still not fully resolved. The 'hairy' cellular appearance and membrane projections seen in HCL are thought to be secondary to their overexpression of β -actin [22] and pp52 or leukocyte-specific intracellular phosphoprotein (LSP1) [29]. A polymerized actin (or F-actin) supports the filamentous membrane projections of HCL. It is believed that F-actin and LSP1 are two pivotal cellular components for development and maintenance of the hairy projections seen in HCL [8]. The 'hairy' morphology of these leukaemic cells can also be attributed to their overexpression of the Rho family of small GTPases [30]. These include CDC42, RAC1 and RHOA. These proteins have been shown to induce actin spike formation when they are overexpressed in non-HCL cells. The precise molecular mechanism by which HCL cells overexpress β -actin, F-actin and Rho GTPases is not clear nor is it clear whether these features relate to the mutations activating MAP kinase pathway in HCL and HCLv.

FIRST-LINE TREATMENT

The disease course of HCL is usually indolent and a watch-and-wait approach can be employed in asymptomatic patients who have received careful instructions on signs and symptoms of disease progression. Patients developing pancytopenia and symptomatic splenomegaly require treatment. Prior to 1984, splenectomy was considered treatment of choice for HCL [31]. The introduction of interferon-alpha for HCL improved survival over splenectomy and made the use of systemic therapy for HCL treatment common [32]. Today, purine nucleoside analogues are considered the standard initial therapy for HCL. Treatment with single agent pentostatin (2-deoxyco-formycin) [33] or cladribine (2-chlorodeoxyadenosine) [34,35] has shown equal efficacy with similar endpoints in HCL patients. Pentostatin results in complete remission rates of more than 75% [33], with 10-year overall survival rates ranging from 80 to 90% of patients [36]. Pentostatin is administered at 4 mg/m² intravenously in 2-week intervals until patients achieve complete remission or maximum response. Pentostatin is well tolerated, but adverse effect seen with purine analogue includes prolonged myelosuppression with subsequent immunosuppression (with decreased CD4⁺ and CD8⁺ cells) leaving patients at an increased risk for opportunistic infections. More common adverse effects of pentostatin are neutropenic fevers, nausea, vomiting, photosensitivity, skin rash and cardiac toxicity including possible cardiac arrhythmias [8,9].

Cladribine has become the preferred first choice of treatment in HCL because of its safer drug profile and easier administration regimen than pentostatin. Treatment with cladribine typically consists of a single 5–7 day course at 0.1 mg/kg/day via intravenous infusion until complete remission is attained. Approximately 76–91% of patients treated with cladribine are expected to achieve complete remission with nearly 40% of these patients relapsing [36]. The main adverse effects of cladribine therapy are neutropenic fevers and thrombocytopenia.

There are no data supporting advantage of one purine analogue over the other [37[■]]. Choice is at the discretion of provider based on severity of cytopenias and whether there is presence of renal impairment. Pentostatin is contraindicated in patients with renal impairment (glomerular filtration rate <60 ml/min). Dose reduction is required for those with glomerular filtration rate between 40 and 60 ml/min. Pentostatin is preferred in those with severe cytopenias.

