

Management Approaches to Hairy Cell Leukemia; Overview

Akeelah Abdullah Al-Haddad, Batool Saad Alsalam, Huriyyah Alawi AlJarrash,

Halah Ahmad Alfaraj, Ranim Yahya Nasr

King Salman Hospital, Riyadh, Saudi Arabia

Corresponding author: Akeelah Abdullah Al-Haddad, E-mail: Akeelah.hdd@hotmail.com,

Mobile number: 00966567989356

ABSTRACT

Hairy cell leukemia is a rare disease comprising about 2% of lymphoid neoplasms. In this review, the biology, diagnostic criteria, and current therapeutic options in HCL-V and HCL-JV are presented. We conducted a database; PubMed and Embase comprehensive search up to December 2017, we search a relevant trail to our concern topic (hairy cell leukemia). HCL-V is a distinct clinico-pathological entity. However, differentiating HCL-V from classical HCL and splenic marginal zone lymphoma (SMZL), which are both connected with noticeable splenomegaly and circulating neoplastic cells with 'hairy' projections remain a problem. Patients with HCL-V are usually older, splenomegaly is less typical and leucopenia with granulocytopenia and monocytopenia are generally not seen. Bone marrow is usually easily aspirable, hypercellular with mild myelofibrosis.

Keywords: Hairy cell leukemia, treatment, irradiation, leukemia, management.

INTRODUCTION

Hairy-cell leukemia variant (HCL-V) is an unusual B-cell neoplasm accounting for 10-20% of HCL patients and 0.4% of chronic lymphoid malignancies, representing around 60-75 new HCL-V patients every year in the US ^[1]. The disease impacts the elderly populace without sexual predominance. Its features are intermediate in between those of classic HCL (HCL-C) and prolymphocytic leukemia ^[2]. The mean age of the patients is 71 years. HCL-V was initially identified by *Cawley et al.* ^[1] and was later called prolymphocytic variation of HCL. Unlike HCL-C, HCL-V is immune to most conventional therapies, consisting of interferon- α (IFN- α) and purine nucleoside analogs (PNA). Recently; HCL-V has been included in the World Health Organization (WHO) classification as a provisional entity, and it is no longer considered to be biologically associated to HCL-C ^[3]. HCL-V is more aggressive disease than classic form of HCL ^[3]. A research showed that median survival was roughly 9 years with only 15% survival over 15 years. It also revealed that 42% of patients died of unrelated reasons ^[4]. Final result showed that typical survival of HCL-V patients is considerably much shorter compared to that of HCL-C.

Hairy cell leukemia is a rare disease comprising about 2% of lymphoid neoplasms ^[1]. In this review, the biology, diagnostic criteria, and current therapeutic options in HCL-V and HCL-JV are presented.

METHODOLOGY

We Conducted a database; PubMed and Embase comprehensive search up to December 2017, we

search a relevant trail to our concern topic (hairy cell leukemia); using following Mesh words:

- hairy cell leukemia;
- leukemia;
- management;
- treatment;
- staging

To identify the most related articles in the literature. To discuss more supported evidence-based review. In addition, we scanned the references list of each identified articles for more relevant studies. Search was restricted to English language articles and only human subjected studies.

DISCUSSION

• Diagnosis

HCL-V patients are defined by splenomegaly, a high leukocyte count without neutropenia or monocytopenia and hyper-cellular marrow that can be easily aspirated ^[5]. Morphologically, HCL-V cells are similar to leukemic cells of B-cell prolymphocytic leukemia and HCL-C cells ^[6]. It consists of abundant villi, an extremely basophilic cytoplasm and central, rounded, sometimes bilobed, indented hyperchromatic nuclei with noticeable nucleoli ^[7]. HCL-V cells are smaller sized, have greater nuclear cytoplasmic ratios and no ribosome-lamella complexes ^[6]. On the other hand, leukemic cells of patients with HCL-V just infrequently demonstrate reactivity to tartrate resistant acid phosphate (TRAP) ^[6]. The immunophenotype of the leukemic cells in HCL-V is CD11c+, CD10, CD23, CD24, CD25, CD27 and CD5 and have variable expression of CD103. Furthermore,

antigens of mature B lymphocytes, CD19, CD20 and CD22 and FMC-7 with light chain limitation are existing [5]. A study by *Del Giudice et al.* [8] peripheral blood leukemic cells revealed CD123 antigen only in 9% of the patients with HCL-V. CD52 antigen was found on 99% of neoplastic cells from the spleen of patients with this condition, whereas immunophenotyping of HCL-V cells usually discloses negativity for Annexin A1 (ANXA1). Cytogenetic abnormalities in HCL-V have been periodically reported in patients with HCL-V. A research study by *Brito-Babapulle et al.* 2 of 6 instances with HCL-V had irregularities of chromosome 17p [9].

