TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Subcutaneous and Intravenous Cladribine Treatment of Hairy Cell Leukemia Patients: Do We Still Need Intravenous Cladribine?

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ABSTRACT

Background Hairy cell leukaemia (HCL) is an uncommon neoplasm representing approximately 2% leukaemias and < 1% lymphoid neoplasms. Although HCL remains an incurable disease, first-line treatment with intravenous (IV) or subcutaneous (SC) cladribine (2-CdA) often leads to long-term remissions. Although long-term data are available for IV administration, similar comparable data for SC administration are lacking.

Material and Methods Demographic data, laboratory and clinical parameters of 20 patients with HCL, and IV and SC administrations of cladribine in primary treatment were analyzed.

Results All patients were administered 2-CdA as the first-line therapy. 2-CdA was administered intravenously to 11 patients and subcutaneously to 9 patients. The hospitalization times were shorter in the SC route, and the incidence of febrile neutropenia was less; therefore, statistical significance could not be determined. There was no difference between the route of administration and the treatment response. A correlation was recorded between the level of anaemia before treatment and the time to treatment response. In addition, a correlation was recorded between the level of anaemia before treatment and minimal residual disease status after treatment. The median overall survival (OS) was 43.5 months (confidence interval 95%: 1.5-79 months), and 2- and 5-year OS was 95%. There was no increase in the incidence of second primary cancer.

Conclusions The outcomes of HCL patients treated with SC 2-CdA are quite good, and, in most patients, one cycle of SC 2-CdA was adequate for long-term disease control. SC 2-CdA is an easily applicable option for outpatients, and their side effects are often easily manageable.

Turk J Int Med 2023:5(2);109-116
DOI: 10.46310/tjim.1239905

Keywords: *Hairy cell leukemia, 2-chlorodeoxyadenosine, 2-CdA, subcutaneous cladribine.*

Received: January 23, 2023; Accepted: March 29, 2023; Published Online: April 29, 2023

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INTRODUCTION

Hairy cell leukaemia (HCL) is an uncommon malignancy, representing approximately 2% of leukaemias and < 1% of lymphoid neoplasms.[1] The median age of onset is 50-55 years. The male-female ratio is approximately 4:1.[2,3] Most patients present with symptoms of splenomegaly or cytopenia, fatigue, infection, and hemorrhagic signs.[4,5] These signs are usually not accompanied by symptom B. Palpable splenomegaly is a classic feature of HCL. Pancytopenia is present in 60-80% of patients with HCL.[3-5] Circulating tumour cells specific to HCL are usually observed in the peripheral blood. Cytoplasmic slender protrusions give the cell a "hairy" appearance. Tartrate-resistant acid phosphate activity can be demonstrated in any patient, although the proportions of positive cells vary across patients. However, it is not a specific finding for HCL. Hairy cells strongly express pan-B cell antigens and typically express CD11c, CD25, CD103, CD123 (bright), and cyclin D1 (usually weak). Annexin A1 and BRAF V600E mutations are detected in approximately 75% of all HCL cases. Therefore, it should be remembered that HCL, as in other indolent lymphomas, cannot be cured. Asymptomatic patients are not treated. If patients present with signs of disease or a decrease in their haematological parameters, they should be treated. In general, the haematological parameters that indicate the need for treatment include at least one of the following: haemoglobin (Hgb) 11 g/dL, thrombocyte count 100,000/mL, or absolute neutrophil count 1000/mL.[6,7] Symptomatic splenomegaly may be an indication for treatment. Nucleoside analogues, such as pentostatin and cladribine, have been introduced recently and have emerged as effective therapeutic options with promising results.[8,9] The first choice, in this case, is 2-chlorodeoxyadenosine (cladribine, 2-CdA). 2-CdA is administered continuously through intravenous (IV) in most clinical trials, and it is still used in several centres as the first-line therapy for patients with HCL. However, although the plasma half-life is short, 2-CdA accumulates in leukemic cells and has a longer intracellular half-life, which makes it feasible to adopt subcutaneous (SC) applications.[10,11]