SALVAGE TREATMENT

Complete remission in HCL is defined as morphologic resolution of leukaemic cells on morphologic review of peripheral blood and bone marrow without immunohistochemical stains as well as resolution of cytopenias (normalization of blood counts), hepato-splenomegaly and adenopathy [37[■]]. Early relapse of HCL has been associated with the presence of minimal residual disease (MRD) [38]. There is no consensus definition for MRD and MRD has been variably detected on the basis of flow cytometry, PCR for immunoglobulin heavy chains, as well as immunohistochemical staining [38,39]. Regardless, currently, only symptomatic relapse is recommended to be treated in HCL, as patients can continue to have improvement in clearance of HCL cells even after achieving defined complete remission. Although there are no widely accepted guidelines on how or when patients achieving complete remission should be screened for MRD, it is commonly recommend to wait several months after achieving complete remission before examining the bone marrow for MRD. There is also no official consensus on treatment of relapsed disease, but patients with first time, late relapse (>5 years since initial treatment) can be treated with the same purine analogue [37[■]]. In cases of intermediate relapse disease (2–5 years since initial treatment), second-line treatment remains a purine analogue, which can be different than the initial agent, with or without the addition of Rituximab [39,40]. This approach of combining purine analogue therapy with the anti-CD20 mAb Rituximab has shown promising outcome in those with relapse disease following initial treatment with purine analogues. Ravandi *et al.* [41] reported a 100% complete remission rate of patients treated with 8 weeks of Rituximab 1 month after patients had received standard therapy (Cladribine). Of those receiving cladribine, only 12 of 27 had achieved complete remission prior to treatment with Rituximab. On the basis of these data, the addition of Rituximab may improve outcome and increase complete remission rate in patients who relapse after treatment with cladribine alone. When relapse occurs at less than 2 years since initial therapy, the diagnosis of HCL must be recon-firmed with testing for *BRAFV600E* mutation. Once confirmed, enrolment in a clinical trial testing possible therapeutic modalities involving agents such as immunotoxins and B-rapidly accelerated fibrosarcoma kinase (BRAF) and/or mitogen-activated protein kinase (MEK) inhibitors should be considered. Retreatment with the same purine analogue therapy along with Rituximab and use of bendamustine have also previously been reported in case series.

ROLE OF BRAF INHIBITORS AND OTHER NOVEL THERAPY

Given that nearly 100% of classic HCL patients bear the *BRAFV600E* mutation and the data implicating *BRAFV600E* mutations in the initiating cells for HCL, two clinical trials have been initiated to understand the safety and efficacy of the BRAF inhibitor vemurafenib for

patients with relapsed and/or refractory HCL (NCT01711632 and EudraCT 2011-005487-13; Table 1 [42–50]). In addition, several case reports and case series have noted a rapid and dramatic efficacy of vemurafenib as well as dabrafenib in HCL [44–51]. Table 1 summarizes the published clinical experience and publicly presented intermediate clinical results of the ongoing phase II studies examining the efficacy of RAF inhibition for HCL.

Other promising novel therapeutic agents currently being studied for HCL include the recombinant immunoconjugates targeting CD22, known as BL22 and the modified form of BL22 known as moxetumomab pasudotox. On the basis of early phase clinical trial results [52], which revealed an overall response rate of 86% and a complete remission rate of 46% in relapsed and refractory HCL, a phase III clinical trial of moxetumomab pasudotox is now underway for HCL patients with relapsed/refractory HCL (NCT01829711).

CONCLUSION

Due to a series of clinical and biological advances, HCL has moved from a disease with an obscure cause and treatment to a disease with a well defined molecular pathogenesis and therapeutic management strategy. Current standard therapy with either cladribine or pentostatin will result in a durable complete remission in 75–90% of patients. Roughly 40% of treated patients will eventually develop relapse disease, some that may become refractory to retreatment with purine analogues. The discovery of the *BRAFV600E* mutation, which is a disease-defining genetic event in the pathogenesis of classic HCL, has led to both biologic and therapeutic advances in this disease. From a biological standpoint, future efforts to understand what mutations, if any, coexist with the *BRAFV600E* mutation in HCL will be enlightening. From a standpoint of therapy, imminent publication of the two ongoing prospective phase II studies of vemurafenib in HCL patients with relapsed/refractory disease will be critical in defining the role of these agents in HCL. Moreover, future efforts to understand the possible use of vemurafenib in combination with other therapeutic approaches in HCL, such as with Rituximab, will also be very important. Finally, it may also be fruitful to address the potential role of RAF inhibition as frontline therapy of HCL as well as the possible use of MEK inhibitors in the therapy of HCLv and IGHV4-34 and HCL with gain-of-function *MAP2K1* mutations.

