ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/medsci.2023-98368

The Incidence of BRAF V600E Mutations and the Impact of Cladribine Treatment on the Incidence of BRAF V600E Mutations and Survival in Hairy Cell Leukemia Patients: A Case-Control Study

Tüylü Hücreli Lösemi Hastalarında BRAF V600E Mutasyonu Sıklığı ve Kladribin Tedavisinin Mutasyon Sıklığı ve Sağkalım Üzerindeki Etkisi: Bir Vaka Kontrol Çalışması

Deniz ÖZMEN[a], Aynur DAĞLAR ADAY[b], Meliha NALÇACI[c], Melih AKTAN[c]

[a]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Division of Hematology, İstanbul, Türkiye
[b]İstanbul University Faculty of Medicine, Department of Medical Genetics, İstanbul, Türkiye
[c]İstanbul University Faculty of Medicine, Division of Hematology, İstanbul, Türkiye

ABSTRACT Objective: Hairy cell leukemia (HCL) is a rare and indolent lymphoproliferative disease characterized by the infiltration of hairy shaped leukemic B cells with specific immunophenotypic features in the bone marrow, spleen and liver resulting in progressive pancytopenia and splenomegaly. Purine analogs are preferred as the first-line treatment for HCL. This study investigates the significance of BRAF V600E mutations in HCL diagnosis and prognosis, focusing on their baseline and post-cladribine treatment incidences and impacts on patient survival. **Material and Methods:** This retrospective, case-control study comprises HCL patients diagnosed and treated between July 2012 and June 2014. The study group includes 22 HCL patients (newly diagnosed n=10, remission n=12). The control group comprises B-cell chronic lymphoproliferative disease patients (n=10). All HCL patients underwent cladribine treatment. Patient demographics, clinical characteristics, and survival outcomes were recorded. **Results:** The mean age of the predominantly male (81.8%) study group was 51.1±10.2 years. No significant differences in demographic and clinical features existed between the groups (p>0.05). The incidence of BRAF V600E mutation among HCL patients, initially 69.2%, fell to 20% post-treatment. Yet, no significant disparity in overall survival and mortality rates was found between HCL patients with/without BRAF V600E mutation (p=0.256 and p=0.999). **Conclusion:** The proportion of HCL patients with BRAF V600E mutations decreased from 69.2% to 20% post-cladribine. However, persistence of the mutation didn't significantly affect HCL patient survival and mortality.

Keywords: Hairy cell leukemia; BRAF V600E mutation; cladribine; mortality rate; survival

ÖZET Amaç: Tüylü hücreli lösemi [hairy cell leukemia (HCL)] splenomegali ve ilerleyici pansitopeni ile seyreden, kemik iliği, dalak ve karaciğerin tüylü görünümlü lösemik B hücreleri ile infiltre olduğu, yavaş seyirli, spesifik immünofenotipik bulgulara sahip, nadir görülen bir hastalıktır. Günümüzde, HCL'nin tedavisinde ilk basamakta pürin analogları tercih edilmektedir. Bu çalışmada, BRAF V600E mutasyonunun HCL tanı ve prognozundaki önemi, kladribin tedavisi öncesi ve sonrası insidansları ve hasta sağkalımı üzerine etkileri araştırılmaktadır. **Gereç ve Yöntemler:** Bu retrospektif vaka-kontrol çalışmasının popülasyonu, Temmuz 2012-Haziran 2014 arasında tanı ve tedavi gören HCL hastalarından oluşmaktadır. Çalışma grubu 22 HCL hastasını (yeni tanı n=10, remisyon n=12) içerirken, kontrol grubu B hücreli kronik lenfoproliferatif hastalığı olan hastaları (n=10) kapsamaktadır. Tüm HCL hastalarına kladribin tedavisi uygulanmıştır. Hastaların demografik ve klinik özellikleri kaydedilmiştir. **Bulgular:** Çalışma grubu, ağırlıklı olarak erkek (%81,8) ve ortalama yaş 51,1±10,2 idi. Gruplar arasında demografik ve klinik özelliklerde anlamlı bir fark bulunmamıştır (p>0,05). Başlangıçtaki BRAF V600E mutasyonu pozitifliği oranı %69,2 iken, tedavi sonrası %20'ye düşmüştür. Ancak BRAF V600E mutasyonu olan ve olmayan HCL hastaları arasında genel sağkalım ve ölüm oranlarında belirgin bir fark görülmemiştir (p=0,256 ve p=0,999). **Sonuç:** Kladribin tedavisi sonrası BRAF V600E mutasyonlu HCL hastalarının oranı %69,2'den %20'ye düşmüştür. Ancak kladribin tedavisi sonrası mutasyonda negatifleşmenin HCL hastalarında sağkalım ve mortalite üzerinde anlamlı bir etkisi bulunmamaktadır.

