REVIEW

Recent advances in understanding and managing hairy cell leukemia [version 1; peer review: 4 approved]

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V1 First published: 27 Apr 2018, 7(F1000 Faculty Rev):509
<https://doi.org/10.12688/f1000research.13265.1>

Latest published: 27 Apr 2018, 7(F1000 Faculty Rev):509
<https://doi.org/10.12688/f1000research.13265.1>

Abstract

Hairy cell leukemia is a rare B-cell malignancy that is characterized by an indolent course. It was initially described as a distinct entity in 1958. Before the establishment of modern treatment, median survival was only 4 years. Since then, major advances in the treatment and understanding of the biology and genomic landscape of hairy cell leukemia have been made. This review summarizes the present understanding of hairy cell leukemia with particular focus on the development of novel and targeted approaches to treatment.

Keywords

hairy cell leukemia, BRAF, vemurafenib

Open Peer Review

Approval Status

	1	2	3	4
version 1 27 Apr 2018				

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Author roles: Roider T: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; Falini B: Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Dietrich S: Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: Sascha Dietrich was supported by a grant of the Hairy Cell Leukemia Foundation, the Heidelberg Research Centre for Molecular Medicine (HRCMM), and a BMBF Junior Group grant.

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How to cite this article: Roider T, Falini B and Dietrich S. **Recent advances in understanding and managing hairy cell leukemia [version 1; peer review: 4 approved]** F1000Research 2018, 7(F1000 Faculty Rev):509 <https://doi.org/10.12688/f1000research.13265.1>

First published: 27 Apr 2018, 7(F1000 Faculty Rev):509 <https://doi.org/10.12688/f1000research.13265.1>

Introduction

Hairy cell leukemia (HCL) is a rare mature B-cell malignancy, which was initially described by Bouroncle *et al.* in 1958¹. HCL has an incidence of 0.3 cases per 100,000 individuals². It occurs about four times more often in men than in women, with a median age at diagnosis of 55 years³. HCL cells are characterized by thin cytoplasmic hair-like projections, giving the disease its name⁴. Leukemic hairy cells accumulate in the bone marrow and cause pancytopenia, which is the most common finding at initial presentation. HCL patients report symptoms of fatigue, infections, and, occasionally, left-sided abdominal pain caused by splenomegaly. In contrast to many B-cell malignancies, lymphadenopathy is rare in HCL patients⁵. A severe fibrotic reaction is commonly found in the bone marrow of HCL patients, which often complicates a diagnostic bone marrow aspiration. The diagnosis is usually based on the detection of typical morphological features and a unique immunophenotype with flow cytometry of peripheral blood and/or histological and immunohistochemical (IHC) analysis of trephine biopsies. HCL cells show a characteristic gene expression profile signature that points to their origin from memory B cells^{6,7}. Although standard treatment with purine analogues is very effective in the majority of patients with HCL, there is a small subset of relapsed and refractory HCL patients who qualify for investigational therapies with monoclonal antibodies or small molecule compounds⁸. In this review, we will discuss these novel therapeutic agents as well as recent advances in understanding the molecular pathogenesis of HCL.

The biology of HCL

In 2011, Tiacci *et al.* discovered that classical HCL is characterized by a gain-of-function mutation of the BRAF serine/threonine protein kinase (V600E)^{9,10}. In the initial validation series, all HCL patients showed this particular mutation, while a set of 195 B-cell lymphomas and leukemias did not harbor a mutated *BRAF* gene. The vast majority of *BRAF*-V600E mutations in HCL are heterozygous. Homozygous mutations are rare but have been suggested to be associated with a more aggressive disease course¹¹. Recurrent deletions of the *BRAF* gene locus on chromosome 7q34 have been described in HCL and lead to loss of heterozygosity¹². *BRAF* mutations, different from V600E, seem to be extremely rare in HCL and have been described in only two patients so far¹³. The incidence of *BRAF* mutations in nearly 100% of HCL cases at diagnosis (encompassing the whole disease spectrum), their somatic nature, their presence in the entire tumor clone, and their high stability at relapse strongly suggest that the pathogenesis of HCL critically depends on constitutively activated BRAF^{10,14,15}.

