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Original Article

The Prevalence of BRAF V600E Mutation in Hairy Cell Leukemia: A Systematic Review and Meta-Analysis Study

Abstract

Background: BRAF V600E mutations were recently identified in the leukemic cells from patients with hairy cell leukemia (HCL) that this mutation in exon 15 is considered the disease-defining mutation in HCL. **Objectives:** This meta-analysis aimed to report the prevalence of BRAF V600E mutation in HCL patients. **Methods:** Three databases including PubMed, Scopus, and Web of Science up to 2017 were searched for the prevalence of BRAF mutation in HCL patients. A random effects meta-analysis was performed using the Comprehensive Meta-Analysis software version 2.0 with the event rate (ER) and 95% confidence interval (95% CI). **Results:** Out of 552 articles identified from the search, 11 were included included and were analyzed for meta-analysis study. The studies in meta-analysis included 437 patients with HCL, of which 353 (80.8%) patients had BRAF V600E mutation. The pooled ER of the studies was 81.5% (95% CI: 69.5%–89.5%). The Begg's test did not show publication bias, but the Egger's test showed publication bias. **Conclusions:** With regard to the mentioned limitations, the prevalence of BRAF mutation in HCL patients was >80%. In future studies, considering sex, age, and other variables can exactly show the correlation between these variables with the detection of BRAF mutation.

Keywords: *BRAF, hairy cell leukemia, prevalence*

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Introduction

Hairy cell leukemia (HCL) is a chronic B-cell lymphoid leukemia characterized by pancytopenia, splenomegaly, myelofibrosis, and the presence in peripheral blood, bone marrow, and spleen of atypical lymphoid cells with a hairy aspect.[1] There are approximately 1000 and 1600 new cases of HCL per year in the US and Europe, respectively. The prevalence of the disease is unknown, although HCL accounts for 2% of all types of leukemia, and the incidence of HCL increases annually.[2] Variant HCL (HCLv) is now included in the World Health Organization classification as a provisional entity and is no longer considered to be biologically related to classic HCL (HCLc). The clinical course of HCLv is variable, but usually more aggressive, and the median survival of patients with HCLv is significantly shorter than that of HCLc.[3] HCLc is a B-cell malignancy with distinctive immunophenotype, typically expressing CD20, CD22, CD25, CD11c, CD103, CD123, annexin A1, and tartrate-resistant acid phosphatase.[4] HCLc responds to purine nucleoside analogs, while HCLv cases are resistant and are more aggressive compared with the classic variant.[5] Clinically, HCL has an indolent course with splenomegaly, progressive cytopenias, low numbers of circulating leukemia cells, and no lymphadenopathy. BRAF V600E mutations were recently identified in the leukemic cells from patients with HCL.[6] This mutation in exon 15 is considered the disease-defining mutation in HCL, but single HCL cases lacking this mutation have been described.[7] It has demonstrated BRAF V600E-negative cases of HCL.[8] In some studies, BRAF V600E mutations were found in 100% cases of HCL.[9,10] The aim of this meta-analysis study was to report the prevalence of BRAF V600E mutation in HCL patients.

Methods

Search strategies and study criteria

The studies were searched in three databases (PubMed, Scopus, and Web of Science) up to December 2017 using the keywords of hairy cell leukemia or HCL

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and BRAF for the prevalence of BRAF mutation in HCL patients.

Study selection

One author (E.S) searched the articles and then the second author (M.S) was blinded to the first author. If there was any disagreement between the two authors, the problem was resolved with negotiation. All studies were searched for the evaluation of the prevalence of BRAF mutation in HCL patients. The inclusion criteria for the studies selected were as follows: (i) studies reporting the prevalence of BRAF and (ii) only studies with English language abstract. The exclusion criteria included the case reports, review articles, incomplete reports (no sufficient information), and letters.

Data extraction

The name of author, year of publication, publication country, total number of patients, and number of patients with BRAF mutation were the relevant data extracted from every study.

Statistical analysis

A random effects meta-analysis was performed by the Comprehensive Meta-Analysis software version 2.0 (CMA 2.0; Biostat Inc, Englewood, NJ). The event rate (ER) of the studies included was calculated for the estimation of the prevalence of BRAF mutation in HCL patients. Heterogeneity between estimates was evaluated by the Q and I^2 statistics that, for the Q statistic, heterogeneity was considered if $P < 0.1$. Confidence interval (CI) was 95% and P (two-sided) <0.05 was considered to be statistically significant in this meta-analysis. The publication bias was assessed through funnel plot analysis with the Begg's and Egger's tests.

