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Research paper

Single agent vemurafenib or rituximab-vemurafenib combination for the treatment of relapsed/refractory hairy cell leukemia, a multicenter experience

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ABSTRACT

Background: Hairy cell leukemia (HCL) is a rare mature B-cell malignancy that is primarily treated with purine analogues. However, relapse remains a significant challenge, prompting the search for alternative therapies. The BRAF V600E mutation prevalent in HCL patients provides a target for treatment with vemurafenib.
Patients and methods: This multicenter retrospective study included nine patients with relapsed/refractory (R/R) HCL from six different centers. Patient data included demographics, prior treatments, clinical outcomes, and adverse events.
Results: Patients received different treatment regimens between centers, including vemurafenib alone or in combination with rituximab. Despite the differences in protocols, all patients achieved at least a partial response, with seven patients achieving a complete response. Adverse events were generally mild with manageable side effects. The absence of myelotoxic effects and manageable side effects make BRAF inhibitors attractive, especially for patients ineligible for purine analogues or those with severe neutropenia.

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Conclusion: Single agent vemurafenib or in combination with rituximab appears to be a promising therapeutic option for R/R HCL. Further research is needed to establish standardized treatment protocols and to investigate long-term outcomes.

1. Introduction

Classical hairy cell leukemia (HCL) is a rare mature B-cell malignancy with distinctive clinicopathological features [1,2]. It is characterized by pancytopenia and susceptibility to infection.[1] Standard treatment is based on chemotherapy with purine analogs [3,4]. The purine nucleoside analogues (PNAs) cladribine and pentostatin are highly active first-line therapeutic treatments for HCL [5]. These agents result in complete response (CR) rates of 85–90% [5–7]. It is also effective in re-induction. However, relapse remains an important problem in these patients [8]. In addition to poor responders, up to 58% of patients who achieve CR relapse within 5 years of initial treatment [9]. Repeated use of the same purine nucleoside analogue is effective in some patients, but the CR rate and duration of response are typically shortened following subsequent courses [10].

The BRAF V600E kinase-activating mutation plays a pathogenetic role in HCL. It leads to constitutive activation [11]. It has been found that the BRAF p.V600E somatic mutation is present in 90–100% of patients with classic HCL, and this has been described as a disease-defining genetic event [12] Patients with HCL harbor BRAF mutations, this makes BRAF inhibitors a potential therapeutic approach [13]. In a clinical trial involving relapsed and refractory (R/R) HCL patients, BRAF V600E targeting with vemurafenib contributed to response in 91% of patients (including 35% CR) [14]. Vemurafenib-resistant leukemic cells retain strong CD20 expression which is a potential target for the anti-CD20 monoclonal antibody rituximab; rituximab frequently induces responses but induces few complete remissions in patients with refractory or relapsed HCL [13–15]. Combining BRAF inhibitors with anti-CD20 monoclonal antibodies may also be even more effective than using BRAF inhibitors alone [13,16].

The optimal treatment for relapsed/refractory HCL remains unestablished. In this study, we aimed to present nine patients with R/R HCL from different centers who received vemurafenib as single agent or in combination with rituximab.

2. Methods

Patients who were over the age of 18 and diagnosed with relapsed/refractory Hairy Cell Leukemia and followed up in six different centers were included in the study. Demographics previously received treatments and responses achieved, mutation status and both hematologic, marrow and splenic responses after vemurafenib monotherapy or combination were recorded retrospectively. All patients were positive for the BRAF V600E mutation. BRAF V600E mutation was analyzed by PCR from peripheral blood or immunohistochemical staining of bone marrow paraffin sections in patients. Diagnosis and response to treatment were evaluated using consensus guidelines for HCL. Spleen sizes were measured by ultrasound, magnetic resonance imaging or computed tomography. We defined splenomegaly of >12 cm (median spleen diameter). Responses were assessed by complete blood count, bone marrow findings and peripheral blood using standardized criteria. Adverse events were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The study was approved by the ethics committee of Medipol University in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (Date: 27–07–2023, Number: 611).