Chung *et al.* reported that *BRAF*-V600E mutations are already present in hematopoietic stem cells (HSCs) or B-cell lymphoid progenitors of HCL patients and that these patients exhibit marked alterations in hematopoietic stem/progenitor cell (HSPC) frequencies¹⁶. Transplantation of *BRAF*-V600E-mutant HSCs from an HCL patient into immunodeficient mice resulted in stable engraftment of *BRAF*-V600E-mutant human hematopoietic cells, revealing the functional self-renewal capacity of HCL HSCs. However, none of the transplanted mice

developed typical HCL, strongly suggesting that the development of a full HCL phenotype may require a permissive epigenetic background (likely restricted to a particular stage of B-cell differentiation) and/or the acquirement of further genetic lesions¹⁶.

The *BRAF*-V600E mutation constitutively activates BRAF, providing oncogenic signaling through the MEK-ERK cascade^{10,17} (Figure 1). Both *in vitro* and *in vivo* studies have demonstrated that BRAF-dependent phospho-ERK activation is a critical signaling event in HCL^{10,18,19}. Moreover, *in vitro* treatment of primary purified HCL cells with BRAF and MEK inhibitors has resulted in marked dephosphorylation of MEK/ERK, silencing of the RAF-MEK-ERK pathway transcriptional output, loss of the specific HCL gene expression profile signature, change of the characteristic morphology of the leukemic cells (from “hairy” to “smooth”), and eventually apoptosis^{14,15,20}.

Aberrant expression of cell cycle-related proteins such as cyclin D1 has been shown to be reversible using inhibitors of activated BRAF signaling, suggesting that expression is not a constitutive disease trait but elicited by MEK/ERK signaling and oncogenic BRAF mutations, respectively¹⁸. This could have a significant effect on the assessment of minimal residual disease (MRD) when considering inhibitor treatment because the profile of the marker cyclin D1 might be dynamic, as well as on targeted drug therapy, which may be shortened due to the on-target effect of inhibitors.

Differential diagnosis of HCL

Historically, there were two different forms of HCL: the more-common classical HCL (90%) and the less-frequent HCL variant (10%). HCL variant is characterized by a more aggressive disease course and poor response to purine analogs²¹. Most importantly, HCL variant cases are commonly negative for *BRAF*-V600E mutation, indicating that HCL variant is a biologically distinctive entity. A small subset of patients with bona fide classical (HCL) who also do not harbor any *BRAF* mutation has been reported only in a single study²². However, these cases are often characterized by an IGHV4-34 immunoglobulin rearrangement, which is in general absent in classical HCL and is associated with a poor a prognosis as HCL variant²².

Almost 50% of HCL-variant and IGHV4-34-expressing HCL cases were found to harbor activating mutations in the *MAP2K1* gene encoding MEK1²³. All but one of the identified mutations (n=15) have been described and are known to strongly increase phospho-ERK levels and consequently cell proliferation²³. These findings underline the importance of constitutive MEK-ERK signaling, even in this HCL-like disorder.

HCL cells typically show a distinctive immunophenotype co-expressing CD19, CD20, CD11c, CD25, CD103, and CD123. In contrast, HCL variant lacks the expression of CD25 and CD123²⁴. Moreover, HCL cells strongly express CD200, which can also be used as another distinctive marker to differentiate HCL^{25,26}. *BRAF*-V600E is now regarded as a specific oncogenic mutation occurring only in HCL²⁷. Another distinctive feature of HCL is the expression of annexin A1, which is

Figure 1. RAF-MEK-ERK signaling pathway in hairy cell leukemia. The figure shows the RAF-MEK-ERK signaling pathway in hairy cell leukemia and highlights targets for therapeutic intervention.

easily accessible by immunohistochemical staining²⁸. In addition to HCL variant, the 2016 revision of WHO classification of lymphoid neoplasms recognizes two other entities resembling HCL: splenic marginal zone lymphoma (SMZL), usually associated with *NOTCH2* mutations, and splenic diffuse red pulp small B-cell lymphoma (SDRPBCL), still listed as a provisional entity, whose genomic landscape has not been yet clarified²⁷. Table 1 summarizes the most important differential diagnoses of HCL and their characteristic markers.

