Am J Transl Res 2024;16(2):466-476
www.ajtr.org /ISSN:1943-8141/AJTR0154266

Original Article

Clinical analysis of hairy cell leukemia: the rare indolent hematological malignancy

He Huang[1*], Yanquan Liu[2*], Minjuan Zeng[2], Xiaojun Chen[3], Yue Yin[4], Huidong Guo[5], Zhimin Yan[6], Jie Lin[7]

[1]Department of Cardiovascular Medicine (Cardiology), The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China; [2]Department of Hematology, The First Dongguan Affiliated Hospital of Guangdong Medical University, Dongguan 523808, Guangdong, China; [3]Department of Hematology, The Affiliated Hospital of Putian University, Putian 351100, Fujian, China; [4]Fujian Institute of Hematology, Fujian Medical University Union Hospital, Fuzhou 350001, Fujian, China; [5]Department of Pathology, The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China; [6]Department of Hematology, The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China; [7]Department of Intensive Medicine (Comprehensive ICU), The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China. [*]Equal contributors.

Received November 5, 2023; Accepted January 30, 2024; Epub February 15, 2024; Published February 28, 2024

Abstract: Objective: To analyze the clinical features, diagnosis and treatment and prognosis of the rare hairy cell leukemia (HCL), in order to provide new references for the clinical and basic research of HCL. Methods: The clinical data of 17 patients with HCL admitted to Fujian Medical University Union Hospital, the Affiliated Hospital of Putian University and the First Affiliated Hospital of Gannan Medical University from January 1, 2016 to July 1, 2023 were collected and retrospectively studied, and the clinical features, diagnosis and treatment effects and prognosis of patients with HCL were analyzed. The Kaplan-Meier method was used for survival analysis. Meanwhile, the latest literature from PubMed was retrieved to systematically discuss the research progress in the diagnosis and treatment of HCL. Results: In this study, there were 11 males and 6 females, the median age at diagnosis was 59.5 (30-81) years old, and the median time from the onset of clinical symptoms or signs to diagnosis was 4.5 (0.5-28.5) months. There were 9 cases (52.94%) with lymphoma B symptoms (fever, night sweating, and weight loss), 15 cases (88.24%) were accompanied by splenomegaly (3 cases of mild splenomegaly, 4 cases of moderate splenomegaly, and 8 cases of megasplenomegaly), the positive rate of *BRAF*^{V600E} mutation is 76.47% (13/17). All patients in this study were treated, of which 11 were treated with Cladribine, 3 with Interferon, 2 with FC regimen, and 1 with R-CVP regimen + Cladribine. The median follow-up time was 39 (range, 2-83) months, 3 patients died, all due to failure of chemotherapy due to disease progression. The prognosis of HCL-v patients was significantly worse than that of cHCL patients (P=0.01), and there was no significant difference in the impact of different treatment regiments on the OS of HCL patients (P=0.328). Conclusion: HCL is a rare clinically indolent hematological tumor, which is sensitive to Cladribine, with the emergence of precision treatments such as the novel molecular-targeted drugs and immunotherapy also plays an indispensable role in clinical practice of HCL.

Keywords: Hairy cell leukemia, diagnosis, identification, chemotherapy, cladribine, prognosis

Introduction

Hairy cell leukemia (HCL) is a rare clinically indolent B-lymphocyte proliferative tumor and was first reported by Bouroncle in 1958 [1]. The typical clinical features and manifestations of HCL are pancytopenia with splenomegaly, but they are not the only. The morphological examination of bone marrow cells found that "hairy cell" is a critical basis for the diagnosis of HCL, and HCL accounts for 2% of all types of lymphocytic leukemia. HCL is common in middle-aged and elderly men, the median age of onset is 55-60 years, and the ratio of male to female is about 4 to 5:1. The immunophenotype of HCL tumor cells usually express CD11c, CD22, CD20, CD25, CD103 and other antigens, and HCL also expresses specific tartrate resistant acid phosphatase (TRAP) and Annexin A1. In addition, B-Raf proto-oncogene, serine/threo-

https://doi.org/10.62347/WFQM3371

nine kinase V600E mutant type (*BRAF*^{V600E}) mutation is a typical molecular marker of HCL, but unfortunately, the pathogenic mechanism of HCL has not yet been clarified clearly [2]. HCL subtypes include classic hairy cell leukemia (cHCL) and hairy cell leukemia variant (HCL-v), however, the two have differences in clinical features, immunophenotype, gene mutation type, therapeutic response and prognosis, and are classified as two independent disease types in the classification criteria of hematopoietic and lymphatic system tumors of the World Health Organization (WHO) [3]. Purine analogues are the standard first-line treatment for cHCL, and a single drug and a single course of treatment can achieve sustained complete remission in most patients [2-5], while the treatment response of HCL-v is poor, and there is no standard first-line treatment [5, 6]. This study retrospectively analyzed the clinical data of 17 patients with HCL admitted to the Fujian Medical University Union Hospital, the Affiliated Hospital of Putian University and the First Affiliated Hospital of Gannan Medical University from January 1, 2016 to July 1, 2023, and systematically discussed the clinical features, efficacy and prognosis of HCL. This paper will be expected to provide reference for the clinical diagnosis and treatment and basic research of HCL.