Although a cure is not achieved through this approach, complete remission (CR) is achieved with Hgb > 11 g/dL (without transfusion), thrombocyte >100x10^9/L, neutrophil > 1.5x10^9/L, morphologically undetectable HCL cells in the peripheral blood and bone marrow, absence of organomegaly in physical examination, and the absence of symptoms.[12] Piro *et al.*[13] reported 11 CR and one partial response (PR) for 12 patients with HCL who were treated with a single 7-day course of 2-CdA. Other studies have reported similar outcomes.[14-16] In 20-50% of the HCL patients who achieved CR with 2-CdA treatment, minimal residual disease (MRD) was subsequently demonstrated by immunohistochemical methods.[17,18] Disease recurrence has been associated with MRD in HCL.[19] If the response is inadequate or relapse occurs before 12 months, alternative purine analogues may be administered alone or in combination with rituximab, rituximab alone, interferon administration, or via referral to clinical trials.[20] Recently, vemurafenib, a BRAF inhibitor, was applied in treating resistant and relapsing HCL with significant outcomes.[21] The development of recombinant immunotoxins targeting CD25 or CD22 is ongoing.[22,23] In this study, we retrospectively analyzed the demographic data, treatments, length of hospital stay, treatment responses, complications, and survival rates of 20 patients with HCL who were diagnosed during 2015-2021.

MATERIAL AND METHODS

Twenty patients diagnosed with HCL and followed up at the Bursa Uludag University Hematology Department Clinic between 2015 and 2021 were included in the study. The inclusion criteria were pathological, flow cytometric, and morphologically confirmed HCL diagnosis, treatment for HCL diagnosis, and age > 18 years. Data on the clinical features of the patients, signs and symptoms at the time of presentation, laboratory values at the time of diagnosis, imaging and pathology reports, treatments applied, treatment modalities (IV and SC), treatment responses, the length of hospital stay, and the short- and long-term complications were retrospectively reviewed.

The standard protocol at our centre was IV administration. However, we used SC when there was no IV form. Then, we compared the outcomes with IV and SC applications. No difference was recorded between the groups regarding age, gender, spleen size, and laboratory results. Accordingly, we did not change the diagnosis, supportive treatment, or follow-up.

The treatment protocols in the studies included 0.14 mg/kg SC 2-CdA for five days or 0.1 mg/kg IV 2-CdA for seven days. In the study, the response evaluation was performed clinically and through the laboratory, every two weeks, and a bone marrow biopsy was performed approximately six months after the treatment. Response measures were made as suggested by Grever's consensus guidelines in 2017.[12]

Patients were classified as those with morpholog-

ical evidence of disease, those with MRD+, or those without any evidence of the disease. The morphological illness was defined as lymphoid infiltrates that could be identified on sections stained with hematoxylin and eosin. MRD required the absence of lymphoid infiltrates on the hematoxylin- and eosin-stained sections but the presence of HCL-specific B cells on flow cytometry or an HCL-specific lymphoid infiltrate on immunohistochemical staining alone. The samples were considered to have no residual HCL evidence if no lymphoid infiltrates were detected in the hematoxylin- and eosin-stained sections, < 5% CD20+ B lymphocytes, and no flow cytometric evidence of monoclonal B cells.

Statistical Analysis

Data were analyzed with IBM SPSS V23. Kaplan-Meier method was used for survival analysis. The conformity to the normal distribution was evaluated using the Shapiro-Wilk test. Categorical variables according to groups Chi-square and Fisher's Exact tests were used for comparison. An independent two-sample t-test was applied to compare normally distributed data according to paired groups. The Mann-Whitney U test was performed to compare non-normally distributed data. The data were presented as the mean ± SD for quantitative data. Categorical data as deviation and median (minimum: maximum) were presented as frequency (percentage). The significance level was set to $p < 0.05$.

Table 1. Demographic and clinical characteristics of twenty patients.