Anahtar Kelimeler: Tüylü hücreli lösemi; BRAF V600E mutasyonu; kladribin; ölüm oranı; sağkalım

TO CITE THIS ARTICLE:
Özmen D, Dağlar Aday A, Nalçacı M, Aktan M. The incidence of BRAF V600E mutations and the impact of cladribine treatment on the incidence of BRAF V600E mutations and survival in hairy cell leukemia patients: A case-control study. Turkiye Klinikleri J Med Sci. 2024;44(2):69-75.

Correspondence: Deniz ÖZMEN
İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Division of Hematology, İstanbul, Türkiye
E-mail: dnzozm@hotmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Medical Sciences.

Received: 04 Jul 2023 ***Received in revised form:*** 10 Jan 2024 ***Accepted:*** 12 Feb 2024 ***Available online:*** 18 Apr 2024

Hairy cell leukemia (HCL) is a rare chronic, B-cell lymphoproliferative disorder characterized by massive splenomegaly, pancytopenia, and typically hairy appearing cells.[1,2] Bone marrow, spleen, and liver are infiltrated by these cells. In addition to many hairy cells circulating in peripheral blood, the absence of lymphadenopathy is another characteristic finding of this disease.[2,3] Its diagnosis is usually based on cytomorphology, immunophenotyping, and immunohistopathology.[4]

Flow cytometric analysis revealed that HCL has bright co-expressions of the cluster of differentiation 19 (CD19), CD20, CD22, CD25, CD103, and CD11c, depending on its variants.[2,5-7] Although these features are beneficial in diagnosing HCL and differentiating it from other B-cell lymphoproliferative diseases, gene expression profiles focusing on BRAF (v-raf murine sarcoma viral oncogene homolog B1) V600E mutations may provide evident data in cases with atypical morphologies or immunophenotypes.[1,3]

As a member of the serine/threonine protein kinase family, BRAF is essential in the RAS- RAF - MEK-ERK signaling pathway that regulates cell proliferation and survival.[8] The BRAF V600E mutation has been previously demonstrated via whole-exome sequencing in patients with HCL.[2,4,9-11] It is regarded as the disease-defining genetic lesion for the typical/classical variant of HCL.[8] Other B-cell variants, including HCL-variant unclassifiable splenic leukemia/lymphoma, splenic marginal zone lymphoma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, and mantle cell lymphoma are devoid of this mutation.[4,8] Identification of BRAF V600E mutations has clarified the controversial issues regarding the pathogenesis and biology of HCL.[7] To give an example, the use of purine analogs in the treatment of HCL has been associated with BRAF V600E mutations.[3,12]

In this context, this study was carried out to investigate the incidence of baseline and post-treatment BRAF V600E mutations in HCL patients treated with cladribine and the impact of pre- and post-treatment BRAF V600E mutation incidence on clinical parameters, including survival, in these patients.

MATERIAL AND METHODS

STUDY DESIGN

This study was designed as a retrospective, case-control study. Local ethics committee approval was obtained from Clinical Research Ethics Committee of İstanbul University-Faculty of Medicine (date: June 29, 2012, number: 1221). The study was carried out in accordance with the ethical principles set forth in the Declaration of Helsinki. Written informed consent could not be obtained from the patients due to the study's retrospective design.