The majority of the HCL-V patients have interstitial bone marrow seepage with scattered hairy cells lying within sinusoids [3], and approximately 20% of the patients have a mixed, interstitial and nodular pattern. Additionally, pure sinusoidal and intrasinusoidal bone marrow involvement was additionally occasionally reported [7]. Histological features of HCL-V in the spleen resemble those found in HCL-C with primary involvement of the red pulp [6]. They are both (HCL-C and HCL-V) rare in Japan. Nevertheless, one more distinctive variant of HCL called HCL-Japanese version (HCL-JV) has been identified in this nation. Hairy cell leukemia-JV was proposed as a provisional subtype of HCL by Katayama. A review of literature relating to 36 Japanese patients identified as atypical HCL with some findings not generally seen in HCL. Finally, *Machii et al.* reported a series of 29 Japanese patients with similar signs and symptoms, and additionally specified this subtype of HCL. HCL-JV is a lot more regular in women. Patients with HCL-JV possess splenomegaly without peripheral lymphadenopathy. Nonetheless, in comparison to HCL-C, but just like HCL-V, HCL-JV patients generally demonstrate leukocytosis and a conveniently aspirable bone marrow [11]. HCL-JV cells have an abundant pale cytoplasm with lengthy microvilli, round hyperchromatic nuclei, inconspicuous nucleoli and seldom consist of ribosome-lamella facilities [10]. HCL-JV, like HCL-V, is typically CD11c and CD22 favorable, always CD24 and CD25 unfavorable, and usually CD103 unfavorable [11]. The leukemic cells like CD22+, CD10, CD24 and serological Ig are usually negative or weakly favorable by HCL-JV. A significant high ratio j + type to k + type has been likewise located [11]. Tartrate-resistant acid phosphatase staining is adverse in up to half of situations. Likewise, HCL-C and HCL-V leukemic cells preferentially infiltrate splenic red pulp. HCL-

JV shows instead an indolent professional program as in the situations of HCL-C.

A kind of polyclonal B-cell lymphocytosis with attributes appearing like HCL-JV has likewise been reported [12]. Surface CD11c+, CD22+, CD24+, CD25, IgG and CD5-phenotype and the weak TRAP activity in the lymphoid cells corresponded those of the HCL-JV. Nonetheless, research studies of Ig genetics rearrangements and expression revealed the polyclonal spreading of B-cells. It is recommended that the B-cells of these patients are the nonmalignant equivalents of leukemic cells in HCL-JV.

• Treatment

The therapeutic method to HCL-V is still debated. Various therapy approaches active in HCL-C achieve partial or no response in HCL-V and remission is normally shorter compared to in HCL-C [13]. In addition, HCL-V seems to be resistant to therapeutic techniques, which is generally very effective in the therapy of HCL-C such as splenectomy, interferon a (IFN-a), and PNA. Clinical actions for splenectomy, IFN-a and PNA in HCL-JV are likewise substandard to those seen in HCL-C [10,12].

Splenectomy and splenic irradiation

About 90% of HCL-C patients have splenomegaly, and splenectomy has been the first effective therapy in this disease. Over 80% of patients with HCL-C show hematological renovation and at the very least 40% accomplished a complete remission. Appropriate professional and hematological responses after splenectomy has been observed in 13 out of 19 patients (74%) with HCL-V, reported by *Matutes et al.* [3], and median response period was 4 years. Nevertheless, in various other researches, much less than 1/3rd of HCL-V patients acquired a partial response and no CR was observed [1]. Some authors recommend that previous splenectomy could boost the action to chlorambucil and PNA in HCL-V patients. These outcomes suggest that splenectomy ought to be considered in HCL-V since it fixes the cytopenias and removes a considerable bulk of the disease.