Testing for the *BRAF*-V600E mutation in routine clinical practice can be helpful as an additional marker if there is any diagnostic uncertainty. For relapsed and refractory patients, we strongly recommend evaluating the *BRAF* mutation status, since this may serve as a therapeutic target. The limited number of HCL cells present in the peripheral blood requires highly sensitive molecular assays to detect *BRAF* mutations (e.g. allele-specific polymerase chain reaction)⁹. Alternatively, *BRAF*-V600E mutation-specific antibodies can be used for immunohistochemical staining in bone marrow biopsies^{29,30}. However, further validation of the diagnostic utility of these reagents in a larger number of cases is required.

Cooperating mutations of *BRAF*-V600E in HCL

In addition to the *BRAF*-V600E mutation, the most common genetic alteration in classical HCL was a copy number loss of chromosome 7q. The minimally deleted region of this copy

number alteration includes the wild-type locus of *BRAF*. This genetic lesion subdivides individuals with classical HCL into those with hemizygous versus heterozygous mutations of *BRAF*¹². A whole-exome sequencing study of relapsed and refractory HCL patients revealed known cancer-associated genes, such as *EZH2* and *ARID1A*, as well as novel inactivating mutations of the cell cycle inhibitor *CDKN1B* (p27)³¹. In a cohort of 81 mostly untreated HCL patients, the incidence of *CDKN1B* mutations was 16%³¹. While a clinical impact of *CDKN1B* mutations was not found, the data identify *CDKN1B* as the second most commonly mutated gene in HCL. *CDKN1B* is a critical element of cell-cycle control and a known tumor suppressor in different solid cancers³². *CDKN1B* prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes and thereby regulates cell-cycle progression in the G1 phase. Interestingly, BRAF-induced senescence in premalignant naevi is circumvented by deletion or mutation of *CDKN2A* in invasive melanoma³³. In *BRAF*-mutated hairy cell leukemia, *CDKN1B* loss may serve as a mechanism to escape oncogene-induced senescence³¹. In addition to *CDKN1B* mutations cooperating with *BRAF*-V600E, recurrent, inactivating mutations in *KMT2C* (*MLL3*) were identified in 15% and 13% of classical HCL and HCL variant, respectively¹². Another study described somatic mutations or deletions of the *Krüppel-like factor 2* (*KLF2*) in 4 of 24 (16%) HCL patients examined³⁴, but *KLF2* mutations are more frequent in other B-cell malignancies, such as SMZL (31%) and diffuse large B-cell lymphoma (26%)^{34,35}. Although we have

Table 1. Differential diagnoses in HCL and their characteristic features.

	HCL	HCL variant	SMZL	SDRPBCL
Frequency	0.3/100,000	0.03/100,000	0.13/100,000	n/a
Ratio m:f	4:1 (m:w)	1–2:1 (m:w)	1:3 (m:w)	1–2:1 (m:w)
Median age	50–55	>70	65–70	65–75
Lymphocytosis	≤10%	≥90%	≥50%	≥50%
Immunophenotype	CD11c ⁺ CD103 ⁺ CD25 ⁺ CD200 ⁺ CD23 ⁺ CD5 ⁺	CD11c ⁺ CD103 ^{+/–} CD25 ⁺ CD200 ⁺ CD23 ⁺ CD5 ⁺	CD11c ⁺ CD103 ^{+/–} CD5 ^{+/–} CD200 ⁺ CD23 ^{+/–} CD5 ^{+/–}	CD11c ⁺ CD103 ⁺ CD25 ^{+/–} CD23 ⁺ CD5 ^{+/–}
Immunohistochemistry	DBA.44 ⁺ Cyclin D1 ⁺ Annexin A1 ⁺	DBA.44 ⁺ Cyclin D1 ^{+/–} Annexin A1 ⁺	DBA.44 ⁺ Cyclin D1 ⁺ Annexin A1 ⁺	DBA.44 ⁺ Cyclin D1 ⁺ Annexin A1 ⁺
Genotype	<i>BRAF</i> -V600E mutation	<i>BRAF</i> wildtype, ≈50% <i>MEK1</i> mutations, ≈50% IGHV4-34 rearrangement	<i>BRAF</i> wildtype, frequent <i>NOTCH2</i> mutations	<i>BRAF</i> wildtype