POPULATION AND SAMPLE

This study's population consisted of patients diagnosed with and treated for HCL in the Department of Hematology, Faculty of Medicine, İstanbul University, İstanbul, Türkiye, between July 2012 and June 2014. The study group consisted of 22 HCL patients who were newly diagnosed (n=10) or in remission (n=12). The diagnosis of HCL was made based on the morphological findings of the bone marrow aspiration and biopsy and the flow cytometric immunophenotyping characteristics.[1,13] Giemsa-stained peripheral blood and bone marrow slides were prepared to determine the morphological spectrum of the disease. Hairy cell infiltration intensity of >90%, and tartrate-resistant acid phosphatase and Annexin A1 positivity in the bone marrow aspirates were the primary findings indicating HCL diagnosis.[14] Additionally, peripheral blood samples/bone marrow aspirates were stained with a multi-colored B-cell chronic lymphoproliferative disorder antibody panel to characterize the expression profile of the clonal cells.[1] CD20, CD103, CD25, and CD11c were the monoclonal antibodies investigated in this study (Becton Dickinson Biosciences, San Jose, CA, USA).

On the other hand, patients who were consecutively diagnosed with B-cell chronic lymphoproliferative diseases diagnosed based on the World Health Organization criteria were included in the study as the control group (n=10).[15]

MOLECULAR WORK-UP

Peripheral blood samples were taken from the patients during their admission to the outpatient clinics.

Genomic DNA was isolated from these blood samples using a commercially available kit (Roche Diagnostic GmbH, Mannheim, Germany). After DNA copy-number analysis, single nucleotide polymorphism analyses were performed for the BRAF V600E mutation via the quantitative reverse transcriptase polymerase chain reaction method (Roche Light cycler 480 system) in the DNA samples obtained from the patients in both the study and control groups. The primer sets for the BRAF V600E mutation are given below:[7]

Forward primer set 1: 5'- TAG GTG ATT TTG GTC TAG CTA CAG T-3'

Forward primer set 2: 5'- GGT GAT TTT GGT CTA GCT ACA AA-3'

Backward primer: 5' GGC CAA AAA TTT AAT CAG TGG A-3'

TREATMENT AND FOLLOW-UP

All patients received a single cycle of cladribine treatment at a dose of 0.1 mg/kg/day via continuous intravenous infusion for seven days.[7] In selected cases, rituximab monotherapy or dual therapy with cladribine was used.

Patients with complete absence of hairy cells in the peripheral blood or bone marrow and normal peripheral blood count values, i.e., hemoglobin >12 g/dL, total lymphocyte count >3x10^9/L, absolute neutrophil count >1.5x10^9/L, and platelet count >100x 10^9/L, absence of palpable adenopathy, hepatosplenomegaly, and constitutional symptoms were deemed to be in complete remission.[7,12]

A second blood sample was obtained from the patients to investigate the post-treatment status of the BRAF V600E mutation in newly-diagnosed patients or patients with remission during the outpatient follow-up period following the completion of the treatment featuring purine analogs.

Overall survival (OS) was determined based on the data obtained from the patients' medical records and via telephone calls in April 2023. The interval between the start of treatment to death or the last follow-up was defined as OS.

VARIABLES

The patient's medical records were used to obtain demographic characteristics, i.e., age at diagnosis and gender, and clinical characteristics, i.e., pre-and post-treatment status of the BRAF V600E mutations, details of the treatment modalities used for HCL, OS, and follow-up outcomes.

The patients were grouped according to their disease status as newly-diagnosed and in remission. Additionally, patients' pre-treatment BRAF V600E mutations were grouped as mutated and non-mutated. The study's primary outcome was the differences between the survival data based on these two parameters.