Materials and methods

Subjects and diagnosis methods

The clinical data of 17 patients with HCL admitted to the Fujian Medical University Union Hospital, the Affiliated Hospital of Putian University and the First Affiliated Hospital of Gannan Medical University from January 1, 2016 to July 1, 2023 were retrospectively analyzed. All patients were treated in accordance with the National Comprehensive Cancer Network (NCCN) HCL Diagnosis and Treatment Guidelines and the 2016 WHO classification criteria for hematopoietic and lymphatic system tumors, among which the diagnosis was mainly based on bone marrow cell morphology and flow immunotyping [3, 4]. All HCL patients included in this study underwent routine bone marrow (or peripheral blood) flow cytometry immunotyping, pathological immunohistochemical staining and other examinations in the hospital.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) The clinical manifestations were consistent with indolent B-lymphocytic leukemia, and the HCL was newly diagnosed after admission and had not received any clinical intervention treatment in other hospitals; (2) The initial diagnosis of HCL was confirmed by peripheral blood smear, bone marrow routine (cytochemical staining), bone marrow pathological biopsy, flow immunotyping, molecular biological examination and other classical diagnostic methods of blood diseases.

Exclusion criteria: (1) HCL was initially considered only after outpatient bone marrow puncture without admission; (2) HCL converted from other hematologic malignancies; (3) Previous history of other malignant tumors (complex or multiple cancers); (4) Recurrent HCL; (5) Treatment-related (post-chemotherapy or post-transplant) HCL; (6) HCL patients with serious lack of clinical history data.

Clinical baseline data collection

This study is a clinical retrospective study, and the clinical data collected mainly include: Gender, age, B symptoms (fever > 38°C, night sweats, weight loss > 10% within 6 months), whole blood cell analysis (routine blood analysis), imaging (abdominal CT, abdominal color ultrasound), bone marrow smear and biopsy, bone marrow or peripheral blood flow immunotyping, bone marrow or peripheral blood *BRAF*^{V600E} gene mutation detection, treatment plan and efficacy data. This study was approved by the Ethics review Committee of the Fujian Medical University Union Hospital, the Affiliated Hospital of Putian University and the First Affiliated Hospital of Gannan Medical University (approval numbers: 2011KY092A, PTF-YYL23071 and LLSC033102, respectively), and the patients or their families signed an informed consent form.

Therapeutic schedule (regimen)

All the patients with HCL included in this study were treated, and the treatment plan was based on WHO or NCCN guidelines [3, 4]. Within 2 to 3 days of the chemotherapy cycle, the patient's routine blood and blood biochemical tests were reviewed. In case of infection symptoms such as fever, the etiological detection

and chest CT examination were undertaken immediately. According to the clinical symptoms and auxiliary examination results, the patient was actively given a series of symptomatic supportive treatments such as blood transfusions, granulocyte colony-stimulating factor leucocytosis, anti-infection treatment, and improvement of circulation care.

Efficacy evaluation

According to the corresponding standards of the latest HCL international diagnosis and treatment guidelines [5], the patients were evaluated for efficacy for 6 months of treatment. They were divided into complete remission (CR), partial remission (PR), stable disease (SD), disease progression (PD), and relapse. It must be clear that the CR standards are: (1) Routine blood examination is close to normal, HGB > 110 g/L (without blood transfusion), PLT > 100×10^9/L, ANC > 1.5×10^9/L; (2) The size of spleen is nearly normal; (3) No hairy cells were seen in the peripheral blood or bone marrow. The PR criteria are: (1) The indicators of routine blood examination are close to normal; (2) The spleen shrinks by at least 50%; (3) Hairy cell infiltration is improved by at least 50% as shown in the bone marrow examination. The SD criteria is the patients of hairy cell leukemia who do not meet the criteria of CR or PR. The PD criteria is that compared with before treatment, the volume of the spleen continues to increase or the blood cell lineage [HGB and (or) PLT and (or) ANC] decreases by 25%, and bone marrow suppression after chemotherapy needs to be excluded. Relapse is usually a recurrence of hairy cells on peripheral blood and/or bone marrow examination but no evidence of hematological relapse. Hematological relapse means that the three blood cell lines are below the lower limit of CR or PR again. Besides, the clinically undetermined CR (CRu) and PR (PRu) are not re-examined for bone marrow examination but the routine blood examination returns to the normal range, which meets the remaining efficacy standards of CR and PR.

Prognosis follow-up

The electronic inpatient record system was used to follow up the indicators of patients' recent return to the hospital for re-examination and hospitalization status, and the follow-up was conducted by telephone contact. The follow-up date was October 1, 2023. The overall survival (OS) was defined as the interval between the date of diagnosis and the onset of death or loss of follow-up (the end point of follow-up). Progression-free survival (PFS) is defined as the interval between the date a patient begins treatment with a standard regimen and the onset of disease progression or death due to any factor. Relapse-free survival (RFS) was defined as the interval between the time a patient obtained CR after antitumor therapy and the onset of relapse or termination of follow-up.

Statistical analysis

Statistical analysis and plotting were performed by GraphPad Prism 7 software, and SPSS 20.0 software was used for data processing. Measurement data are expressed as median (range), and counting data are expressed as cases and percentages. The survival curve was plotted by Kaplan-Meier method.