HCL, hairy cell leukemia; IGHV, immunoglobulin heavy-chain variable; SDRPBCL, splenic diffuse red pulp small B-cell lymphoma; SMZL, splenic marginal zone lymphoma

better described the genetic landscape of HCL during recent years, the function of mutations cooperating with *BRAF*-V600E remains to be elucidated.

Conventional therapeutic strategies in HCL

At initial diagnosis, most patients will require treatment owing to hematopoietic insufficiency. Accepted indications to start treatment are hemoglobin <11 g/dL, platelet count <100,000/μL, or absolute neutrophil count <1,000/μL. Less frequently, increased susceptibility to infections or symptomatic splenomegaly may also serve as criteria to start treatment⁵. The introduction of the purine analogs cladribine and pentostatin into the treatment landscape of HCL significantly improved the outcome of HCL patients³⁶. Prospective randomized studies comparing pentostatin and cladribine as first-line treatment have not been conducted, but retrospective studies suggested equivalent activity of both drugs with induction of complete remission (CR) in approximately 85% of untreated patients^{37–39}. The median treatment-free survival for patients with CR after treatment with purine analogs was more than 10 years in most studies^{40–42}. In contrast, patients with a partial remission (PR) had a significantly shorter treatment-free survival of 3 years^{43,44}. Although achievement of CR, beyond first-line treatment, is associated with similar good outcome, the proportion of patients with insufficient response and early relapse increases with each treatment round^{38,44}. Apart from pentostatin and cladribine, there are hardly any effective, approved treatment options: interferon alpha, splenectomy, and rituximab monotherapy should be considered only in a small subset of patients⁵. Recently, multiple biology-based treatment options have become available for refractory HCL patients, which will be discussed below.

Therapeutic targeting of *BRAF*-V600E

Based on the discovery of the *BRAF*-V600E mutation in virtually all patients with classical HCL¹⁰, as well as the success of *BRAF* inhibitor treatment in melanoma⁴⁵, it was intuitive that *BRAF* inhibition is a promising treatment strategy for patients with HCL. The first patient exposed to the *BRAF* inhibitor vemurafenib indeed showed an immediate and striking response, proving oncogene-dependence and clinical activity^{18,46}. The dynamics of the response were notable, with a spleen size reduction of more than 6 cm in only 6 days and improvement of blood count (hemoglobin, platelets, and granulocytes) within 1 month⁴⁶. Soon after the initial report, multiple studies confirmed the efficacy of both vemurafenib^{47–49} and (because of availability) later dabrafenib⁵⁰. One report also presented the use of vemurafenib in a primary refractory patient with severe pulmonary aspergillosis⁵¹, where the avoidance of myelotoxicity may be particularly advantageous. Individual dosing regimens of vemurafenib with a minimum of 240 mg twice daily were reported in a series of 21 patients with refractory and relapsed HCL. Both antitumor and side effects were found to be independent of vemurafenib dosing⁵². Indeed, the initial melanoma study demonstrated response at the 2 × 240 mg level of dosing. Dose finding studies often pick dose levels based on the incidence of side effects rather than target inhibition. Therefore, the data suggest that individual dosing regimens in *BRAF*-driven cancers warrant reassessment in trials with implications for cost of cancer care.