STATISTICAL ANALYSIS

The descriptive statistics obtained from the collected data were expressed mean±standard deviation values in the case of continuous variables determined to conform to the normal distribution, as median with minimum-maximum values in the case of continuous variables determined not to conform to the normal distribution, and as numbers and percentages in the case of categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normal distribution characteristics of the numerical variables.

The Fisher's exact test was used to compare the differences between categorical variables in 2x2 tables. The Mann-Whitney U test was used to compare two independent groups where numerical variables had no normal distribution.

Jamovi project 2.3.24.0 (Jamovi, version 2.3.24.0, 2023, retrieved from https://www.jamovi.org) (Jamovi, Sydney, Australia) and JASP 0.17.1 (Jeffreys' Amazing Statistics Program, version 0.17.1, 2023, retrieved from https://jasp-stats.org) (University of Amsterdam, Netherlands) software packages were used in the statistical analyses. The probability (p) statistics of ≤0.05 were deemed to indicate statistical significance.

RESULTS

The mean age of the study group, i.e., 22 HCL patients, was 51.1±10.2 years. The study group mainly consisted of males (81.8%). There were no significant differences between HCL patients (study group) and patients with B-cell chronic lymphoproliferative diseases (control group) in demographic characteristics (p>0.05) (Table 1).

TABLE 1: Demographic characteristics of the study and control groups.

	Groups		
	Study (n=22)	Control (n=10)	p value
Age at diagnosis (year)†	51.1±10.2	55.5±9.2	0.243
Sex‡			
Female	4 (18.2)	0 (0.0)	0.283
Male	18 (81.8)	10 (100.0)	

†Mean±standard deviation, ‡n (%).

Multicolor flow cytometry revealed that all HCL patients were positive for CD20, CD103, CD25, and CD11c.

The pre-and post-treatment of the BRAF V600E mutations are detailed in Table 2. None of the patients in the control group had BRAF V600Emutations. BRAF V600E mutations were detected in 9/13 cases (69.2%) before treatment. Of these nine patients, eight were newly-diagnosed HCL patients, indicating that 80% of the newly-diagnosed patients had BRAF V600E mutations before the treatment.

Treatment modalities used in patients with HCL are detailed in Table 3. Cladribine was used in all patients. After the treatment, BRAF V600E mutations were detected in only three patients who were in remission. Therefore, the post-treatment incidence of the BRAF V600E mutation decreased to 20.0% (three out of 15 cases with test results) (Table 2).

The median follow-up time was 113 and 152 months in patients with and without BRAF V600E mutations (p=0.296). The comparison of the study's outcomes between the subgroups created based on the pre-treatment presence of BRAF V600E mutations did not reveal any significant difference between the groups (p>0.05). The mortality rate was higher, albeit not significantly, in non-mutated patients than in mutated patients (p=0.999). There was also no significant difference between mutated and non-mutated patients in OS (p=0.256) (Table 4).

TABLE 2: Pre- and post-treatment status of BRAFV600E mutations in the study and control groups.

	Study Group			
	Overall (n=22)	New diagnosis (n=10)	In remission (n=12)	Control group (n=10)
Pre-treatment BRAFV600E‡				
Negative	4 (18.2)	2 (20.0)	2 (16.7)	12 (100.0)
Positive	9 (40.9)	8 (80.0)	1 (8.3)	0 (0.0)
Unknown	9 (40.9)	0 (0.0)	9 (75.0)	0 (0.0)
Post-treatment BRAFV600E‡				
Negative	12 (54.5)	3 (30.0)	9 (75.0)	--
Positive	3 (13.6)	0 (0.0)	3 (25.0)	--
Unknown	7 (31.8)	7 (70.0)	0 (0.0)	--

‡n (%).

TABLE 3: Treatment modalities in patients with hairy cell leukemia.

	Overall (n=22)	Patients with a new diagnosis (n=10)	Patients with remission (n=12)
Medications‡			
Cladribine	22	10 (100.0)	12 (100.0)
Rituximab	3	1 (10.0)	2 (16.7)
Interferon	1	0 (0.0)	1 (8.3)
Other modalities‡			
Splenectomy	1	0 (0.0)	1 (8.3)
Radiotherapy	1	0 (0.0)	1 (8.3)

‡n (%).