Gender (Female/Male)	4/16
Age (years)	44.5 (30:78)
Clinical Presentation	
Leukocytosis	3 (15)
Pancytopenia	14 (70)
Anemia, thrombocytopenia, bicytopenia	3 (15)
Blood values	
Haemoglobin (g/dL)	10.4 (5.6-15)
Platelets ($\times 10^9$/L)	61,000 (11,000-154,000)
Leukocytes ($\times 10^9$/L)	2,550 (1,200-97,000)
Neutrophil ($\times 10^9$/L)	755 (210-9,880)
Splenomegaly	14 (70)
Bone marrow reticulin fibrosis degree	
4+/4	10 (50)
3+/4	7 (35)
Not evaluated	3 (15)
Bone marrow cellularity	
Hypercellular	10 (50)
Hypocellular	1 (5)
Heterogeneous	9 (45)
Treatment	
IV cladribine	11 (55)
SC cladribine	9 (45)
Control bone marrow	
Normocellular	6 (30)
MRD cannot be excluded	7 (35)
Not done	7 (35)
Response status	
Complete response	18 (90)
Partial response	1 (5)
Could not be evaluated	1 (5)
Overall survival (months)	43.5 (1.5:79)
Final status	
Alive	19 (95)
Dead	1 (5)

Data were expressed n (%) or median (min:max). IV: intravenous, SC: subcutaneous, MRD: minimal residual disease.

RESULTS

The study population comprised 20 patients (4 women and 16 men). The most common complaint was fatigue. At the time of admission, 14 of the patients had pancytopenia. Fourteen of the patients had splenomegaly, and three of them were massive. The peripheral blood values included moderate anaemia (median Hgb 10.4 g/dL), thrombocytopenia (median 61×109/L), leukopenia (median 2.5×10^9/L), and neutropenia (median 0.755×10^9/L). In bone marrow examination, cellularity was hypercellular in 10 patients and reticulin fibrosis 4+/4 was detected. The demographic and clinical characteristics of the patients are summarized in Table 1. All patients were purine analogue naive at the time of inclusion. At study onset, all patients showed indications for treatment due to symptoms, peripheral cytopenia, and/or organomegaly. 2-CdA monotherapy was administered to all patients as the first-line therapy. Granulocyte-colony stimulating factor (G-CSF) was applied in the neutropenic period. 2-CdA was administered at the dose of 0.09 mg/kg in 11 patients via continuous infusion for seven days and, in 9 patients, at the dose of 0.14 mg/kg for five days via the SC route. A statistically significant difference was recorded between the median length of stay according to the cladribine groups (p = 0.003). While the median of the IV group was 22.0, the median of the SC group was 0.0. In SC application, the incidence of febrile neutropenia (FEN) was lower (22.2% vs 54.5%), albeit not statistically significant. FEN developed in 8 patients during cladribine treatment. While 6 of 8 patients who developed FEN received cladribine by the IV route, two received cladribine by the SC route. Culture positivity could be detected in 5 of 8 patients, and infection-related early mortality was observed in one patient. Reproductive characteristics of patients complicated with FEN were given in Table 2. In addition, no correlation was recorded between the level of neutropenia and FEN and between neutropenia and the length of stay. There was no difference between the route of administration and the treatment response. Time to response was longer in patients with Hgb levels < 11 g/dL relative to those with higher Hgb levels (median 30 vs 45 days) p = 0.014). There was no correlation among the spleen size, leukocyte, neutrophil, thrombocyte levels, and response time.

In the statistical analysis performed on 13 patients after excluding seven patients without a control bone marrow biopsy, a significant correlation was found between the Hgb level of < 11 g/dL and the group in which MRD could not be excluded pathologically (71% vs 28%) (p = 0.048). There was no correlation

Table 2. Culture characteristics of patients complicated with febrile neutropenia.