Clinical trials

Soon after the discovery of *BRAF*-V600E in HCL, investigators from Italy and the United States designed a single-arm

phase II trial testing vemurafenib at standard dosing in relapsed and refractory HCL⁵³. The Italian study (EudraCT 2011-005487-13) comprised 28 *BRAF*-V600E-positive HCL patients of whom 21 experienced early relapse after treatment with purine analogs and 15 were disease refractory to prior therapy. Vemurafenib was given for a median of 16 weeks and was reduced to below 2×960 mg in 17 of 28 patients owing to side effects. Drug-related side effects, mostly rash and arthralgia, were generally grade 1–2 and reversible in all patients. Three patients with either cutaneous basal-cell carcinoma (n=2) or superficial melanoma were all successfully treated with a simple excision. Overall response rate was 96%, with rates of 35% CR and 61% PR obtained after a median of 8 and 9 weeks, respectively. Of note, in all patients with CR, minimal residual disease status was evaluated by immunohistochemistry and showed persisting hairy cells in the range of $\leq 10\%$ at the end of treatment. The median relapse-free survival was 9 months; the relapse-free survival was significantly longer among patients who had a CR than among those who had a PR (19 months versus 6 months). In the same report⁵³, investigators from Memorial Sloan Kettering Cancer Center (MSKCC) reported on 26 patients with HCL who were refractory to purine analogs or who had achieved suboptimal response to purine analogs. Eligible patients received vemurafenib 960 mg twice daily continuously in cycles of 4 weeks for three cycles. Patients with PR or CR with detectable minimal residual disease (MRD) could receive vemurafenib for up to three additional cycles at the discretion of treating physicians. The side effect profile was similar to the Italian study and included rash, photosensitivity, arthralgia, hand-foot syndrome, and febrile neutropenia. Four patients developed new squamous cell carcinoma (n=3) and cutaneous basal-cell carcinoma (n=1), which were successfully resected. Vemurafenib was reduced to 480 mg twice daily in 14 patients. Blood counts recovered in all patients and 41% of the patients achieved CR. At 1 year after response, the cumulative incidence of relapse was 27% (95% CI, 7 to 51)⁵³.

The combined results of these two prospective studies provide good evidence that vemurafenib has potent antitumor activity in patients with relapsed and refractory *BRAF* mutant HCL and confirm the central role of MAP kinase signaling in the pathogenesis of HCL.

Retreatment with vemurafenib

Despite striking anti-HCL activity of vemurafenib, relapses after drug discontinuation are common, even in patients with

CR. Although it cannot be excluded that the selection of highly refractory patients in these studies contributed to the high proportion of early relapses, responses achieved with vemurafenib appear to be less durable than responses achieved with purine analogs.

Relapsing patients can successfully be retreated with vemurafenib^{52,53}. Furthermore, Bailleux *et al.* reported that vemurafenib at a dose of 240 mg once daily was sufficient to maintain a complete hematological remission after an initial induction treatment with low-dose vemurafenib (2×240 mg)⁵⁴. Whether continuous or intermittent treatment with vemurafenib is superior remains to be shown, but studies in *BRAF* mutant melanoma mouse models suggest that intermittent treatment might be advantageous⁵⁵. Some genetic lesions have been reported to cause resistance to *BRAF* inhibition in HCL, including *RAS*⁵³, *PI3K*⁵², and *IRS1* mutations or loss of *NF1* and *NF2*¹². However, resistance formation in HCL seems to be a rare event compared to melanoma patients in whom almost all tumors inevitably develop resistance to vemurafenib within months.

Perspective

There is compelling evidence that *BRAF* inhibitors are clinically highly efficacious in HCL. However, the high percentage of incomplete responses and the lack of sustained remissions off drug call for the development of combination approaches. *BRAF* inhibitors could, for instance, be combined with anti-CD20 monoclonal antibodies to potentially eradicate *BRAF* inhibitor-resistant hairy cell leukemia cells. Patients with metastatic melanoma have been successfully treated with combined *BRAF* and MEK blockade⁵⁶, and the discovery of the reactivation of the MAPK pathway as a probable mode of resistance to vemurafenib in some patients also validates the use of this therapy. Studies for both approaches are on their way.

Competing interests

The author(s) declared that they have no competing interests.