Results

Clinical features

Among the 17 patients with HCL included in this study, there were 11 males and 6 females. The median age at the time of diagnosis of HCL was 59.5 years (30-81) years. The median time from the appearance of clinical symptoms or signs to diagnosis is 4.5 (0.5-28.5) months. All patients were newly diagnosed patients, the clinical manifestations and the number of cases were as follows: 9 cases (52.94%) of fatigue, 6 cases (35.29%) of bleeding (such as gum bleeding, skin or mucosal bleeding and so on), and 13 cases of infection symptoms (all of which were respiratory infection), 7 cases (41.18%) with lymphoma B symptoms (fever, night sweating, and weight loss), 15 cases (88.24%) were accompanied by splenomegaly (3 cases of mild splenomegaly, 4 cases of moderate splenomegaly, and 8 cases of megasplenomegaly), and 4 cases (23.53%) of lymphadenopathy; the positive rate of *BRAF*^{V600E} mutation is 76.47% (13/17). The clinical characteristics and corresponding laboratory test indicators of the 17 patients with HCL included in this study were shown in **Table 1**.

Table 1. Clinical characteristics and features of 17 patients with hairy cell leukemia

Case Number	Gender	Age	Clinical manifestations						Peripheral blood						*BRAF*^{V600E} mutation
			Infection	Fatigue	Splenomegaly	Bleeding	Swollen lymph nodes	B symptoms	WBC (×10^9/L)	HGB (g/L)	LY (×10^9/L)	NEU (×10^9/L)	MONO (×10^9/L)	PLT (×10^9/L)	
1	Male	45	Negative	Negative	Positive	Negative	Negative	Negative	12.23	86	15.21	2.82	0.06	78	Positive
2	Female	30	Positive	Negative	Positive	Negative	Negative	Positive	2.46	38	1.30	0.42	0.65	63	Positive
3	Male	58	Positive	Positive	Positive	Positive	Positive	Positive	1.91	101	0.69	0.51	0.04	27	Positive
4	Female	43	Positive	Negative	Positive	Negative	Negative	Negative	1.28	57	0.70	0.22	0.84	89	Negative
5	Male	57	Positive	Positive	Positive	Positive	Positive	Negative	0.86	46	0.41	0.25	0.06	19	Positive
6	Female	49	Positive	Negative	Positive	Negative	Negative	Negative	1.65	147	0.25	0.68	0.01	72	Positive
7	Male	54	Positive	Positive	Positive	Negative	Negative	Positive	0.51	98	2.4	0.72	0.09	41	Positive
8	Male	64	Negative	Negative	Positive	Negative	Negative	Negative	5.42	113	0.32	0.47	1.47	96	Negative
9	Female	60	Positive	Positive	Positive	Positive	Negative	Positive	3.15	69	2.51	0.36	0.02	37	Positive
10	Male	81	Positive	Positive	Positive	Positive	Positive	Positive	9.17	61	1.08	0.49	0.00	9	Positive
11	Male	74	Positive	Negative	Positive	Negative	Negative	Negative	0.43	74	0.71	0.62	0.01	59	Positive
12	Male	59	Negative	Positive	Negative	Negative	Negative	Negative	12.21	92	9.12	1.13	0.04	38	Negative
13	Male	75	Positive	Negative	Positive	Negative	Negative	Positive	5.97	123	1.98	1.64	0.03	79	Positive
14	Female	67	Positive	Positive	Positive	Positive	Negative	Negative	3.95	56	2.13	0.96	0.06	41	Positive
15	Male	77	Positive	Positive	Positive	Negative	Positive	Negative	1.29	68	0.21	0.82	0.09	89	Positive
16	Female	69	Negative	Positive	Negative	Negative	Negative	Positive	4.75	74	3.08	1.21	0.13	73	Positive
17	Male	71	Positive	Negative	Positive	Positive	Negative	Negative	11.23	103	7.65	2.21	0.23	98	Negative

Note: HCL: hairy cell leukemia; WBC: white blood cell count; HGB: hemoglobin; LY: lymphocyte count; NEU: neutrophil count; MONO: monocyte count; PLT: platelet count; *BRAF*^{V600E}: B-Raf proto-oncogene serine/threonine protein kinase V600E mutant.

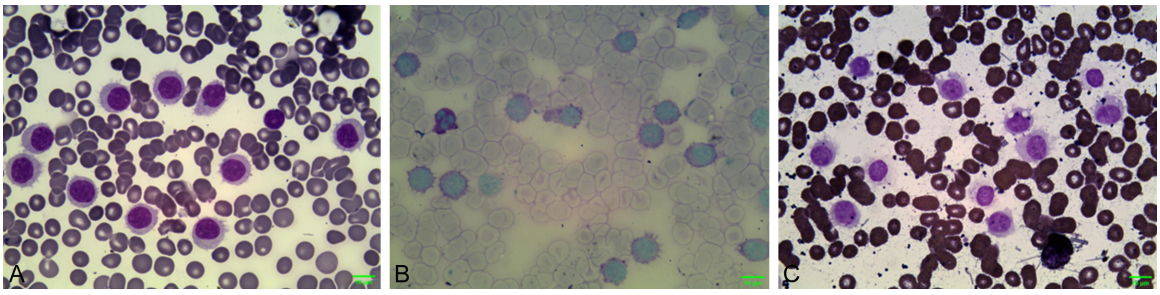

Figure 1. Morphology of bone marrow cells in hairy cell leukemia. A. Wright-Giemsa staining of bone marrow ×400, showing typical hair-like raised hairy cells; B. Periodic acid-Schiff (PAS) staining ×400; C. Peroxidase (POX) staining ×400.