3. Results

Table 1 summarizes the demographics, previous treatments and clinical outcomes of the nine patients. The age range was 32–75 years, seven were male and two were female. BRAF V600E mutation was positive in eight patients, one of patients was unknown. At the diagnosis three patients had no splenomegaly (Patient 1, 2, 8), four patients had splenomegaly (range 17–21 cm). Spleen size at diagnosis was not available for Patient 7. The first indication for treatment in all patients was cytopenias, one patient had additional B symptom (Patient 3) and four patients (Patient 3, 5, 6, 9) had additional symptomatic splenomegaly. All patients received at least one line of treatment (range 1–4 lines). Patients were heavily pretreated. Except for one patient, all other patients had used PNA (cladribine and/or pentostatine) before BRAF inhibitor-based therapy.

Previous treatments included rituximab monotherapy, splenectomy, cladribine monotherapy, pentostatine, rituximab plus cladribine, ibrutinib, pegylated interferon and interferon-α. Patient 1 received rituximab only as first-line treatment. He was a 68-year-old frail patient. Patient 2 received cladribine and was followed up for 60 months in partial response (PR). Patient 3 underwent splenectomy due to lack of response to cladribine and achieved CR 96 months after splenectomy. Patient 4 received three lines of treatment. PR was achieved with interferon, but unfortunately, she progressed rapidly. Subsequently, a 42-month CR was achieved with cladribine. Pegylated interferon was then administered, but the treatment was changed to a BRAF inhibitor-based therapy due to progressive disease. Patient 5 was effectively treated with 2 courses of cladribine. The response times were 24 and 52 months, respectively. Rituximab was given in the third line and a PR of 8 months was achieved. Pentostatin, a purine nucleoside analogue, was given in the fourth line, but a BRAF inhibitor -based treatment plan was made due to progressive disease. Patient 6 received first-line cladribine, but no response was achieved. Patient 7 was diagnosed in 2007 and received 4 courses of cladribine. While the depth and duration of response was longer in the first 2 treatments (74 and 68 months), the depth and duration of response decreased in the other cladribine treatments. Patient 8 was a very elderly patient who had received four lines of treatment and had not responded to any treatment except interferon. Therefore, monotherapy with vemurafenib was initiated and a CR was maintained for 24 months. Patient 9 was a 32-year-old young patient who relapsed after four lines of treatment. Vemurafenib was started as monotherapy and a CR was maintained for 28 months.

The indications for pre-BRAF based therapies were cytopenias in all patients, symptomatic intra-abdominal lymphadenopathy in one patient and B symptoms in one patient. Minimal residual disease (MRD) assessment could not be performed in any patient with pre-BRAF or post-BRAF inhibitor-based therapies. No patients were reported to harbor any accompanying mutations like CDKN1B or KLF2. Different treatment protocols were applied in different centers. The schedule of rituximab, the dose and duration of vemurafenib, and the decision to use vemurafenib in combination with rituximab or as monotherapy varied between centers.

Three patients (Patient 1,2,4) received Vemurafenib 960 mg BID for 2 months in combination with Rituximab 375 mg/m2/week for eight doses and CR was obtained. Patient 1–2 were in CR for 3 months, and Patient 4 was in CR for 15 months. One of the patients (Patient 5) received Vemurafenib 960 mg BID for 4 months in combination with Rituximab 375 mg/m2/week for four doses and PR was obtained. However, this patient developed grade 2 maculopapular lesions on the plantar surface that limited physical activity. The side effect did not lead to discontinuation of treatment and was controlled upon completion of treatment. For 10 months he has been followed in PR. Three patients (Patient 3,8,9) received low dose vemurafenib monotherapy

Table 1
Patients Demografics, Previous Treatments and Clinical Outcomes.