Results

Out of 552 articles identified from the search, after excluding the studies, 25 studies were assessed for eligibility. Of these 25 studies, 14 studies were excluded based on reasons. Finally, 11 studies were included and were analyzed for meta-analysis study [Figure 1].

The characteristics of the studies included in the meta-analysis are shown in Table 1. The studies included were between 2011 and 2016. Three studies were reported from Germany,[7,11,12] five studies from USA,[8,10,13-15] one study from Australia,[16] one study from Iraq,[17] and one study from Italy.[18] The studies in the meta-analysis included 437 patients with HCL, of which 353 (80.8%) patients had BRAF V600E mutation.

The prevalence of BRAF mutation in HCL patients in the meta-analysis study is shown in Figure 2. The pooled ER of the studies was 81.5% (95% CI: 69.5%–89.5%) with $I^2 = 77.7\%$.

Publication bias

Funnel plot of the studies for the prevalence of BRAF mutation in HCL patients is shown in Figure 3. The Begg's test did not show publication bias ($P = 0.051$), but Egger's test showed the publication bias ($P = 0.010$).

Table 1: The characteristics of the studies in meta-analysis (n=11)

The first author, year	Country	Total number of HCL patients	Number of BRAF positivity patients
Tiacci E, 2011[18]	Italy	48	30
Andrulis M, 2012[11]	Germany	32	32
Blombery PA, 2012[10]	USA	59	38
Schnittger S, 2012[12]	Germany	117	115
Verma S, 2012[15]	USA	12	12
Xi L, 2012[8]	USA	69	42
Brown NA, 2015a[13]	USA	22	17
Brown NA, 2015b[14]	USA	29	24
Tschernitz S, 2014[7]	Germany	24	21
Thomas C, 2015[16]	Australia	20	20
Altaee Z, 2016[17]	Iraq	5	2

HCL – Hairy cell leukemia

Discussion

This meta-analysis showed that the prevalence of BRAF V600E mutation in HCL patients was 81.5%. Boyd *et al*.[19] used high resolution melting analysis for detection of BRAF exon 15 mutations on formalin-fixed, paraffin-embedded (FFPE) tissues that this method may provide a useful tool for specialist hematopathology laboratories. Vemurafenib is used in treating patients with BRAF V600E mutation in HCL. BRAF mutation provides further opportunities for the use of a targeted therapy approach to improve outcome in HCL patients, especially for patients with relapsed or treatment-refractory disease.[20] The frequent nature of activating BRAF V600E mutations in HCL is fundamental in the pathogenetic understanding of this entity and will likely become an entity defining genetic aberration in future classifications.[11] Therefore, the detection of BRAF V600E mutations in HCL has important diagnostic utility.[13]

Two studies[19,21] reported that the BRAF V600E mutation was present in all patients with HCL, and Xi *et al*.[8] reported in 79% of their HCLc cases using a pyrosequencing assay. Tiacci *et al*.[18] showed that BRAF V600E mutation can serve as a new diagnostic tool to distinguish HCL from other morphologically similar B-cell neoplasms.

There are several methods used in the studies including Sanger sequencing, high-resolution melting, allele-specific polymerase chain reaction, and pyrosequencing that most of them used either fresh or frozen tissue or stringent criteria for accepting FFPE specimens.[14] As these studies investigated only exon 15 of the BRAF gene, one study extended our sequencing approach to exon 11, which harbors a second hotspot of BRAF mutations in solid tumors.[7] In the routine diagnostic setting, It is suggested the screening of BRAF V600E-negative HCL for alternative exon 11 mutations.[7]