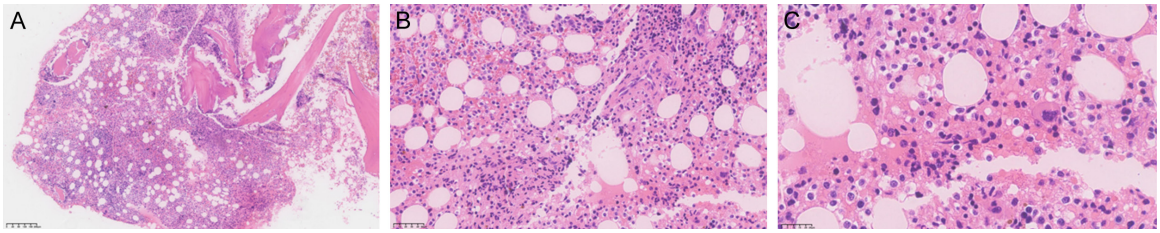

Figure 2. Bone marrow biopsy and pathology of the HCL patient. The hematoxylin-eosin (H&E) staining was performed on (A) 10×, (B) 40×, (C) 80×, and they represent low magnification, medium magnification and high magnification respectively.

Bone marrow morphology and cytochemical staining

In 17 patients with HCL, all patients were treated with bone marrow morphology examination. The typical hairy cells can be seen under the microscope by special cytochemical staining (as shown in **Figure 1**). These hairy cells (leukemia cells) are slightly larger than normal lymphocytes, with rich cytoplasm and light blue color. The ciliated, pseudopod-like raised "hairs" can be seen on the edges of the cells.

Bone marrow biopsy and pathology

As shown in **Figure 2**, the bone marrow biopsy pathology of HCL patients showed active bone marrow hyperplasia (70%-80%), hyperplasia of naive cells, scattered and focal distribution, and interstitial fibrous tissue hyperplasia at low magnification. In the medium magnification field of view, we found that the cells of hairy cell leukemia are medium size, the cytoplasm is rich and clear, the nucleus is centered, round or oval, and the chromatin is fine. The partial mature granulation and red series were scattered, the segmented nuclei were dominant, and megakaryocytes were rare. Finally, we observed with a high magnification field of view that the hair cells were diffused, the cytoplasm was clear, and the perinuclear halo was visible. The appearance of a single cell was "fried egg like", and the appearance of multiple hair cells was "honeycomb briquettes".

Flow cytometry immunophenotyping

All patients with HCL included in this study underwent flow immunotyping detection, 7 of the HCL patients underwent peripheral blood flow cytometry, and the median proportion of HCL cells was 25.7% (11.4%-41.8%), and the other 10 patients underwent bone marrow flow cytometry, and the median proportion of HCL cells was 36.4% (13.2%-74.3%). Moreover, we found that almost all HCL patients expressed CD19, CD20, CD11c, CD22 and CD25, and the remaining immunotyping characteristics and results of HCL patients included in this study by flow cytometry were shown in **Table 2**.

Treatment response and efficacy

All the HCL patients included in this study were treated, and the treatment plans were shown in **Table 3**. Among the 17 patients, 11 cases were

Table 2. The flow cytometry immunophenotyping in 17 HCL patients [*n* (%)]

Antigen type	Expression degree				
	Strong expression	Expression	Partial expression	Weak expression	No expression
CD19	12 (70.59)	2 (11.76)	2 (11.76)	1 (5.88)	0 (0)
CD20	12 (70.59)	4 (23.53)	0 (0)	1 (5.88)	0 (0)
CD11c	11 (64.71)	3 (17.65)	1 (5.88)	1 (5.88)	1 (5.88)
CD22	13 (76.47)	2 (11.76)	1 (5.88)	0 (0)	1 (5.88)
CD23	8 (47.06)	3 (17.65)	2 (11.76)	1 (5.88)	3 (17.65)
CD25	10 (58.82)	4 (23.53)	2 (11.76)	1 (5.88)	0 (0)
CD103	9 (52.94)	4 (23.53)	0 (0)	1 (5.88)	3 (17.65)
CD123	6 (35.29)	5 (29.41)	0 (0)	3 (17.65)	3 (17.65)
CD200	5 (29.41)	4 (23.53)	2 (11.76)	2 (11.76)	4 (23.53)
CD5	2 (11.76)	2 (11.76)	3 (17.65)	5 (29.41)	5 (29.41)
CD10	2 (11.76)	2 (11.76)	1 (5.88)	3 (17.65)	8 (47.06)
FMC7	5 (29.41)	5 (29.41)	0 (0)	4 (23.53)	3 (17.65)
CD79b	4 (23.53)	6 (35.29)	2 (11.76)	3 (17.65)	2 (11.76)
sIgM	2 (11.76)	3 (17.65)	0 (0)	2 (11.76)	10 (58.82)
sIgD	2 (11.76)	4 (23.53)	1 (5.88)	4 (23.53)	6 (35.29)
cKappa	2 (11.76)	2 (11.76)	1 (5.88)	5 (29.41)	7 (41.18)
cLambda	2 (11.76)	3 (17.65)	0 (0)	3 (17.65)	9 (52.94)