No	Route	Culture positivity	Culture site	Isolated pathogens	Antibiotherapy	Duration (days)	Early mortality
1	IV	Absent	-	-	Piperacillin tazobactam+metronidazole	10	Absent
2	IV	Present	Blood	*Salmonella enteritidis*	Cefepime+ciprofloxacin	14	Absent
3	IV	Absent	-	-	Piperacillin tazobactam+ciprofloxacin Meropenem	3 7	Absent
4	IV	Present	Blood	*Klebsiella pneumoniae*	Meropenem Vancomycin	36 48	Absent
5	IV	Present	Wound	*Staphylococcus aureus,* *Enterococcus faecalis*	Piperacillin tazobactam Teicoplanin Meropenem+daptomycin Colistin	15 20 7 16	Present
6	IV	Absent	-	-	Piperacillin tazobactam	10	Absent
7	SC	Present	Brain abscess	*Aspergillus fumigatus*	Liposomal Amphotericin B	30	Absent
8	SC	Present	Sputum	*Acinetobacter ursingii,* *Acinetobacter junii*	Piperacillin tazobactam Meropenem Teicoplanin	3 20 12	Absent

IV: intravenous, SC: subcutan.

Table 3. Comparative results of intravenous and subcutaneous administration.

	IV cladribine	SC cladribine	*P* value
Length of hospital stay (days)	22 (11-35)	0 (0-40)	0.003*
Febrile neutropenia	54.5%	22.2%	0.197**
Overall response rate	90.9%	100%	
Time to response (days)	45 (23-120)	30 (30-60)	1.000*

Data were expressed n (%) or median (min:max). IV: intravenous, SC: subcutaneous.
*Mann-Whitney U test, **Fisher's Exact test.

among the spleen size, leukocyte, neutrophil, thrombocyte levels, and MRD. The CR rate to treatment was 90%, and the overall response rate (ORR) was 95%. PR was detected in one patient who was administered IV 2-CdA. In one patient, response evaluation could not be performed due to early mortality after receiving IV 2-CdA; the patient died due to septic shock on the 30th day of treatment. Details about the application were given in Table 3. A statistically significant difference was found between the median overall survival (OS) of the cladribine groups ($p = 0.023$). While the median of the IV group was 51.9 months, the median of the SC group was 29.7 months. The median follow-up period in all patients was 44 months. While the median follow-up period of cladribine was 56.9 months in the IV group, it was 29.7 months in the SC group. The median OS was not reached (95% confidence interval [CI]: 1.5-79 months) (Figure 1). The median 2-year and 5-year OS was calculated as 95%. No secondary malignancy was detected during the follow-up period.

DISCUSSION

HCL is a rare indolent lymphoma. The results of cladribine treatment are quite successful for HCL. Especially the easy applicability of the SC form makes it preferable to patients and doctors. However, data on the SC form are scarce. In this study, we retrospectively evaluated the clinical features, treatments, treatment results, length of hospitalization, FEN frequency, presence of secondary malignancy, and survival of 20 patients diagnosed with HCL and being followed up between 2015 and 2021. Our study's male/female ratio was 4:1, similar to that in the literature, and the median age was 44.5 years. The median age of the patients was lower than in several studies.[24-27] At admission, 70% of the patients had pancytopenia and splenomegaly. The introduction of pentostatin and subsequent 2-CdA in the 1980s and 1990s completely changed the course of HCl with a CR of 80-90% and a long-term response rate of approximately 90% achieved long-term survival.[13,28,29] All the patients in our study were administered 2-CdA as the first-line therapy. 2-CdA was administered at the dose of 0.09 mg/kg in 11 patients via continuous infusion for seven days and, in 9 patients, at the dose of 0.14 mg/kg for five days via the SC route. G-CSF was administered to all patients during the neutropenic period.

Infections seen during cladribine treatment are among the common complications of treatment. A review by Maevis *et al.*30 reported the frequency of fever in patients treated with cladribine between 40-69%. Not all fevers may be associated with infection. In Klorshid *et al.*'s study[31], the fever frequency (related or not associated with infection) was 35%. In our study, the frequency of fever was 40%, which was compatible with the literature. Hospitalization times were significantly shorter, and the incidence of febrile neutropenia was lower with SC application than with IV application.