TABLE 4: Outcomes of hairy cell leukemia patients with and without pre-treatment BRAFV600E mutation.

	Patients		
	BRAFV600E mutated (n=9)	BRAFV600E non-mutated (n=4)	p value
Follow-up time (month)§	113.0 (3.0-146.0)	152.0 (12.0-194.0)	0.296*
Prognosis‡			
Survived	6 (85.7)	3 (75.0)	0.999**
Non-survived	1 (14.3)	1 (25.0)	
Overall survival (month)§	110.0 (3.0-140.0)	150.5 (12.0-193.0)	0.256*

§Median (minimum-maximum); ‡n (%); *Mann-Whitney U test; **Fisher's exact test.

TABLE 5: Outcomes of the patients with hairy cell leukemia.

	Patients with		
	Overall (n=20)	New diagnosis (n=8)	Remission (n=12)
Prognosis‡			
Survived	16 (80.0)	6 (75.0)	10 (83.3)
Non-survived	4 (20.0)	2 (25.0)	2 (16.7)
Overall survival (months)§	143.5 (3.0-230.0)	111.5 (3.0-129.0)	163.5 (49.0-230.0)
Survival time (months)§	136.5 (3.0-230.0)	110.0 (3.0-122.0)	155.0 (48.0-230.0)

§Median (minimum-maximum); ‡n (%).

Of the 20 patients with follow-up data, 16 (80%) were alive at the last follow-up. The overall mortality rate of the patients with HCL was 20.0%. The median OS of the study group was 143.5 months, ranging from three to 230 months. The distribution of mortality rate and OS by the disease-based subgroups is given in Table 5.

The findings of this case-control study revealed that the rate of HCL patients with BRAF V600E mutations, which was 69.2% at baseline, decreased to 20% after cladribine treatment.

However, the persistence of BRAF V600E after cladribine treatment had no significant effect on OS and mortality in patients with HCL.

DISCUSSION

Although earlier studies reported BRAF V600E mutation as a genetic hallmark of HCL, more recent studies reported the prevalence of BRAF V600E mutations between 70.6% and 89.1%.[1,3,16-20] In one of these studies conducted in India, Bibi et al. detected BRAF V600E mutations in 89.1% of the HCL patients.[1] In another study conducted in India, Gupta et al. detected BRAF V600E mutations in all four patients tested among 16 patients with HCL.[7] Wei et al. reported that BRAF V600E mutations were detected in patients with classic HCL.[21] In comparison, in this study, BRAF V600E mutations were detected in 69.2% of the HCL patients. Patients with classic HCL are rarely non-mutated for BRAF mutations.[14] The HCL patients included in this study were not stratified according to the type of HCL, i.e., classic or variant HCL. Nonetheless, it may be speculated that the BRAF V600E mutations detected in HCL patients might be attributed to an undiagnosed variant of HCL.

It has been suggested that BRAF V600E mutation status may indicate minimal residual disease in HCL.[4] Schnittger et al. confirmed the efficacy of using BRAF V600E mutation status in diagnosing classical HCL and monitoring its residual disease.[4] In parallel, several studies reported 45% incidence of residual disease in mutated HCL cases after cladribine treatment.[1] Nevertheless, the impact of the BRAF V600E mutations on the development of residual disease could not be assessed in this study. Future stud-

ies are needed to shed light on the probable relationship between BRAF V600E mutation status and HCL prognosis. In sum, it can be speculated that the detection of BRAF V600E mutations after treatment may not indicate the need for treatment.