Splenic irradiation might be also helpful, particularly in elderly patients with high surgical threat. One case reported the situation of a 79-year old guy with HCL-V treated with splenic radiotherapy in whom a CR was accomplished. Two various other patients with HCL-V got a PR after splenic irradiation [14], yet this treatment was ineffective in three other patients [4]. Another patient, treatment was fractionated into 10 weekly dosages for a total amount of 10, and 3 months after

radiotherapy, the spleen returned to its normal dimension, the WBC count was normal and the bone marrow biopsy revealed practically overall disappearance of the lymphoid infiltration. A case report of a patient with HCL-V, treated with splenic irradiation and subsequently with alemtuzumab [15]. Irradiation undermined splenomegaly from 12 to 4 cm listed below the left costal margin and minimized the variety of circulating leukemic cells. These results indicate that splenic irradiation could have a beneficial impact in some patients with HCL-V, particularly in senior patients with massive splenomegaly and bad efficiency status.

Interferon A

Interferon α is an effective agent in HCL-C. Nonetheless, currently its use in the treatment of HCL is restricted since PNAs produce higher and durable remissions. Moreover, IFN- α is less convenient to the patient compared to PNA. Unlike HCL-C, patients with HCL-V are resistant to IFN- α . All 7 patients with HCL-V treated with IFN- α by *Sainati et al.* [6] showed no unbiased action. In the team of 14 patients treated with IFN- α reported by *Matutes et al.* [3] just 2 (14%) of them accomplished a temporary partial response (PR). These bad outcomes may associate with a reduced number of IFN- α receptors, which are abundant in typical HCL. However, IFN- α appears to be extra effective in HCL-JV. In patients with HCL-JV, a total 35% feedback to INF- α reported [10].

Purine nucleoside analogs

The purine nucleoside analogs, cladribine (2-CdA) and pentostatin (DCF), are the drugs of selection in the treatment of HCL-C. These drugs induce a similar high reaction rate and a long total survival in HCL-C. Nevertheless, the results of the treatment of HCL-V with PNA are bad (Table 1). In the research, 2-CdA was given up 2-h infusions of 0.12 mg/kg for 5 days. Only 4 out of 6 patients did not react to 2-CdA therapy and only two entered a PR lasting for 60 + and 29 + months. The mean variety of 2-CdA cycles was 3.5. *Tetreault et al.* carried out 2-CdA to four patients with HCL-V over a 7 year period. Of these 4 patients, one attained a CR and 2 a PR. Nonetheless, these results are likewise substandard to those accomplished with 2-CdA in HCL-C. A study reported three patients with HCL-V who were treated with 2-CdA at an everyday dose of 0.1 mg/kg by continual intravenous infusion for 7 days. One of them was

previously treated with splenectomy and IFN- α and 2 patients were without treatment. The patients got from one to three 2-CdA training courses. Two PR and one CR were achieved lasting from 15+ to 127 + months. These reports indicate that 2-CdA is dramatically less active in HCL-V compared to in HCL-C. The analysis of 19 situations released thus far shows an action rate of 55% consisting of just 2 CR [16]. It is in comparison to stunning CR rates in HCL-C treated with 2-CdA, in which of overall CR rate over 80% is obtained with a single cycle whereas the majority of HCL-V patients needed more compared to one cycle to preserve PR. Three situations of HCL-JV were also treated with 2-CdA 0.09 mg/kg/ day by constant infusion for 7 days and no feedback was noted [17]. Of 3 other patients with HCL-VJ treated with 2-CdA in two records there was one CR and one PR [18]. One multi-center research study revealed that, the remission rate was only 35.7%. Nonetheless, the effectiveness of 2-CdA in HCL-JV is unclear. Despite this, a CR was accomplished in some patients treated with this representative. Low efficacy of 2-CdA in the treatment of SMZL has been additionally reported [19].

Pentostatin is also less active in HCL-V than in HCL-C. Of 12 patients treated with this agent in 3 reports, there were 7 PR and no CR. Similarly, in a group of 15 patients with HCL-V reported by *Matutes et al.* [3] pentostatin induced only a PR in 8 of 15 (54%) patients and no CR was attained. On the various other hand, a situation of a patient with the aplastic variation of HCL effectively treated with pentostatin. Hematological enhancement was additionally observed in HCL-V in Japan in a patient refractory to 2- CdA and consequently treated with pentostatin. Another patient reported by *Ribeiro et al.* [20] attained a PR after pentostatin treatment. These situations demonstrate that comparable to 2-CdA, HCL-V patients treated with pentostatin have a poorer clinical result and a lower feedback rate compared to those patients with HCL-C. The data on making use of fludarabine in HCL-V in a comparable way to HCL-C is limited. In HCL-C, fludarabine is not as reliable as 2-CdA or pentostatin. According to *Matutes et al.* [4] just one out of 3 patients with HCL-V treated with fludarabine achieved a PR. An extra PR in a patient with HCL-V was reported by *Kantarjian et al.* [21].