In Inbar *et al.*'s study[27], SC was administered to 32% of 203 HCL patients, and IV 2-CdA was administered to 68%. PFS and OS were not significantly

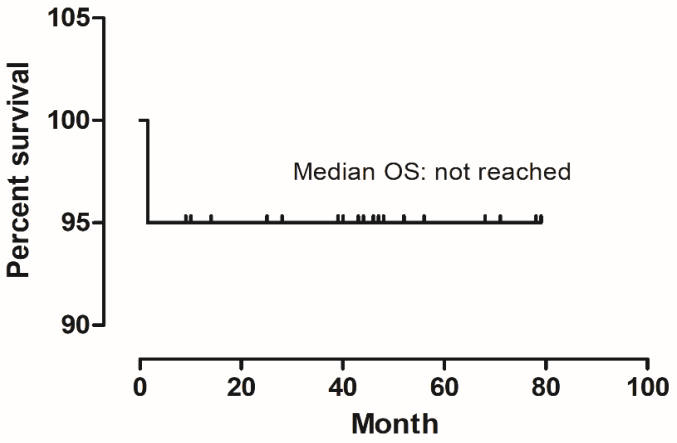

Figure 1. Survival of patients.

different in patients.[27] In our study, there was no difference between the administration route and treatment response. The complete response rate to treatment was 90%, and ORR was 95%. PR was detected in one patient who was administered IV 2-CdA. Response assessment could not be performed on a patient due to early mortality (died due to septic shock on the 30th day of treatment). The hospital stay was significantly longer in those treated with IV 2-CdA. We evaluated the treatment response by performing bone marrow control at six months. The median OS was 43.5 months (95% CI, range: 1.5-79 months), and the 2-year and 5-year OS was 95%, with a median 44-month follow-up.

Past studies have revealed a correlation between anaemia, thrombocytopenia, and disease-free survival (DFS).[28] A recent study also reported a correlation among anaemia, age, ECOG status, and survival, consistent with previous findings that link anaemia and thrombocytopenia with lower DFS. Anaemia appears to affect long-term survival and not early mortality.[29] Our study detected no significant correlation among age, spleen size, anaemia, leukocytosis, thrombocytopenia, LDH levels, bone marrow fibrosis degree, and OS. However, a statistically significant correlation was recorded among the Hgb level, treatment response, and MRD. In patients with Hgb > 11 g/dL, the response time to treatment was shorter than that in the group with a value < 11 g/dL. Moreover, while MRD was negative in the control bone marrow biopsies of patients with Hgb > 11 g/dL, MRD could not be excluded in the control bone marrow biopsies of patients with Hgb < 11 g/dL.

Other late complications, such as relapse and second neoplasms, have been described because of better control of the disease and more prolonged survival.[32] In a Swedish study, 18% of the patients had secondary primary cancer; the most significant associations were non-Hodgkin lymphoma and melanoma.[33] A survey that reported skin cancer incidence among 267 patients at the Memorial Sloan Kettering Cancer Center found a corresponding incidence of 11.3%.[34] Although it remains a controversial issue, purine analogues are believed to not contribute to the emergence of secondary malignancies.[35-38] In our study, no secondary malignancy was detected during the follow-up period. However, this result may be attributable to the small number of patients and the short follow-up period. The patients should be followed closely regarding the development of secondary malignancy in the long term.

In one of our patients, recurrence was detected in the first year of the control bone marrow biopsy, but it was followed for approximately 2.5 years without any treatment indication. The response was then obtained with the second course of cladribine. Unlike in other cases, MRD positivity was evident in this patient's 6-month control bone marrow biopsy. Recurrence may not have been observed due to our cases' relatively short follow-up period.

We did not observe any increase in the incidence of the second neoplasm in the patients in our study during the follow-up period. We believe this might be related to the small number of patients and the short follow-up period.

CONCLUSIONS

In summary, this study confirmed the efficacy of 2-CdA treatment in HCL, similar to that in the literature. In general, ease of application, good tolerance, and long-term safety data are the primary reasons for choosing 2-CdA. Moreover, we showed that the SC application is more practical than the IV application; hospitalization and febrile rates are significantly lower, and the response rates are at least as good as in the IV form. In most patients, a single course of SC 2-CdA is sufficient for long-term disease control. Although the frequency of infection is less in the SC form, severe infections may also occur in the SC form. Therefore the patients should be followed closely. We have demonstrated that the Hgb level can affect response time and MRD status; this finding deserves confirmation by further studies and more extensive series. Our response and survival data agree with the current literature, reaffirming purine analogues' role in HCL management.