Grant information

Sascha Dietrich was supported by a grant of the Hairy Cell Leukemia Foundation, the Heidelberg Research Centre for Molecular Medicine (HRCMM), and a BMBF Junior Group grant.

Acknowledgments

All authors contributed equally to this work.

References

1. BOURONCLE BA, WISEMAN BK, DOAN CA: **Leukemic reticuloendotheliosis.** *Blood.* 1958; **13**(7): 609–30.
[PubMed Abstract](#)
2. Teras LR, DeSantis CE, Cerhan JR, *et al.*: **2016 US lymphoid malignancy statistics by World Health Organization subtypes.** *CA Cancer J Clin.* 2016; **66**(6): 443–459.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
3. Tadmor T, Polliack A: **Epidemiology and environmental risk in hairy cell leukemia.** *Best Pract Res Clin Haematol.* 2015; **28**(4): 175–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Schrek R, Donnelly WJ: **“Hairy” cells in blood in lymphoreticular neoplastic disease and “flagellated” cells of normal lymph nodes.** *Blood.* 1966; **27**(2): 199–211.
[PubMed Abstract](#)
5. Grever MR, Abdel-Wahab O, Andritsos LA, *et al.*: **Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia.** *Blood.* 2017; **129**(5): 553–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Tiacci E, Liso A, Piris M, *et al.*: **Evolving concepts in the pathogenesis of hairy-cell leukaemia.** *Nat Rev Cancer.* 2006; **6**(6): 437–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Basso K, Liso A, Tiacci E, *et al.*: **Gene expression profiling of hairy cell leukemia reveals a phenotype related to memory B cells with altered expression of chemokine and adhesion receptors.** *J Exp Med.* 2004; **199**(1): 59–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Robak T, Matutes E, Catovsky D, *et al.*: **Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** *Ann Oncol.* 2015; **26** Suppl 5: v100–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
9. Tiacci E, Schiavoni G, Forconi F, *et al.*: **Simple genetic diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation.** *Blood.* 2012; **119**(1): 192–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Tiacci E, Trifonov V, Schiavoni G, *et al.*: **BRAF mutations in hairy-cell leukemia.** *N Engl J Med.* 2011; **364**(24): 2305–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
11. Samuel J, Macip S, Dyer MJ: **Efficacy of vemurafenib in hairy-cell leukemia.** *N Engl J Med.* 2014; **370**(3): 286–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
12. Durham BH, Getta B, Dietrich S, *et al.*: **Genomic analysis of hairy cell leukemia identifies novel recurrent genetic alterations.** *Blood.* 2017; **130**(14): 1644–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Tschernitz S, Flossbach L, Bonengel M, *et al.*: **Alternative BRAF mutations in BRAF V600E-negative hairy cell leukaemias.** *Br J Haematol.* 2014; **165**(4): 529–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Tiacci E, Pettrossi V, Schiavoni G, *et al.*: **Genomics of Hairy Cell Leukemia.** *J Clin Oncol.* 2017; **35**(9): 1002–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Falini B, Martelli MP, Tiacci E: **BRAF V600E mutation in hairy cell leukemia: from bench to bedside.** *Blood.* 2016; **128**(15): 1918–27.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Chung SS, Kim E, Park JH, *et al.*: **Hematopoietic stem cell origin of BRAFV600E mutations in hairy cell leukemia.** *Sci Transl Med.* 2014; **6**(238): 238ra71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Ribas A, Flaherty KT: **BRAF targeted therapy changes the treatment paradigm in melanoma.** *Nat Rev Clin Oncol.* 2011; **8**(7): 426–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Dietrich S, Hüllein J, Hundemer M, *et al.*: **Continued response off treatment after BRAF inhibition in refractory hairy cell leukemia.** *J Clin Oncol.* 2013; **31**(19): e300–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Tiacci E, Schiavoni G, Martelli MP, *et al.*: **Constant activation of the RAF-MEK-ERK pathway as a diagnostic and therapeutic target in hairy cell leukemia.** *Haematologica.* 2013; **98**(4): 635–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Pettrossi V, Santi A, Imperi E, *et al.*: **BRAF inhibitors reverse the unique molecular signature and phenotype of hairy cell leukemia and exert potent antileukemic activity.** *Blood.* 2015; **125**(8): 1207–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Robak T: **Hairy-cell leukemia variant: recent view on diagnosis, biology and treatment.** *Cancer Treat Rev.* 2011; **37**(1): 3–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Xi L, Arons E, Navarro W, *et al.*: **Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation.** *Blood.* 2012; **119**(14): 3330–2.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Waterfall JJ, Arons E, Walker RL, *et al.*: **High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias.** *Nat Genet.* 2014; **46**(1): 8–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