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KEY POINTS

- HCL is an indolent clonal disorder characterized by the *BRAFV600E* mutation in nearly 100% of patients and aberrant B-lymphoid cells with a characteristic 'hair-like' morphologic appearance.
- Standard therapy of HCL with purine nucleoside analogues is effective in achieving complete remission in patients with symptomatic disease.
- Relapse and refractory disease is common in HCL even after standard therapy.
- Discovery of the *BRAFV600E* mutation in HCL has created a rationale for alternative targeted salvage therapies for HCL in which BRAF inhibitors are showing promising outcomes.

Table 1

Case series, case reports, and ongoing clinical trials reporting the use of RAF inhibitors in the treatment of hairy cell leukaemia

Reference	Number of patients enrolled in study/demographics	Vemurafenib dosing	Dose duration	Response	Comments
Park <i>et al.</i> [42]	Multicentre phase II clinical trial with 22 patients enrolled (NCT01711632)	960 mg p.o. b.i.d. starting dose	3 or 6 months of therapy on protocol	Of 17 patients evaluated for disease response, there was 17/17 ORR (100%) with 6 patients achieving CR and 7 achieving PR	Of the 6 patients achieving CR, 2 had MRD and 4 without MRD
Tiacci <i>et al.</i> [43]	Multicentre phase II clinical trial with 28 patients enrolled (EudraCT 2011-005487-13)	960 mg p.o. b.i.d. starting dose	3 or 6 months of therapy on protocol	25/26 evaluable patients (96%) had ORR; 9/26 patients achieved CR, while 16/26 achieved PR after a median of 8 and 9 weeks of therapy, respectively	All patients achieving CR had evidence of MRD at the end of therapy. Retreatment with vemurafenib was effective in those relapsing after CR but less effective in those with relapse after initially achieving PR
Dietrich <i>et al.</i> [44,45]	One patient with relapsed/refractory HCL	240 mg p.o. b.i.d. $\times$ 16 days and then 720 mg/day thereafter	56 days	Achieved CR	No evidence of MRD 6 months after stopping therapy
Follows <i>et al.</i> [46]	One patient with relapsed/refractory HCL	240 mg p.o. b.i.d.	58 days	Achieved PR	BM at 60 days post treatment was compatible with early relapse
Munoz <i>et al.</i> [47]	One patient with relapsed/refractory HCL	960 mg p.o. b.i.d.	4 months	All counts normalized and marrow HCL percentage went from 68% pretreatment to 10–20% following 4 months therapy	
Peyrade <i>et al.</i> [48]	One patient with relapsed/refractory HCL	240 mg p.o. b.i.d.	56 days	Achieved CR	Follow-up after 1 month from treatment (~90 days) showed normal counts and blood morphology showed no evidence of HCL
Blachly <i>et al.</i> [49]	One patient with relapsed/refractory HCL and concurrent <i>BRAF</i> V600E mutant melanoma	Dabrafenib 150 mg p.o. b.i.d.	6 cycles (28 days/cycle)	Achieved CR	HCL CR achieved after 6 cycles. He has completed a total of 18 cycles prior to this publication and remains without evidence of recurrent melanoma
Sascha <i>et al.</i> [50]	Case series of 21 patients all of whom received a median of 3 prior treatment lines prior to study	Started at 240 mg b.i.d. in 18 individuals and the same dose continued for 14 patients. Four individuals received higher treatment dose of 960 or 720 mg	Median therapy duration was 90 days	7 patients achieved CR, while 13 achieved PR	Patient receiving doses >480 mg ($n=7$) did not have more significant CR than those with dosing at 480 mg

b.i.d., twice daily; BM, bone marrow; CR, complete response; HCL, hairy cell leukaemia; MRD, minimal residual disease; ORR, overall response rate; PA, purine analogue; p.o., orally; PR, partial response.