Acknowledgements

None

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Uludag University, Faculty of Medicine, Bursa, Turkey. (Decision number: 2022-4/9, date: Fabruary 2022).

Authors' Contribution

Study Conception: FÖ,; Study Design: FÖ, TE,; Supervision: VÖ, RA,; Literature Review: TE,; Critical Review: VÖ, TE,; Data Collection and/or Processing: SC, TDK,; Statistical Analysis and/or Data Interpretation: TE, İEP,; Manuscript preparing: TE.

REFERENCES

1. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006 Jan 1;107(1):265-76. doi: 10.1182/blood-2005-06-2508.
2. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer. 2011 Nov 22;105(11):1684-92. doi: 10.1038/bjc.2011.450.
3. Frassoldati A, Lamparelli T, Federico M, Annino L, Capnist G, Pagnucco G, Dini E, Resegotti L, Damasio EE, Silingardi V. Hairy cell leukemia: a clinical review based on 725 cases of the Italian Cooperative Group (ICGHCL). Italian Cooperative Group for Hairy Cell Leukemia. Leuk Lymphoma. 1994 Apr;13(3-4):307-16. doi: 10.3109/10428199409056295.
4. Catovsky D. Hairy-cell leukaemia and prolymphocytic leukaemia. Clin Haematol. 1977 Feb;6(1):245-68.
5. Golomb HM, Catovsky D, Golde DW. Hairy cell leukemia: a clinical review based on 71 cases. Ann Intern Med. 1978 Nov;89(5 Pt 1):677-83. doi: 10.7326/0003-4819-89-5-677.
6. Cornet E, Delmer A, Feugier P, Garnache-Ottou F, Ghez D, Leblond V, Levy V, Maloisel F, Re D, Zini JM, Troussard X; French Society of Haematology. Recommendations of the SFH (French Society of Haematology) for the diagnosis, treatment and follow-up of hairy cell leukaemia. Ann Hematol. 2014 Dec;93(12):1977-83. doi: 10.1007/s00277-014-2140-y.
7. Jones G, Parry-Jones N, Wilkins B, Else M, Catovsky D. Revised guidelines for the diagnosis and management of hairy cell leukaemia and hairy cell leukaemia variant*. Br J Haematol. 2012 Jan;156(2):186-95. doi: 10.1111/j.1365-2141.2011.08931.x.
8. Broccoli A, Argnani L, Cross M, Janus A, Maitre E, Troussard X, Robak T, Dearden C, Else M, Catovsky D, Zinzani PL. A 3-decade multicenter European experience with cladribine as upfront treatment in 384 patients with hairy cell leukemia. Blood Adv. 2022 Jul 26;6(14):4224-7. doi: 10.1182/bloodadvances.2022007854.
9. Yousaf M, Khan MA, Iftikhar R, Chaudary QU, Shahbaz N, Ahmad U, Javed H. Treatment outcomes of patients with hairy cell leukaemia; A 16-year experience at a tertiary care center in Pakistan. J Ayub Med Coll Abbottabad. 2022 Oct-Dec;34(4):797-801. doi: 10.55519/JAMC-04-10177.
10. Juliusson G, Heldal D, Hippe E, Hedenus M, Malm C, Wallman K, tolt CM, Evensen SA, Albertioni F, Tjønnfjord G, et al. Subcutaneous injections of 2-chlorodeoxyadenosine for symptomatic hairy cell leukemia. J Clin Oncol. 1995 Apr;13(4):989-95. doi: 10.1200/JCO.1995.13.4.989.