24. Venkataraman G, Aguhar C, Kreitman RJ, *et al.*: **Characteristic CD103 and CD123 expression pattern defines hairy cell leukemia: usefulness of CD123 and CD103 in the diagnosis of mature B-cell lymphoproliferative disorders.** *Am J Clin Pathol.* 2011; **136**(4): 625–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Sandes AF, de Lourdes Chauffaille M, Oliveira CR, *et al.*: **CD200 has an important role in the differential diagnosis of mature B-cell neoplasms by multiparameter flow cytometry.** *Cytometry B Clin Cytom.* 2014; **86**(2): 98–105.
[PubMed Abstract](#)
26. Pillai V, Pozdnyakova O, Charest K, *et al.*: **CD200 flow cytometric assessment and semiquantitative immunohistochemical staining distinguishes hairy cell leukemia from hairy cell leukemia-variant and other B-cell lymphoproliferative disorders.** *Am J Clin Pathol.* 2013; **140**(4): 536–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Swerdlow SH, Campo E, Pileri SA, *et al.*: **The 2016 revision of the World Health Organization classification of lymphoid neoplasms.** *Blood.* 2016; **127**(20): 2375–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
28. Falini B, Tiacci E, Liso A, *et al.*: **Simple diagnostic assay for hairy cell leukaemia by immunocytochemical detection of annexin A1 (ANXA1).** *Lancet.* 2004; **363**(9424): 1869–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Andrusis M, Penzel R, Weichert W, *et al.*: **Application of a BRAF V600E mutation-specific antibody VE1 for the diagnosis of hairy cell leukemia.** *Am J Surg Pathol.* 2012; **36**(12): 1796–800.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Uppal G, Ly V, Wang ZX, *et al.*: **The utility of BRAF V600E mutation-specific antibody VE1 for the diagnosis of hairy cell leukemia.** *Am J Clin Pathol.* 2015; **143**(1): 120–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
31. Dietrich S, Hüllein J, Lee SC, *et al.*: **Recurrent CDKN1B (p27) mutations in hairy cell leukemia.** *Blood.* 2015; **126**(8): 1005–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Chu IM, Hengst L, Slingerland JM: **The Cdk inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy.** *Nat Rev Cancer.* 2008; **8**(4): 253–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Michaloglou C, Vredeveld LC, Soengas MS, *et al.*: **BRAF^{V600E}-associated senescence-like cell cycle arrest of human naevi.** *Nature.* 2005; **436**(7051): 720–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
34. Piva R, Deaglio S, Famà R, *et al.*: **The Krüppel-like factor 2 transcription factor gene is recurrently mutated in splenic marginal zone lymphoma.** *Leukemia.* 2015; **29**(2): 503–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
35. Clipson A, Wang M, de Leval L, *et al.*: **KLF2 mutation is the most frequent somatic change in splenic marginal zone lymphoma and identifies a subset with distinct genotype.** *Leukemia.* 2015; **29**(5): 1177–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
36. Grever M, Kopecky K, Foucar MK, *et al.*: **Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study.** *J Clin Oncol.* 1995; **13**(4): 974–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Catovsky D, Matutes E, Talavera JG, *et al.*: **Long term results with 2′deoxycoformycin in hairy cell leukemia.** *Leuk Lymphoma.* 1994; **14** Suppl 1: 109–13.
[PubMed Abstract](#)
38. Hoffman MA, Janson D, Rose E, *et al.*: **Treatment of hairy-cell leukemia with cladribine: response, toxicity, and long-term follow-up.** *J Clin Oncol.* 1997; **15**(3): 1138–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Piro LD, Carrera CJ, Carson DA, *et al.*: **Lasting remissions in hairy-cell leukemia induced by a single infusion of 2-chlorodeoxyadenosine.** *N Engl J Med.* 1990; **322**(16): 1117–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Else M, Dearden CE, Catovsky D: **Long-term follow-up after purine analogue therapy in hairy cell leukaemia.** *Best Pract Res Clin Haematol.* 2015; **28**(4): 217–29.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
41. Else M, Dearden CE, Matutes E, *et al.*: **Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis.** *Br J Haematol.* 2009; **145**(6): 733–40.
[PubMed Abstract](#) | [Publisher Full Text](#)