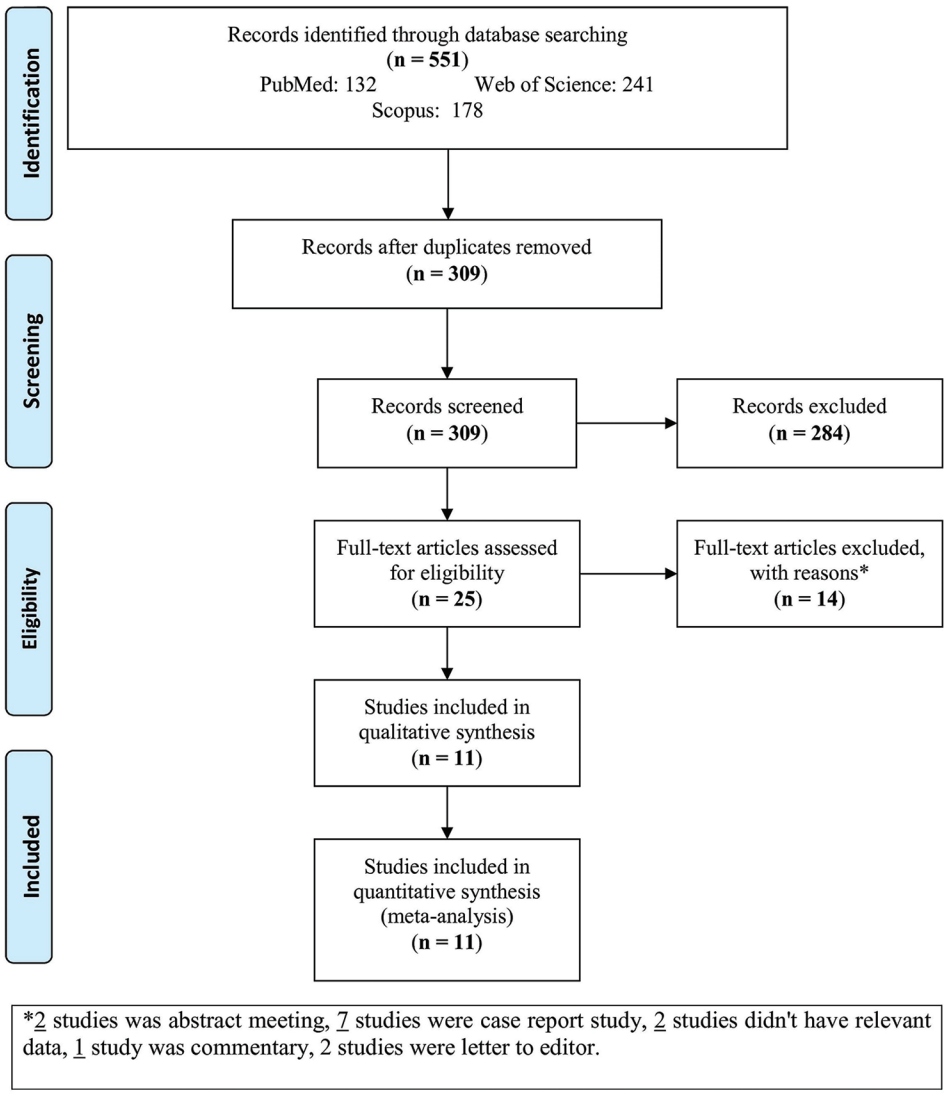

Figure 1: Flowchart of the study

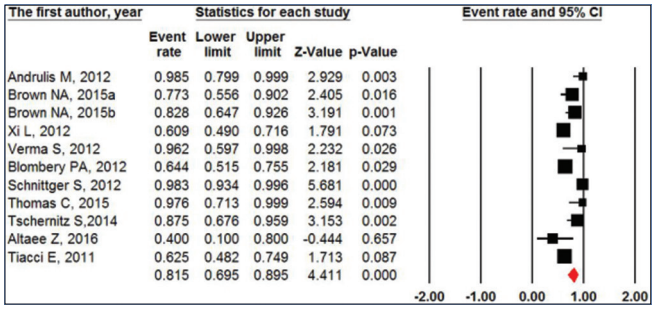

Figure 2: Forest plot of the prevalence of the studies included in the meta-analysis (*n* = 11)

One study[6] reported that the BRAF V600E mutation was detected in 100% of HCLc versus none of the HCLv patients. Another study[8] showed that BRAF was mutated in 79% of HCLc and none of the HCLv patients. Therefore, used methods, different subtypes of HCL, and exons checked can change the percentage of BRAF mutation and cause the difference between the results in the studies.

Limitations

1. Difference in the detection methods of BRAF mutation in HCL patients
2. Low number of patients in more studies
3. Unknown age and gender in a number of studies
4. Difference in the number of patients in subgroups of HCL among the studies (HCLc and HCLv).

Conclusions

With regard to the mentioned limitations, the prevalence of BRAF mutation in HCL patients was >80%. In the future studies, sex, age, and other variables can exactly show the correlation between these variables with the detection of BRAF mutation.