The technique used to analyze BRAF V600E mutations may impact the results. In fact, studies conducted with different techniques had varying outcomes.[1,3] Additionally, the quality of the samples may be suboptimal if they do not contain sufficient hairy cells for analysis.[2] Genomic alterations associated with BRAF V600E mutations in HCL patients are also debated.[5,22] Furthermore, patient- and disease-related factors may play a role in testing accuracy. All these factors must be considered when interpreting the discrepancies between different studies in BRAF V600E mutation detection rates. The specificity of the technique used to analyze BRAF V600E mutations may be determined based on the non-detection of BRAF V600E mutations in the control group.

LIMITATIONS OF THE STUDY

The primary limitation of this study was that the HCL patients were not stratified according to the variants of HCL cases. Therefore, the potential relationships between different variants of HCL and BRAF V600E mutations could not be evaluated. Another limitation of the study was its retrospective design, which made it impossible to access all data.

CONCLUSION

In conclusion, the rate of HCL patients with BRAF V600E mutation, which was 69.2% at baseline, decreased to 20% after cladribine treatment. However, disappearance of the BRAF V600E mutated genes induced by cladribine treatment had no significant effect on survival and mortality in patients with HCL. On the other hand, BRAF V600E mutation status can be used in the diagnosis of HCL and evaluation of the treatment response. Large-scale studies are needed to shed light on the probable relationship between pre- and post-treatment BRAF V600E mutation status and HCL prognosis.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Melih Aktan, Deniz Özmen;* ***Design:*** *Aynur Dağlar Aday, Deniz Özmen;* ***Control/Supervision:*** *Melih Aktan, Meliha Nalçacı;* ***Data Collection and/or Processing:*** *Deniz Özmen, Aynur Dağlar Aday;* ***Analysis and/or Interpretation:*** *Melih Aktan, Deniz Özmen;* ***Literature Review:*** *Deniz Özmen;* ***Writing the Article:*** *Deniz Özmen;* ***Critical Review:*** *Meliha Nalçacı;* ***References and Fundings:*** *Meliha Nalçacı;* ***Materials:*** *Aynur Dağlar Aday.*