Table 3. Chemotherapy regimens and usage in 17 patients with HCL

Case Number	Chemotherapy regimen	Specific types and usage of chemotherapy drugs
1	FC regimen	Fludarabine 50 mg/m^2, intravenous d1-3; Cyclophosphamide 300 mg/m^2, intravenous d1-3
2	R-CVP regimen + Cladribine	Rituximab 500 mg, day 1; Cyclophosphamide 1.1 g, day 2; Vindesine 4 mg, day 2; Dexamethasone 15 mg, day 1-5 for one course and changed to Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
3	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
4	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
5	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
6	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
7	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
8	Interferon	Interferon 40 μg, qd, intravenous d1-d5
9	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
10	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
11	Cladribine	Cladribine 1.4 mg/kg, once a day for 24 h infusion, day 1-5
12	Interferon	Interferon 40 μg, qd, intravenous d1-d5
13	Cladribine	Cladribine 10 mg, intravenous, once a day, d1-d5
14	FC regimen	Fludarabine 50 mg/m^2, intravenous d1-3; Cyclophosphamide 300 mg/m^2, intravenous d1-3
15	Cladribine	Cladribine 10 mg, intravenous, once a day, d1-d5
16	Cladribine	Cladribine 10 mg, intravenous, once a day, d1-d5
17	Interferon	Interferon 40 μg, qd, intravenous d1-d5

treated with cladribine, 3 cases were treated with interferon, 2 cases were treated with FC regimen and 1 case was treated with R-CVP regimen + cladribine. After obtaining and analyzing the efficacy evaluation data, it was found that there were 10 cases of CR/CRu, 3 cases of

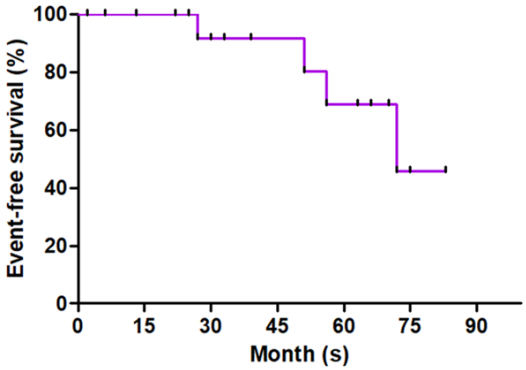

Figure 3. Event-free rate of HCL patients in this study.

PR, 2 cases of SD and 2 cases of PD. The median EFS time of HCL patients included in this study was 53.5 months (as shown in **Figure 3**).

Follow-up and prognostic analysis

The median follow-up time was 39 (range, 2-83) months, and at the latest follow-up, 14 of 17 patients with HCL were still alive. Unfortunately, 3 patients with HCL died, all of which were due to disease progression and failed treatment. We compared the patients according to different HCL subtypes and treatment methods, and the results showed that the prognosis of HCL-v patients was significantly worse than that of cHCL patients (P=0.01), and there was no significant difference in the impact of different treatment regiments on the OS of HCL patients (P=0.328). The survival curve of all HCL patients in this study is shown in **Figure 4**.

Discussion

Hairy cell leukemia (HCL) is a chronic B-cell leukemia/lymphoma that is derived from mature B lymphocytes and is rare in actual clinical work. Currently, the WHO classifies HCL as B-cell non-Hodgkin's lymphoma [7, 8]. HCL is common in middle-aged and elderly male patients. Most patients have varying degrees of cytopenia and splenomegaly and are often accompanied by symptoms such as infection and bleeding. Peripheral blood examinations indicate that mononuclear cell reduction is specific to classic HCL (cHCL). As early as 2008, HCL was classified by WHO into classic hairy cell leukemia (cHCL) and hairy cell leukemia variant (HCL-v) based on immunophenotype and molecular biological characteristics. Generally speaking, mononucleosis in peripheral blood is a specific manifestation of cHCL [9], and related studies have shown that cHCL is prone to increase the difficulty of bone marrow puncture [10].

Generally speaking, every patient admitted to the hospital with a hematological disease will undergo a bone marrow examination. There are some typical characteristics of HCL in bone marrow morphology: HCL cells are medium-sized, kidney-shaped nuclei, with moderately abundant light blue cytoplasm, open chromatin, nucleolar loss, and characteristic serrated cytoplasm. The border of this kind of cell is raised in a "hair-like" way [5]. The HCL patients included in this study have completed the bone marrow morphology examination, and all the patients can be observed the typical morphological features of HCL, which provides definite evidence for the follow-up process of diagnosis and treatment.

The immunophenotype of cHCL cells often expresses CD19, CD20, CD11c, CD25, CD103, CD123 and CD200, while CD27 is negative [11]. For HCL patients that do not express CD5, CD10, CD25, CD123 and Annexin A1, which are HCL-v, antigen detection of CD23, CD25, CD103, CD200 and Annexin A1 can help distinguish cHCL from HCL-v. It is essential to note that HCL-v is a distinct entity under splenic B-cell lymphoma/leukemia and cannot be classified as diffuse red myeloid small B-cell lymphoma of the spleen [3].

The specific mutation *BRAF*^{V600E} is present in the vast majority of cHCL patients, but not in HCL-v. Of course, to avoid false negative results, high-sensitivity detection techniques (such as allele-specific polymerase chain reaction or second-generation sequencing) should be preferred for identification. In contrast to cHCL, HCL-v is usually positive for CD103, and its absence suggests splenic limbic lymphoma [9]. Correspondingly, HCL-v is often associated with cytogenetic abnormalities, such as tumor protein p53 (TP53) mutation, 7q deletion and chromosome 5 amplification, and so on. Therefore, HCL-v has high invasivity, poor prognosis, low sensitivity to purine analogues, and higher recurrence rate than cHCL [12]. In this study, there were only 4 cases with negative *BRAF*^{V600E} mutation, and the positive rate of *BRAF*^{V600E} mutation detected by next-generation sequencing was 76.47% (13/17), which