Table 1. Purine nucleoside analogs in the treatment of hairy-cell leukemia-variant

Treatment	No. of courses	No. of patients	CR No. of pts.	PR No. of pts.	Response duration	Survival from the beginning of treatment	References
2-CdA 0.12 mg/kg/ d i.v. 2-h inf. d1-5	1-3	6	0	2	60 + m, 29 + m	NR	<i>Robak et al. Blasinska-Morawiec et al.</i> ^[16]
2-CdA 0.1 mg/kg/d	2-5	4	1	2	108 + m, 12 m, 8 m	108 + m, 32 + m, 18 m, 36 m	<i>Tetreault et al.</i> ^[17]
2-CdA 0.1 mg/kg/d c.i. i.v./d,ds1-7	1-3	3	1	2	NR	127 + m, 31 + m, 15 + m	<i>Palomera et al.</i>
2-CdA	NR	8	0	4	NR	NR	<i>Matutes et al.</i> ^[3,4]
DCF	NR	15	0	8	NR	NR	<i>Matutes et al.</i> ^[3,4]
DCF4 mg/m2 i.v. every 2 weeks	10	1	0	1	15 m	NR	<i>Dunphy et al.</i>
DCF 4 mg/m2 i.v. every 2 weeks	8	1	1	0	69 + m	69 + m	<i>Ng et al.</i>

Hematopoietic cell transplantation

The inadequate prognosis of patients with HCL-V has led some medical professionals to consider hematopoietic cell transplantation (HCT) but, the data to sustain this method is limited to instance records. We determined in the literature 2 patients treated with this treatment. *Busemann et al.* reported a 60-year-old male at first treated with 2-CdA, IFN- α , VACOP-B, DEXA-BEAM and splenectomy which resulted just in a PR. Ultimately, the patient received 4 dosages of rituximab (375 mg/m²) then solitary doses of this medicine as a result of the progressive disease, and obtained a significant reduction in the distributing leukemic cells. Thereafter the patient was allografted with unmanipulated CD34 + cells from a matched unconnected donor. The patient attained a clinical and molecular remission lasting for regarding 3.5 years. One more patient with HCL-V reported in the literature was treated with autologous HCT^[22]. The patient with aggressive relapsed illness obtained DHAP (cisplatin, cytarabine, dexamethasone) adhered to by high-dose chemotherapy sustained by autologous outer blood stem cells. Clinical and molecular CR was documented 3 months after transplantation and continued for 16 months. These two case reports might show that both allogeneic and

autologous stem cell transplantation are a feasible therapeutic approach in chosen instances with HCL-V.

CONCLUSION

HCL-V is a distinct clinico-pathological entity. However, differentiating HCL-V from classical HCL and SMZL which are both connected with noticeable splenomegaly and circulating neoplastic cells with 'hairy' projections remain a problem. Patients with HCL-V are usually older, splenomegaly is less typical and leucopenia with granulocytopenia and monocytopenia are generally not seen. Bone marrow is usually easily aspirable, hyper-cellular with mild myelofibrosis. Currently, concepts of therapy of this uncommon disease originate from uncontrolled single institutional research studies, or even single situation reports. For these reasons, the outcome of therapy is disappointing without any basic treatment established. Unfortunately, randomized regulated trials are not feasible because of an insufficient variety of cases. Good clinical and hematological responses after splenectomy or splenic irradiation have been observed. Splenectomy can be considered in some patients with HCL-V due to the fact that it corrects cytopenias and removes a

considerable majority of disease. Splenic irradiation might be likewise helpful particularly in elderly patients with a high surgical risk. HCL-V appears to be resistant to therapeutic modalities usually highly efficient in the treatment of HCL-C such as IFN- α and PNA. Nevertheless, Interferon alpha appears to be more effective in the of HCL-JV. Recent research studies suggest that rituximab and anti-CD-22 immunotoxin BL22 may be reliable agents in the therapy of HCL-V. HCL-V remains an incurable disease, and the introduction of new medications and new therapeutic strategies is awaited.