Patient	Age/ Sex	Mutational Status	Treatment indication at the diagnosis	Previous Treatments (response, duration)	Treatment indication before BRAF inhibitor-based regimen	BRAF inhibitor-based treatment (Single agent Vem or R+ Vem) (response, duration)	Prophylaxis	Adverse reactions
1	69/M	BRAF V600E+	Anemia	Rituximab (CR, 48 month)	Neutropenia	Rituximab 375 mg/ m2/week IV (for 2 months) + Vemurafenib 2×960 mg po (for 2 months) (CR, 3 months)	Valaciclovir + TMP-SMX prophylaxis	No side effects
2	32/F	BRAF V600E+	Neutropenia, Thrombocytopenia	Cladribine (PR, 60 month)	Neutropenia and thrombocytopenia	Rituximab 375 mg/ m2/week IV (for 2 months) + Vemurafenib 2×960 mg po (for 2 months) (CR, 3 months)	Valaciclovir + TMP-SMX prophylaxis	No side effects
3	58/F	BRAF V600E+	Neutropenia, Symptomatic splenomegaly (17 cm), B symptom	Cladribine (SD) Splenectomy (CR, 96 month)	Accessory spleen, intra-abdominal 6.5 cm lymphadenopathy and anemia	Vemurafenib 2×240 mg po, continuously (for 15 months) (PR was maintained for 11 months. At the last follow-up, intra-abdominal lap size progression)	No prophylaxis	Acute myocardial infarction at 15 months
4	34/M	BRAF V600E+	Pancytopenia	Interferon (PR, but quickly relapsed) Cladribine (CR, 42 month) Peg-İnterferon (PD)	Neutropenia and Thrombocytopenia	Rituximab 375 mg/ m2/week IV (for 2 months) + Vemurafenib 2×960 mg po (for 2 months) (CR, 15 months)	Tenofovir	No side effects
5	59/M	BRAF V600E+	Pancytopenia, Symptomatic splenomegaly (21 cm)	Cladribine (CR, 34 month) Cladribine (CR, 52 month) Rituximab (PR, 8 month) Pentostatin (SD)	Neutropenia and anemia	Rituximab 375 mg/ m2/week IV (for 1 month) + Vemurafenib 2×960 mg po (for 4 months) (PR, 10 months)	Valaciclovir + TMP-SMX prophylaxis	Grade 2 Maculopapular lesions on the plantar surface, which may limit physical activity, controlled with completion of treatment.
6	43/M	BRAF V600E+	Thrombocytopenia, Symptomatic splenomegaly (20 cm)	Cladribine (SD)	Thrombocytopenia, neutropenia and symptomatic splenomegaly	Rituximab 375 mg/ m2/IV every 15 days (for 3 months) + Vemurafenib 2×480 mg po (for 6 months, dose 2×240 mg after week 8) (CR, 48 months)	Valaciclovir + TMP-SMX prophylaxis	No side effects
7	40/M	BRAF V600E+	Pancytopenia	Cladribine (CR, 74 month) Cladribine (CR, 68 month) Cladribine (PR, 37 month) Cladribine (PR, 8 month)	Thrombocytopenia and neutropenia	Rituximab 375 mg/ m2/IV every 15 days (for 3 months) + Vemurafenib 2×480 mg po (for 6 months, dose 2×240 mg after week 8) (CR, 52 months)	Valaciclovir + TMP-SMX prophylaxis	Grade 1 Maculopapular lesions on the skin, controlled with dose reduction
8	75/M	BRAF V600E+	Thrombocytopenia	Interferon (CR, 22 month) Rituximab (SD) Cladribine (SD) Ibrutinib (PD)	Thrombocytopenia and anemia	Vemurafenib 2×240 mg po, continuously (for 24 months) (CR, 24 months)	No prophylaxis	No side effects
9	32/M	Unknown	Pancytopenia, Symptomatic splenomegaly (20 cm)	Interferon (PR, 6 month) Rituximab + Cladribine (CR, 34 month) Cladribine (CR, 26 month) Rituximab + Cladribine (PR, 30 month)	Pancytopenia	Vemurafenib 2×240 mg po, continuously (for 28 months) (CR, 28 months)	TMP-SMX prophylaxis	Grade 3 arthritis and grade 1 Maculopapular lesions on the skin,