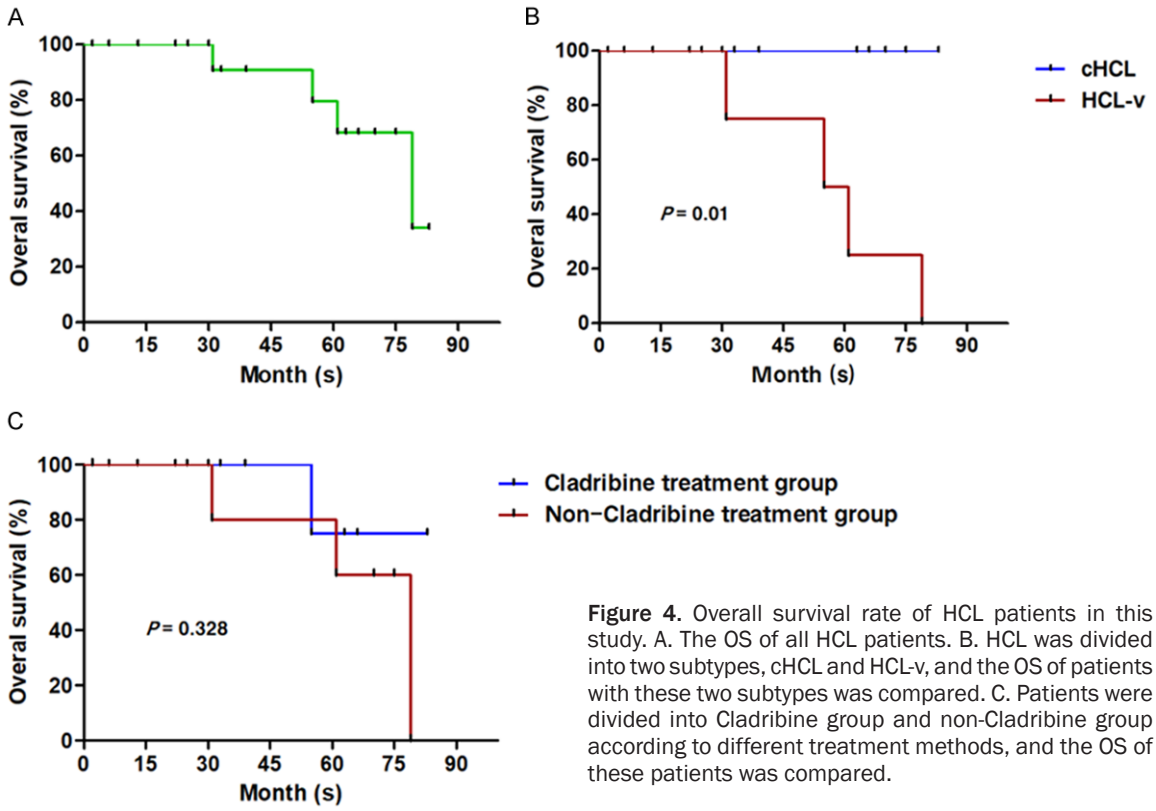

Figure 4. Overall survival rate of HCL patients in this study. A. The OS of all HCL patients. B. HCL was divided into two subtypes, cHCL and HCL-v, and the OS of patients with these two subtypes was compared. C. Patients were divided into Cladribine group and non-Cladribine group according to different treatment methods, and the OS of these patients was compared.

was also basically consistent with the conclusion reported in related studies [13].

After a clear diagnosis of HCL, although the vast majority of patients need to receive treatment, about 10% of patients still need to wait for the indication of treatment before formal treatment, and such patients do not show any therapeutic advantage by taking treatment too early [14]. Of course, studies have also shown that in order to ensure the safety and effectiveness of treatment, when HCL patients present with at least one of the following parameter indicators: HGB < 110 g/L, PLT < 100×10^9/L, ANC < 1.0×10^9/L, severe infection with pancytopenia and moderate or severe spleen enlargement with discomfort, purine nucleoside analogitics should be given in time. However, for some mild and moderate asymptomatic HCL patients with only pancytopenia, HCL disease progression may be maintained for many years without treatment [5].

In general, HCL is sensitive to purine nucleoside analogs (Cladribine and Penstatin) and this has replaced previous splenectomy or interferon therapy, and as a single drug or combined with anti-CD20 monoclonal antibody (Rituximab) can make clinical efficacy stable and CR easier to obtain [15]. It is worth mentioning that Fludarabine, as a classical antimetabolic fluorinated purine nucleoside analogue, has shown good efficacy in the treatment of chronic B-lymphocytic leukemia. Fludarabine alone or in combination with other chemotherapy agents can also achieve remission and long-term survival in HCL patients [16, 17]. A new anti-CD22 recombinant immunotoxin, moxetumomab pasudotox, has made it possible to identify measurable residual disease (MRD) negative and achieve CR without chemotherapy toxicity. It was approved by the FDA as Lumoxiti in 2018 [18, 19]. In addition, clinical studies of oral non-chemotherapy options include Vemurafenib, Dabrafenib or Trametinib targeting $BRAF^{V600E}$±*MEK*, as well as Ibrutinib targeting Bruton tyrosine kinase [20], the above therapeutic means or targets may bring new hope for the future efficacy and prognosis of HCL. Consequently, for HCL treatment evaluation, it includes routine blood tests, physical examination (such as assessing the size of the spleen), routine bone marrow and pathological biopsy. Some researchers believe that it takes

several months for the normal hematopoietic function of the bone marrow of HCL patients treated with Cladribine to recover, so it is often recommended that the bone marrow biopsy review of patients should be carried out 4-6 months after treatment [5], while others suggest that it should be one year after the treatment of Cladribine to evaluate whether the treatment has reached the therapeutic plateau [14]. At present, the therapeutic effect of Cladribine in HCL is reasonable, the side effects and adverse reactions are controllable, and it can be used as an ideal first-line choice for HCL.