REFERENCES

- Cawley JC, Burns GF, Hayhoe FG(1980):** A chronic lymphoproliferative disorder with distinctive features: a distinct variant of hairy-cell leukaemia. *Leuk Res.*,4:547–59.
- Ott G, Balague-Ponz O, de Leval L, de Jong D, Hasserjian RP, Elenitoba-Johnson KS(2009):** Commentary on the WHO classification of tumors of lymphoid tissues: indolent B cell lymphomas. *J Hematopathol.*,2:77–81.
- Matutes E, Wotherspoon A, Brito-Babapulle V, Catovsky D(2001):** The natural history and clinicopathological features of the variant form of hairy cell leukemia. *Leukemia*,15:184–6.
- Matutes E, Wotherspoon A, Catovsky D(2003):** The variant form of hairy-cell leukaemia. *Best Pract Res Clin Haematol.*,16:41–56.
- Zinzani PL, Lauria F, Buzzi M, Raspadori D, Gugliotta L, Bocchia M, et al(1990):** Hairy cell leukemia variant: a morphologic, immunologic and clinical study of 7 cases. *Haematologica*,75:54–7.
- Sainati L, Matutes E, Mulligan S, de Oliveira MP, Rani S, Lampert IA, et al(1990):** A variant form of hairy cell leukemia resistant to alpha-interferon: clinical and phenotypic characteristics of 17 patients. *Blood*,76:157–62.
- Hounieu H, Chittal SM, al Saati T et al.(1992):** Hairy cell leukemia. Diagnosis of bone marrow involvement in paraffin-embedded sections with monoclonal antibody DBA.44. *Am J Clin Pathol.*,98:26–33.
- Del Giudice I, Matutes E, Morilla R et al.(2004):** The diagnostic value of CD123 in Bcell disorders with hairy or villous lymphocytes. *Haematologica*,89:303– 08.
- Brito-Babapulle V, Matutes E, Oscier D, Mould S, Catovsky D(1994):** Chromosome abnormalities in hairy cell leukaemia variant. *Genes Chromosomes Cancer*,10:197–202.
- Katayama I, Mochino T, Honma T, Fukuda M(1984):** Hairy cell leukemia: a comparative study of Japanese and non-Japanese patients. *Semin Oncol.*,11:486–92.
- Sasaki M, Aritaka N, Tsukune Y, Kawahara S, Masuda A, Tsutsui M et al.(2009):** Establishment of a hairy cell leukemia variant cell line, HCLv-07. *Acta Haematol.*,121:63–6.
- Kitani T, Machii T, Inoue R, Kanakura Y(1983):** Hairy cell leukemia: a report of 10 cases in Japan and characterization of anti-hairy cell sera. *Jpn J Clin Oncol.*,13: 497–509.
- Mercieca J, Matutes E, Emmett E, Coles H, Catovsky D(1996):** 2-Chlorodeoxyadenosine in the treatment of hairy cell leukaemia: differences in response in patients with and without abdominal lymphadenopathy. *Br J Haematol.*,93: 409–11.
- Dunn P, Shih LY, Ho YS, Tien HF(1995):** Hairy cell leukemia variant. *Acta Haematol.*,94:105–8.
- Sasaki M, Sugimoto K, Mori T, Karasawa K, Oshimi K(2008):** Effective treatment of a refractory hairy cell leukemia variant with splenic pre-irradiation and alemtuzumab. *Acta Haematol.*,119:45–8.
- Morawiec M, Robak T, Krykowski E, Hellmann A, Urban´ska-Rys´ H(1997):** Hairy cell leukemia-variant treated with 2-chlorodeoxyadenosine – a report of three cases. *Leuk Lymphoma*,25:381–5.
- Machii T, Chou T, Suzuki M, et al(2005):** Cladribine Study Group. Phase II clinical study of cladribine in the treatment of hairy cell leukemia. *Int J Hematol.*,82:230–5.
- Miyazaki M, Taguchi A, Sakuragi S, Mitani N, Matsuda K, Shinohara K(2004):** Hairy cell leukemia, Japanese variant, successfully treated with cladribine. *Rinsho Ketsueki*,45:405–7.
- Lefrère F, Hermine O, François S(2000):** Lack of efficacy of 2- chlorodeoxyadenoside in the treatment of splenic lymphoma with villous lymphocytes. *Leuk Lymphoma*,40:113–7.
- Ribeiro P, Bouaffia F, Peaud PY(1999):** Long term outcome of patients with hairy cell leukemia treated with pentostatin. *Cancer*,85:65–71.
- Kantarjian HM, Schachner J, Keating MJ(1991):** Fludarabine therapy in hairy cell leukemia. *Cancer.*,67:1291–3.
- Busemann C, Schüler F, Krüger W(2010):** Late extramedullary relapse after allogeneic transplantation in a case of variant hairy cell leukaemia. *Bone Marrow Transplantation*,45:1117– 1118.