CR: Complete response, PR: Partial response, TMP-SMX: Trimethoprim/sulfamethoxazole

continuously at a dose of 240 mg BID. CR was obtained in two patients and PR was obtained in one patient. However, Patient 3 had an acute myocardial infarction and treatment was discontinued after month 15. For 11 months, PR was maintained. At the last follow-up visit, an increase in the size of the intraabdominal lymphadenopathy was observed on imaging. The subsequent treatment plan has not yet been determined. Patient 9 developed grade 3 arthritis and grade 1 maculopapular lesions on the skin. Treatment was discontinued when physical limitation was aggravated due to grade 3 arthritis. The last two patients (Patient 6,7) also received Vemurafenib 480 mg BID for 6 months (after 6 weeks the dose was reduced to 240 mg BID) in combination with Rituximab 375 mg/m2/every two weeks for six doses as a different protocol. CR was obtained in both patients. One patient had no adverse reactions, but the other developed grade 1 maculopapular lesions on the extremities. It was controlled with dose reduction after week 6. None of the seven patients experienced serious adverse reactions. One of the patients (Patient 6) has been in CR for 48 months and the other (Patient 7) for 52 months.

Two patients (Patient 3,8) received no infection prophylaxis, six patients received TMP-SMX and/or valacyclovir prophylaxis. One patient (Patient 4) only received tenofovir prophylaxis to prevent hepatitis B reactivation. There were no infectious complications in any of the patients.

4. Discussion

It is currently unclear which regimen should be used first in HCL patients who relapse after PNAs. This study showed that a short non-chemotherapeutic course of vemurafenib alone or in combination with rituximab is a safe and effective treatment for patients with relapsed or refractory disease, with a mild and manageable side-effect profile.

In addition, BRAF inhibitor-based regimens are being investigated in patients who are ineligible for PNAs or progressed after PNAs. Even in previously treated patients with severe neutropenia and infections, these agents have been proposed as relatively safe drugs [17–19]. The absence of a myelotoxic effect is an important advantage of the drug. However, BRAF inhibitors have not yet been approved for use in HCL. As they are widely available as on-label treatments for solid tumors with various BRAF mutations, they are widely used off-label in routine practice [7,8].

All patients in our study were R/R HCL. The main indication for vemurafenib in all patients was cytopenias. Except for two patients, all patients had neutropenia. Six patients received vemurafenib in combination with rituximab. Three patients received vemurafenib monotherapy. Different centers used different schedules, doses and durations for patients receiving vemurafenib alone or in combination with rituximab. There was no consensus between centers regarding treatment. Combination therapy for a limited duration was preferred in most centers. Regardless of which treatment regimen was used, at least a PR was achieved in all patients. We achieved PR in two patients and CR in seven patients, and in two of complete responder patients the duration of CR was quite long (48 and 52 months). The patient with the longest complete response relapsed after four lines of PNA, and BRAF inhibitor-based therapy was used in the fifth line. Treatment with vemurafenib, especially in combination with rituximab, induces deep, long-lasting responses. This makes unlimited treatment unnecessary. Adverse events associated with BRAF inhibitors may be reduced by limiting the duration of treatment. There were no infectious complications. Side effects were limited in combination with rituximab, mostly grade 1–2, and were controlled by dose reduction or completion of treatment. In our study indefinite treatment with monotherapy often resulted in complications that led to discontinuation of the drug.

There are a limited number of studies in literature using vemurafenib as single agent or in combination with rituximab. In a single-center phase 2 study involving 30 R/R HCL patients, Tiacci et al. demonstrated the impressive efficacy and good tolerance of vemurafenib [13]. Vemurafenib 960 mg twice daily for 8 weeks and rituximab 375 mg/m2 for 8 weeks concurrently followed by rituximab 375 mg/m2 for 8 infusions for a total of 18 consecutive weeks. The median number of prior treatments was 3. The overall response rate (ORR) and CR rate was 87%. Median PFS was 78% after a median follow-up of 37 months. MRD negativity and no prior BRAF inhibitor therapy were associated with longer relapse free survival (RFS). Importantly, 65% of patients achieving CR were MRD- and all patients who had previously received BRAF inhibitors alone (n=7) responded to this combination. They found that patients who had previously been treated with BRAF inhibitor monotherapy had deeper and longer responses on subsequent treatment with vemurafenib plus rituximab than they had had with the previous monotherapy [13].