11. Liliemark J, Juliusson G. Cellular pharmacokinetics of 2-chloro-2'-deoxyadenosine nucleotides: comparison of intermittent and continuous intravenous infusion and subcutaneous and oral administration in leukemia patients. Clin Cancer Res. 1995 Apr;1(4):385-90.
12. 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, Falini B. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. Blood. 2017 Feb 2;129(5):553-60. doi: 10.1182/blood-2016-01-689422.
13. Piro LD, Carrera CJ, Carson DA, Beutler E. Lasting remissions in hairy-cell leukemia induced by a single infusion of 2-chlorodeoxyadenosine. N Engl J Med. 1990 Apr 19;322(16):1117-21. doi: 10.1056/NEJM199004193221605.
14. Else M, Ruchlemer R, Osuji N, Del Giudice I, Matutes E, Woodman A, Wotherspoon A, Swansbury J, Dearden C, Catovsky D. Long remissions in hairy cell leukemia with purine analogs. Cancer. 2005 Dec 1;104(11):2442-8. doi: 10.1002/cncr.21447.
15. Chadha P, Rademaker AW, Mendiratta P, Kim B, Evanchuk DM, Hakimian D, Peterson LC, Tallman MS. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience. Blood. 2005 Jul 1;106(1):241-6. doi: 10.1182/blood-2005-01-0173.
16. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. Blood. 1998 Sep 15;92(6):1918-26.
17. Ellison DJ, Sharpe RW, Robbins BA, Spinosa JC, Leopard JD, Saven A, Piro LD. Immunomorphologic analysis of bone marrow biopsies after treatment with 2-chlorodeoxyadenosine for hairy cell leukemia. Blood. 1994 Dec 15;84(12):4310-5.
18. Hakimian D, Tallman M, Kiley C, Peterson L. Detection of minimal residual disease by immunostaining of bone marrow biopsies after 2-chlorodeoxyadenosine for hairy cell leukemia. Blood. 1993 Sep 15;82(6):1798-802.
19. Wheaton S, Tallman MS, Hakimian D, Peterson L. Minimal residual disease may predict bone marrow relapse in patients with hairy cell leukemia treated with 2-chlorodeoxyadenosine. Blood. 1996 Feb 15;87(4):1556-60.
20. NCCN Clinical Practice Guidelines in Oncology, Guidelines for Treatment of Cancer by Site. Version 1.2013. Hairy Cell Leukemia.
21. 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, Tallman MS. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. N Engl J Med. 2015 Oct 29;373(18):1733-47. doi: 10.1056/NEJMoa1506583.
22. Kreitman RJ. Immunoconjugates and new molecular targets in hairy cell leukemia. Hematology Am Soc Hematol Educ Program. 2012;2012:660-6. doi: 10.1182/asheducation-2012.1.660.
23. Park JH, Levine RL. Targeted immunotherapy for hairy cell leukemia. J Clin Oncol. 2012 May 20;30(15):1888-90. doi: 10.1200/JCO.2011.39.8313.