It is true that HCL is a malignant hematologic tumor that is still incurable, but patients can achieve stability or long-term survival after standardized diagnosis and treatment. Peripheral blood cell counts in patients with HCL at CR stage should be close to normal values, that is, HGB > 110 g/L (without transfusion), PLT > 100×10^9/L and ANC > 1.5×10^9/L. In addition, physical examination or imaging to determine whether the splenic enlargement is smaller or less than before is also an important indicator of long-term prognosis. Of course, more than 3 years after the end of treatment, the disappearance of the HCL characteristic hair cells in the bone marrow as assessed by morphology indicates that the patient has obtained MRD-free CR. Paillassa et al. [21] conducted a cohort analysis study on 279 patients with HCL. The median follow-up time of this study was 10 years, the median OS of HCL patients was 27 years, the median relapse-free survival (RFS) was 11 years, and the cumulative 10-year recurrence rate was 39%. Although patients with HCL have a good long-term prognosis, there is a relatively increased risk of developing a second tumor. In conclusion, the HCL patients in this study had a good response to Cladribine, with no adverse events such as serious adverse reactions and death. However, long-term follow-up and more in-depth study are still needed for the prognosis.

In summary, HCL, as a rare hematological malignancy in clinical practice, while patients with HCL can achieve satisfactory efficacy and an acceptable prognosis after treatment with Cladribine. However, it is frustrating that the clinical features of HCL have lack of specificity. The clinical characteristics, immunophenotype, therapeutic response and prognosis of HCL-v are different from those of cHCL. *BRAF*^{V600E} gene mutation is an important basis for distinguishing the cHCL and HCL-v. The response rate of cladribine in cHCL patients is high and the prognosis is satisfactory, however, no standard treatment regimen is recommended for HCL-v, and the prognosis of HCL-v is still unsatisfactory [22]. Nevertheless, with the emergence of precision treatments such as new molecular-targeted drugs and immunotherapy also play an indispensable role in clinical practice of HCL.

Conclusions

HCL is an inert B-cell lymphoma that is extremely rare in clinical practice, and is easily confused with splenic marginal zone lymphoma, myelofibrosis, and infectious diseases. HCL is characterized by a large number of mature small B lymphocytes with “hair-like” protrusions in peripheral blood, bone marrow and spleen. Although the clinical manifestations and characteristics of HCL are not specific, it can be divided into two subtypes: cHCL and HCL-v, and the prognosis of the latter is significantly worse than that of the former. Cladribine or interferon therapy can provide long-term survival for HCL patients, and new targeted drugs or novel immunotherapies need to be further developed.

Acknowledgements

We would like to thank colleagues from Fujian Institute of Hematology and Fujian Medical University Union Hospital for their academic assistance in the publication of this paper. The study was supported by the Science and Technology Research Project of Education Department of Jiangxi Province (No. GJJ2201414); the Science and Technology Project of Jiangxi Provincial Administration of Traditional Chinese Medicine (No. 2022B072); the Science and Technology Foundation of Jiangxi Provincial Health Commission (No. 202130697) and Key Project of Social Science Foundation of Guangdong Medical University (SZZF001).

Written informed consent was obtained from the patient or the patient’s family.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jie Lin, Department of Intensive Medicine (Comprehensive ICU), The First Affiliated Hospital of Gannan Medical University, No. 23 Qingnian Road, Zhanggong District, Ganzhou 341000, Jiangxi, China. Tel: +86-15279797523; ORCID: 0000-0002-2620-2634; E-mail: soso0404@aliyun.com

References

[1] Bouroncle BA, Wiseman BK and Doan CA. Leukemic reticuloendotheliosis. Blood 1958; 13: 609-630.

[2] Kreitman RJ. Hairy cell leukemia: present and future directions. Leuk Lymphoma 2019; 60: 2869-2879.

[3] Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD and Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375-2390.

[4] Wierda WG, Byrd JC, Abramson JS, Bhat S, Bociek G, Brander D, Brown J, Chanan-Khan A, Coutre SE, Davis RS, Fletcher CD, Hill B, Kahl BS, Kamdar M, Kaplan LD, Khan N, Kipps TJ, Lancet J, Ma S, Malek S, Mosse C, Shadman M, Siddiqi T, Stephens D, Wagner N, Zelenetz AD, Dwyer MA and Sundar H. Hairy cell leukemia, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017; 15: 1414-1427.

[5] Grever MR, Abdel-Wahab O, Andritsos LA, Banerji V, Barrientos J, Blachly JS, Call TG, Catovsky D, Dearden C, Demeter J, Else M, Forconi F, Gozzetti A, Ho AD, Johnston JB, Jones J, Juliusson G, Kraut E, Kreitman RJ, Larratt L, Lauria F, Lozanski G, Montserrat E, Parikh SA, Park JH, Polliack A, Quest GR, Rai KR, Ravandi F, Robak T, Saven A, Seymour JF, Tadmor T, Tallman MS, Tam C, Tiacci E, Troussard X, Zent CS, Zenz T, Zinzani PL and Falini B. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. Blood 2017; 129: 553-560.

[6] Robak T, Matutes E, Catovsky D, Zinzani PL and Buske C; ESMO Guidelines Committee. Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 Suppl 5: v100-107.