42. **F** Cornet E, Tomowiak C, Tanguy-Schmidt A, *et al.*: **Long-term follow-up and second malignancies in 487 patients with hairy cell leukaemia.** *Br J Haematol.* 2014; **166**(3): 390–400.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
43. Kraut EH, Grever MR, Bouroncle BA: **Long-term follow-up of patients with hairy cell leukemia after treatment with 2'-deoxycytosine.** *Blood.* 1994; **84**(12): 4061–3.
[PubMed Abstract](#)
44. Saven A, Burian C, Koziol JA, *et al.*: **Long-term follow-up of patients with hairy cell leukemia after cladribine treatment.** *Blood.* 1998; **92**(6): 1918–26.
[PubMed Abstract](#)
45. **F** Flaherty KT, Puzanov I, Kim KB, *et al.*: **Inhibition of mutated, activated BRAF in metastatic melanoma.** *N Engl J Med.* 2010; **363**(9): 809–19.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
46. Dietrich S, Glimm H, Andrusis M, *et al.*: **BRAF inhibition in refractory hairy-cell leukemia.** *N Engl J Med.* 2012; **366**(21): 2038–40.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. **F** Follows GA, Sims H, Bloxham DM, *et al.*: **Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib.** *Br J Haematol.* 2013; **161**(1): 150–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
48. **F** Munoz J, Schlette E, Kurzrock R: **Rapid response to vemurafenib in a heavily pretreated patient with hairy cell leukemia and a BRAF mutation.** *J Clin Oncol.* 2013; **31**(20): e351–2.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
49. **F** Peyrade F, Re D, Ginet C, *et al.*: **Low-dose vemurafenib induces complete remission in a case of hairy-cell leukemia with a V600E mutation.** *Haematologica.* 2013; **98**(2): e20–2.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. **F** Vergote V, Dierickx D, Janssens A, *et al.*: **Rapid and complete hematological response of refractory hairy cell leukemia to the BRAF inhibitor dabrafenib.** *Ann Hematol.* 2014; **93**(12): 2087–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
51. **F** Maurer H, Haas P, Wengenmayer T, *et al.*: **Successful vemurafenib salvage treatment in a patient with primary refractory hairy cell leukemia and pulmonary aspergillosis.** *Ann Hematol.* 2014; **93**(8): 1439–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
52. Dietrich S, Pircher A, Endris V, *et al.*: **BRAF inhibition in hairy cell leukemia with low-dose vemurafenib.** *Blood.* 2016; **127**(23): 2847–55.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Tiaci E, Park JH, de Carolis L, *et al.*: **Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia.** *N Engl J Med.* 2015; **373**(18): 1733–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. **F** Bailleux C, Robert G, Ginet C, *et al.*: **Successful re-treatment of a relapsed V600E mutated HCL patient with low-dose vemurafenib.** *Oncoscience.* 2015; **2**(1): 44–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
55. **F** Das Thakur M, Salangsang F, Landman AS, *et al.*: **Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance.** *Nature.* 2013; **494**(7436): 251–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. **F** Eroglu Z, Ribas A: **Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy.** *Ther Adv Med Oncol.* 2016; **8**(1): 48–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

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