REFERENCES

1. Bibi A, Java S, Chaudhary S, Joshi S, Mascerhenas R, Rabade N, et al. BRAFV600E mutation in hairy cell leukemia: A single-center experience. Indian J Pathol Microbiol. 2018;61(4):532-6. [Crossref] [PubMed]
2. So CC, Chan A, Chung LP, Siu L, Wong WS, Wong KF. A comparison of high resolution melting, allele-specific priming and Sanger sequencing for the detection of BRAFV600E mutation in hairy cell leukaemia from different haematological specimens. Pathology. 2014;46(6):533-7. [Crossref] [PubMed]
3. Tiacci E, Schiavoni G, Forconi F, Santi A, Trentin L, Ambrosetti A, et al. Simple genetic diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation. Blood. 2012;119(1):192-5. Erratum in: Blood. 2013;122(9):1685. [Crossref] [PubMed]
4. Schnittger S, Bacher U, Haferlach T, Wendland N, Ulke M, Dicker F, et al. Development and validation of a real-time quantification assay to detect and monitor BRAFV600E mutations in hairy cell leukemia. Blood. 2012;119(13):3151-4. [Crossref] [PubMed]
5. Durham BH, Getta B, Dietrich S, Taylor J, Won H, Bogenberger JM, et al. Genomic analysis of hairy cell leukemia identifies novel recurrent genetic alterations. Blood. 2017;130(14):1644-8. [Crossref] [PubMed] [PMC]
6. Maitre E, Cornet E, Debliquis A, Drenou B, Gravey F, Chollet D, et al. Hairy cell leukemia: a specific 17-gene expression signature points to new targets for therapy. J Cancer Res Clin Oncol. 2022;148(8):2013-22. [Crossref] [PubMed] [PMC]
7. Gupta R, Yadav S, Mittal N, Rahman K, Sharma A, Gupta A, et al. Clinicopathological spectrum of hairy-cell leukemia: A single-center study with brief review of Indian literature. J Cancer Res Ther. 2020;16(1):120-26. [Crossref] [PubMed]
8. Tadmor T, Tiacci E, Falini B, Polliack A. The BRAF-V600E mutation in hematological malignancies: a new player in hairy cell leukemia and Langerhans cell histiocytosis. Leuk Lymphoma. 2012;53(12):2339-40. [Crossref] [PubMed]
9. Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med. 2011;364(24):2305-15. [Crossref] [PubMed] [PMC]
10. Chung SS, Kim E, Park JH, Chung YR, Lito P, Teruya-Feldstein J, et al. Hematopoietic stem cell origin of BRAFV600E mutations in hairy cell leukemia. Sci Transl Med. 2014;6(238):238ra71. [Crossref] [PubMed] [PMC]
11. Maitre E, Bertrand P, Maingonnat C, Viailly PJ, Wiber M, Naguib D, et al. New generation sequencing of targeted genes in the classical and the variant form of hairy cell leukemia highlights mutations in epigenetic regulation genes. Oncotarget. 20182;9(48):28866-76. [Crossref] [PubMed] [PMC]
12. Smirnova SY, Al-Radi LS, Moiseeva TN, Gemdzhian EG, Yakutik IA, Julhakyan HL, et al. Inhibitor of BRAFV600E Mutation as a Treatment Option for Hairy Cell Leukemia With Deep Neutropenia and Infectious Complications. Clin Lymphoma Myeloma Leuk. 2021;21(7):427-30. [Crossref] [PubMed]
13. Zhang R, Wu Y, Wang X, Lu X, Li Y, Li S, et al. Difference of genomic copy numbers alterations between hairy cell leukemia-variant and classical hairy cell leukemia: a pilot retrospective study in Chinese. Int J Med Sci. 2020;17(3):325-31. [Crossref] [PubMed] [PMC]
14. Gozzetti A, Sammartano V, Bacchiarri F, Raspadori D, Bocchia M. A BRAF-Negative Classic Hairy Cell Leukemia Patient with Long-Lasting Complete Remission after Rituximab and Pentostatin. Turk J Haematol. 2020;37(4):286-7. [Crossref] [PubMed] [PMC]
15. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117(19):5019-32. [Crossref] [PubMed] [PMC]
16. Andrulis M, Penzel R, Weichert W, von Deimling A, Capper D. Application of a BRAF V600E mutation-specific antibody for the diagnosis of hairy cell leukemia. Am J Surg Pathol. 2012;36(12):1796-800. [Crossref] [PubMed]
17. Wang XJ, Kim A, Li S. Immunohistochemical analysis using a BRAF V600E mutation specific antibody is highly sensitive and specific for the diagnosis of hairy cell leukemia. Int J Clin Exp Pathol. 2014;7(7):4323-8. [PubMed] [PMC]
18. Blombery PA, Wong SQ, Hewitt CA, Dobrovic A, Maxwell EL, Juneja S, et al. Detection of BRAF mutations in patients with hairy cell leukemia and related lymphoproliferative disorders. Haematologica. 2012;97(5):780-3. [Crossref] [PubMed] [PMC]
19. Xi L, Arons E, Navarro W, Calvo KR, Stetler-Stevenson M, Raffeld M, et al. Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. Blood. 2012;119(14):3330-2. [Crossref] [PubMed] [PMC]
20. Shao H, Calvo KR, Grönborg M, Tembhare PR, Kreitman RJ, Stetler-Stevenson M, et al. Distinguishing hairy cell leukemia variant from hairy cell leukemia: development and validation of diagnostic criteria. Leuk Res. 2013;37(4):401-9. [Crossref] [PubMed] [PMC]
21. Wei C, Jin XX, Cai H, Wang X, Zhuang JL, 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(4):416-21. Chinese. [PubMed]
22. Maitre E, Tomowiak C, Lebecque B, Bijou F, Benabed K, Naguib D, et al. Deciphering genetic alterations of hairy cell leukemia and hairy cell leukemia-like disorders in 98 patients. Cancers (Basel). 2022;14(8):1904. [Crossref] [PubMed] [PMC]