[7] Kreitman RJ and Pastan I. Development of recombinant immunotoxins for hairy cell leukemia. Biomolecules 2020; 10: 1140.

[8] Troussard X and Cornet E. Hairy cell leukemia 2018: update on diagnosis, risk-stratification, and treatment. Am J Hematol 2017; 92: 1382-1390.

[9] Bigorra L, Larriba I and Gutiérrez-Gallego R. The hairy cell leukaemia oxymoron: monocytotic monocytopenia. Clin Chem Lab Med 2020; 59: e111-e115.

[10] Saven A, Burian C, Koziol JA and Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. Blood 1998; 92: 1918-1926.

[11] Kreitman RJ and Arons E. Update on hairy cell leukemia. Clin Adv Hematol Oncol 2018; 16: 205-215.

[12] Liu Q, Harris N, Epperla N and Andritsos LA. Current and emerging therapeutic options for hairy cell leukemia variant. Onco Targets Ther 2021; 14: 1797-1805.

[13] Salam L and Abdel-Wahab O. Hairy cell leukemia: update and current therapeutic approach. Curr Opin Hematol 2015; 22: 355-361.

[14] Wang TY, Li ZJ, Lyu R, Fu MW, Sui WW, Huang WY, Liu W, An G, Deng SH and Qiu LG. Clinical analysis of 24 patients of hairy cell leukemia treated by cladribine. Zhonghua Xue Ye Xue Za Zhi 2018; 39: 491-495.

[15] Chihara D, Kantarjian H, OBrien S, Jorgensen J, Pierce S, Faderl S, Ferrajoli A, Poku R, Jain P, Thompson P, Brandt M, Luthra R, Burger J, Keating M and Ravandi F. Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: update of a phase II trial. Br J Haematol 2016; 174: 760-766.

[16] Gerrie AS, Zypchen LN and Connors JM. Fludarabine and rituximab for relapsed or refractory hairy cell leukemia. Blood 2012; 119: 1988-1991.

[17] Davids MS, Brander DM, Kim HT, Tyekucheva S, Bsat J, Savell A, Hellman JM, Bazemore J, Francoeur K, Alencar A, Shune L, Omaira M, Jacobson CA, Armand P, Ng S, Crombie J, LaCasce AS, Arnason J, Hochberg EP, Takvorian RW, Abramson JS, Fisher DC and Brown JR; Blood Cancer Research Partnership of the Leukemia & Lymphoma Society. Ibrutinib plus fludarabine, cyclophosphamide, and rituximab as initial treatment for younger patients with chronic lymphocytic leukaemia: a single-arm, multicentre, phase 2 trial. Lancet Haematol 2019; 6: e419-e428.

[18] Robak T, Wolska A and Robak P. Potential breakthroughs with investigational drugs for hairy cell leukemia. Expert Opin Investig Drugs 2015; 24: 1419-1431.

[19] Kreitman RJ, Dearden C, Zinzani PL, Delgado J, Karlin L, Robak T, Gladstone DE, le Coutre P, Dietrich S, Gotic M, Larratt L, Offner F, Schiller G, Swords R, Bacon L, Bocchia M, Bouabdallah K, Breems DA, Cortelezzi A, Dinner S, Doubek M, Gjertsen BT, Gobbi M, Hellmann A, Lepretre S, Maloisel F, Ravandi F, Rousselot P, Rummel M, Siddiqi T, Tadmor T, Troussard X, Yi CA, Saglio G, Roboz GJ, Balic K, Standifer N, He P,

Marshall S, Wilson W, Pastan I, Yao NS and Giles F. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. Leukemia 2018; 32: 1768-1777.

[20] Tiacci E, Park JH, De Carolis L, Chung SS, Broccoli A, Scott S, Zaja F, Devlin S, Pulsoni A, Chung YR, Cimminiello M, Kim E, Rossi D, Stone RM, Motta G, Saven A, Varettoni M, Altman JK, Anastasia A, Grever MR, Ambrosetti A, Rai KR, Fraticelli V, Lacouture ME, Carella AM, Levine RL, Leoni P, Rambaldi A, Falzetti F, Ascani S, Capponi M, Martelli MP, Park CY, Pileri SA, Rosen N, Foà R, Berger MF, Zinzani PL, Abdel-Wahab O, Falini B and Tallman MS. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. N Engl J Med 2015; 373: 1733-1747.

[21] Paillassa J, Cornet E, Noel S, Tomowiak C, Lepretre S, Vaudaux S, Dupuis J, Devidas A, Joly B, Petitdidier-Lionnet C, Haiat S, Mariette C, Thieblemont C, Decaudin D, Validire-Charpy P, Drenou B, Eisenmann JC, Uribe MO, Olivrie A, Touati M, Lambotte O, Hermine O, Karsenti JM, Feugier P, Vaillant W, Gutnecht J, Lippert E, Huysman F, Ghomari K, Boubaya M, Levy V, Riou J, Damaj G, Tanguy-Schmidt A, Hunault-Berger M and Troussard X. Analysis of a cohort of 279 patients with hairy-cell leukemia (HCL): 10 years of follow-up. Blood Cancer J 2020; 10: 62.

[22] Wei C, Jin XX, Cai H, Wang X, Zhuang JL and Zhou DB. Clinical and molecular characteristics and prognosis of classical hairy cell leukemia and hairy cell leukemia variant. Zhonghua Nei Ke Za Zhi 2023; 62: 416-421.