In two phase 2 studies (USA and Italy) involving 54 patients with R/R HCL in which vemurafenib was used as a single agent, vemurafenib was administered 960 mg twice daily for 16–18 weeks [14]. ORR was 96% in the Italian study and 100% in the US study. CR rates were 35% and 42%, respectively. Median follow-up in the Italian study was 23 months. RFS1 was 9 months. RFS1 was 19 months for patients who achieved CR and only 6 months for those who achieved PR. The 1-year RFS and overall survival (OS) rates were 73% and 91%, respectively, in the US study. The results of the US study have recently been updated and after a median follow-up of 40 months, the median RFS1 was 19 months, with no significant difference between patients who achieved CR and those who achieved PR [20].

In three of our patients (Patient 3,8,9), a single agent vemurafenib was used at low dose for a long time. In the 15th month of treatment, patient 3 discontinued treatment following acute myocardial infarction. The patient had no additional cardiovascular risk factors. The mechanisms of cardiotoxicity associated BRAF and MEK inhibitors are incompletely understood. The inhibition of BRAF and MEK negatively interferes with cardiovascular MAPK signaling. This generates oxidative stress and apoptosis of myocytes and impairs angiogenesis, leading to significant cardiovascular diseases. The upregulation of cluster of differentiation 47 also induced by BRAF and MEK inhibition also inhibits the signaling of nitric oxide–cyclic guanosine monophosphate, reduces nitric oxide bioavailability, and thus contributes to recurrent vasoconstriction, hypertension, and an imbalance between thrombotic and antithrombotic states. This could serve as an explanation for the occurrence of myocardial infarction [21]. Our patient (Patient 3) maintained his response for 11 months. Although a new treatment plan has not yet been made, the patient was found to have progressed at the last follow-up. Lower doses of vemurafenib may be effective in HCL. Dietrich et al. analyzed 21 R/R HCL patients, who received vemurafenib at individual dosing regimen outside clinical trials (240–1920 mg/d). There was no difference in recovery of blood counts of patients who received low ($\leq$240 mg twice daily) or high doses of vemurafenib (>240 mg twice daily). Their findings indicate that a short course of BRAF inhibition with a low dose of vemurafenib can effectively inhibit MEK/ERK signaling in vivo, reduce HCL load, and induce CR in HCL patients. They also report stable long-term remissions on low dose vemurafenib, but continuous treatment involves the risk of resistance formation and secondary malignancies [22]. Splenectomy was also performed in this patient (Patient 3) in relapse after PNA. Previous splenectomy has also been associated with a shorter response time. The absence of hairy cell circulation through the spleen may favor the persistence of ERK phosphorylation in leukemic cells at the end of treatment by causing leukemic cells to be continuously directed to the protective marrow microenvironment; this feature is apparently associated with a shorter duration of response [14].

5. Conclusion

Cases show that vemurafenib alone or in combination with rituximab improves the prognosis of HCL patients. Nevertheless, HCL remains an incurable relapsing/refractory disease. Therefore, new therapeutic strategies need to be developed. For patients who have not responded to

purine analogues, this is an effective, short course of treatment that does not require chemotherapy. The absence of myelotoxic effects is an important advantage. It may be useful in providing safe treatment in immunosuppressed and deeply neutropenic patients.

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Ethics approval

The study was approved by the ethics committee of Medipol University in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (Date: 27–07–2023, Number: 611).

Informed consent

Informed consent for publication was obtained from the patients. All the authors have reviewed the manuscript and approved it for publication.

CRediT authorship contribution statement

Muhlis Cem Ar: Supervision, Validation. **Yaşa Gül Mutlu:** Data curation, Supervision. **Leylagül Kaynar:** Resources, Software, Supervision. **Süreyya Yiğit Kaya:** Writing – review & editing, Software, Validation, Writing – original draft. **Senem Maral:** Supervision, Software, Resources. **Elif Melek:** Validation, Data curation, Software. **Gülten Korkmaz:** Data curation. **Fatma Keklik Karadağ:** Data curation. **Özgür Mehtap:** Data curation. **Ömür Gökmen Sevindik:** Methodology, Software, Supervision, Writing – review & editing. **Ümit Yavuz Malkan:** Data curation. **Gülsüm Özet:** Data curation. **Güray Saydam:** Data curation. **Tuğrul Elverdi:** Data curation.

Declaration of Competing Interest

All of the authors declare that there is no conflict of interest.

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