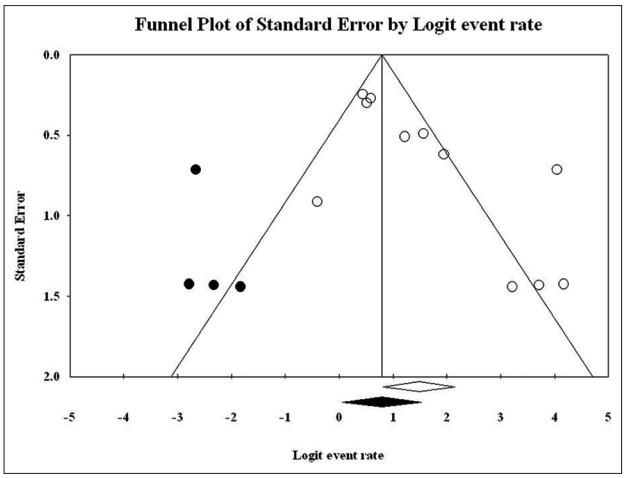

Figure 3: Funnel plot of the random effect of the studies for the prevalence of BRAF mutation in patients with hairy cell leukemia

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Payandeh M, Sadeghi M, Sadeghi E. Hairy cell leukemia: A retrospective study on 11 patients in the Western of Iran. Int J Hematol Oncol Stem Cell Res 2015;9:133-7.
2. Shackelford RE, Heldmann M, Eskandari F, Joshi N, Browning J, Maxwell N, *et al.* Marked retroperitoneal lymphadenopathy in hairy cell leukemia: A case report. Case Rep Oncol 2013;6:493-6.
3. Robak T. Management of hairy cell leukemia variant. Leuk Lymphoma 2011;52 Suppl 2:53-6.
4. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein, H, *et al*. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed., Vol. 2. Lyon, France: World Health Organization; 2008.
5. Hsieh YC, Chang ST, Chuang SS, Lu CL, Tsao CJ, Lin CN, *et al.* Hairy cell leukemia and variant in Taiwan: Report of a variant case and literature review. Int J Clin Exp Pathol 2011;4:183-9.
6. 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;364:2305-15.
7. Tschernitz S, Flossbach L, Bonengel M, Roth S, Rosenwald A, Geissinger E, *et al.* Alternative BRAF mutations in BRAF V600E-negative hairy cell leukaemias. Br J Haematol 2014;165:529-33.
8. 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;119:3330-2.
9. 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;119:192-5.
10. 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;97:780-3.
11. 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;36:1796-800.
12. 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;119:3151-4.
13. Brown NA, Betz BL, Weigelin HC, Elenitoba-Johnson KS, Lim MS, Bailey NG, *et al.* Evaluation of allele-specific PCR and immunohistochemistry for the detection of BRAF V600E mutations in hairy cell leukemia. Am J Clin Pathol 2015a;143:89-99.
14. Brown NA, Weigelin HC, Bailey N, Laliberte J, Elenitoba-Johnson KS, Lim MS, *et al.* Requisite analytic and diagnostic performance characteristics for the clinical detection of BRAF V600E in hairy cell leukemia: A comparison of 2 allele-specific PCR assays. Appl Immunohistochem Mol Morphol 2015b;23:590-600.
15. Verma S, Greaves WO, Ravandi F, Reddy N, Bueso-Ramos CE, O'Brien S, *et al.* Rapid detection and quantitation of BRAF mutations in hairy cell leukemia using a sensitive pyrosequencing assay. Am J Clin Pathol 2012;138:153-6.
16. Thomas C, Amanuel B, Finlayson J, Grieu-Iacopetta F, Spagnolo DV, Erber WN, *et al.* BRAF mutation detection in hairy cell leukaemia from archival haematolymphoid specimens. Pathology 2015;47:349-54.
17. Zahraa M. Al Taee. Investigation of three BRAF V600E mutations related to hairy cell leukemia in Al-Hillah city. Res J Pharm Biol Chem Sci 2016;7:1658.
18. Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, *et al.* BRAF mutations in hairy-cell leukemia. N Engl J Med 2011b;364:2305-15.
19. Boyd EM, Bench AJ, van 't Veer MB, Wright P, Bloxham DM, Follows GA, *et al.* High resolution melting analysis for detection of BRAF exon 15 mutations in hairy cell leukaemia and other lymphoid malignancies. Br J Haematol 2011;155:609-12.
20. Roberts PJ, Der CJ. Targeting the raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007;26:3291-310.
21. 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 2012a;119:192-5.