24. Divino V, Karve S, Gaughan A, DeKoven M, Gao G, Knopf KB, Lanasa MC. Characteristics and treatment patterns among US patients with hairy cell leukemia: a retrospective claims analysis. J Comp Eff Res. 2017 Sep;6(6):497-508. doi: 10.2217/cer-2017-0014.
25. Dinmohamed AG, Posthuma EFM, Visser O, Kater AP, Raymakers RAP, Doorduijn JK. Relative survival reaches a plateau in hairy cell leukemia: a population-based analysis in The Netherlands. Blood. 2018 Mar 22;131(12):1380-1383. doi: 10.1182/blood-2017-12-820381.
26. Hacioglu S, Bilen Y, Eser A, Sivgin S, Gurkan E, Yildirim R, Aydogdu I, Dogu MH, Yilmaz M, Kayikci O, Tombak A, Kuku I, Celebi H, Akay MO, Esen R, Korkmaz S, Keskin A. Multicenter retrospective analysis regarding the clinical manifestations and treatment results in patients with hairy cell leukemia: twenty-four year Turkish experience in cladribine therapy. Hematol Oncol. 2015 Dec;33(4):192-8. doi: 10.1002/hon.2177.
27. Inbar M, Herishanu Y, Goldschmidt N, Bairey O, Yuklea M, Shvidel L, Fineman R, Aviv A, Ruchlemer R, Braester A, Najib D, Rouvio O, Shaulov A, Greenbaum U, Polliack A, Tadmor T. Hairy Cell Leukemia: Retrospective analysis of demographic data and outcome of 203 patients from 12 medical centers in Israel. Anticancer Res. 2018 Nov;38(11):6423-6429. doi: 10.21873/anticanres.13003.
28. Dearden CE, Else M, Catovsky D. Long-term results for pentostatin and cladribine treatment of hairy cell leukemia. Leuk Lymphoma. 2011 Jun;52 Suppl 2:21-4. doi: 10.3109/10428194.2011.565093.
29. Benz R, Arn K, Andres M, Pabst T, Baumann M, Novak U, Hitz F, Hess U, Zenhaeusern R, Chalandon Y, Mey U, Blum S, Rauch D, O'Meara Stern A, Cantoni N, Bargetzi M, Bianchi-Papina E, Rossi D, Passweg J, Lohri A, Berardi S, Li Q, Feller A, Stussi G. Prospective long-term follow-up after first-line subcutaneous cladribine in hairy cell leukemia: a SAKK trial. Blood Adv. 2020 Aug 11;4(15):3699-3707. doi: 10.1182/bloodadvances.2020002160.
30. Maevis V, Mey U, Schmidt-Wolf G, Schmidt-Wolf IG. Hairy cell leukemia: short review, today's recommendations and outlook. Blood Cancer J. 2014 Feb 14;4(2):e184. doi: 10.1038/bcj.2014.3.
31. Khorshid O, Namour AE, El-Gammal MM, Mahmoud TY, Fortpied C, Abdel-Malek R, Ramadan S. Efficacy and safety of cladribine: subcutaneous versus intravenous administration in hairy cell leukemia patients. Mediterr J Hematol Infect Dis. 2015 Oct 16;7(1):e2015058. doi: 10.4084/MJHID.2015.058.
32. Sarvaria A, Topp Z, Saven A. Current therapy and new directions in the treatment of hairy cell leukemia. JAMA Oncol. 2016 Jan;2(1):123-9. doi: 10.1001/jamaoncol.2015.4134.
33. Zheng G, Chattopadhyay S, Sud A, Sundquist K, Sundquist J, Försti A, Houlston R, Hemminki A, Hemminki K. Second primary cancers in patients with acute lymphoblastic, chronic lymphocytic and hairy cell leukaemia. Br J Haematol. 2019 Apr;185(2):232-239. doi: 10.1111/bjh.15777.
34. Watts JM, Kishtagari A, Hsu M, Lacouture ME, Postow MA, Park JH, Stein EM, Teruya-Feldstein J, Abdel-Wahab O, Devlin SM, Tallman MS. Melanoma and non-melanoma skin cancers in hairy cell leukaemia: a surveillance, epidemiology and end results population analysis and the 30-year experience at Memorial Sloan Kettering Cancer Center. Br J Haematol. 2015 Oct;171(1):84-90. doi: 10.1111/bjh.13528.
35. Else M, Dearden CE, Matutes E, Garcia-Talavera J, Rohatiner AZ, Johnson SA, O'Connor NT, Haynes A, Osuji N, Forconi F, Lauria F, Catovsky D. 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 Jun;145(6):733-40. doi: 10.1111/j.1365-2141.2009.07668.x.
36. Au WY, Klasa RJ, Gallagher R, Le N, Gascoyne RD, Connors JM. Second malignancies in patients with hairy cell leukemia in british columbia: a 20-year experience. Blood. 1998 Aug 15;92(4):1160-4.
37. Cheson BD, Vena DA, Barrett J, Freidlin B. Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukemias. J Clin Oncol. 1999 Aug;17(8):2454-60. doi: 10.1200/JCO.1999.17.8.2454.
38. Kurzrock R, Strom SS, Estey E, O'Brien S, Keating MJ, Jiang H, Adams T, Talpaz M. Second cancer risk in hairy cell leukemia: analysis of 350 patients. J Clin Oncol. 1997 May;15(5):1803-10. doi: 10.1200/JCO.1997.15.5.1803.