ISSN: 2469-5696

Ogobuchi-Odo et al. Int J Blood Res Disord 2022, 9:081
DOI: 10.23937/2469-5696/1410081
Volume 9 | Issue 2
Open Access

International Journal of
Blood Research and Disorders

REVIEW ARTICLE

Current Trends in Classic Hairy Cell Leukaemia: Aetiology, Diagnosis and Therapy

Udoka Ogobuchi-Odo, MSc*, Silas Anayo Ufelle, PhD and Ifeoma Uzoma Agbo, MSc

Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, College of Medicine, University of Nigeria, Enugu State, Nigeria

***Corresponding author:** *Udoka Ogobuchi-Odo, Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, College of Medicine, University of Nigeria, Enugu Campus, Enugu State, Nigeria, Tel: +234-805-372-1209*

Abstract

Hairy cell leukaemia (HCL) is a rare B-cell neoplasm characterized by pancytopenia, splenomegaly and presence of hairy leukaemic B-cells in the bone marrow. Its aetiology is not clear but occupational and environmental factors are possible risk factors. It is diagnosed by the monocytopenia and appearance of hairy cell in a thin blood film, immunophenotyping, use of immunohistochemical stains and by molecular detection of BRAF V600E mutation in almost all the patients.

The current first line therapy for classic hairy cell leukaemia is purine nucleoside analogues either pentostatin or cladribine. They are used either alone or combined with rituximab. They induce complete remission in almost all the patients. However, about 50% of patients relapse after a few years. This led to the search for new drugs. Hence, novel drugs are being investigated during clinical trials for the treatment of patients who relapse after treatment with purine analogues or who are refractory to them. Among these novel drugs, moxetumomab pasudotox has been approved by the Food and Drug Administration for the treatment of classic HCL. We review current trends in classic hairy cell leukaemia.

Keywords

Hairy cell leukaemia, BRAF V600E, Purine analogues, Novel drugs

Abbreviation

HCL: Hairy Cell Leukaemia; PA: Purine Analogue; PNA: Purine Nucleoside Analogue; FDA: Food and Drug Administration

Introduction

Hairy cell leukaemia (HCL) is a rare B-cell neoplasm. It is characterized by pancytopenia (specifically monocytopenia), splenomegaly and leukaemic B cells with hairy projections in the bone marrow [1]. It was originally known as leukaemic reticuloendothelios is but later the cell of origin was confirmed to be a mature B cell [2]. The name hairy cell leukaemia was derived from the typical villous cytoplasmic projections. The immunophenotype of classic hairy cell leukaemia is bright surface immunoglobin, with bright co-expression of CD 20, CD 22, CD 11c, CD 103 and CD 25, CD 123 and CD 200. The BRAFV600E mutation is found in almost all patients with classic hairy cell leukaemia [3].

Hairy cell leukaemia constitutes about 2% of lymphoid leukaemias. It affects mainly males, with a male-to-female ratio of 4 to 1. The average age at diagnosis is 58 years. Classic hairy cell leukaemia and its variant form, hairy cell leukaemia variant are now considered as different entities [1,4]. The aetiology of HCL is unclear with occupational and environmental factors considered as possible risk factors [5].

Treatment for classical hairy cell leukaemia has advanced from the use of interferons in the 1980s, purine analogues in the 1990s, monoclonal antibodies in the 2000s to BRAF kinase inhibitors in the present decade. These advances in therapy have led to outstanding prognosis, with many of the patients attaining durable remissions and extended survival [6,7]. This article reviews current trends in classic hairy cell leukaemia with emphasis on aetiology, diagnosis and therapy.

Aetiology of Hairy Cell Leukaemia

The aetiology of hairy cell leukaemia is unclear. Occupational and environmental factors which possibly

Citation: Ogobuchi-Odo U, Ufelle SA, Agbo IU (2022) Current Trends in Classic Hairy Cell Leukaemia: Aetiology, Diagnosis and Therapy. Int J Blood Res Disord 9:081. doi.org/10.23937/2469-5696/1410081

Accepted: August 27, 2022: **Published:** August 29, 2022

increase the risk of hairy cell leukaemia are exposure in cattle farms, pesticides, petroleum products, and ionizing radiation. There are uncommon anecdotal case reports of HCL running in families [5].

Diagnosis of Classic Hairy Cell Leukaemia

Peripheral blood film

A peripheral blood film is stained with Wright's stain and is carefully examined and a white blood cell differential count is done. Monocytopenia is a comparatively sensitive and distinct indication of classic hairy cell leukaemia. Leukaemic cells are rare. Hairy cells are medium in size with fairly abundant pale blue cytoplasm, kidney shaped nuclei, open chromatin, no nucleoli, and a unique serrated cytoplasmic border [8].

Bone marrow aspirate and trephine biopsy

Bone marrow aspirate is difficult to obtain because of fibrosis caused by the hairy cell infiltrate. It is important to obtain enough specimen because the bone marrow trephine biopsy often shows patchy infiltration. The hairy cell infiltrate is characterized by scattered lymphoid cells. The pattern of the bone marrow involvement is interstitial and diffuse which gives a "honeycomb" appearance. There is "blood lake" pseudo-sinus formation with extravasation of red cells into involved sites. Reticulin fibrosis may be seen but there is no deposition of collagen [9].

There are cases of classic hairy cell leukaemia where the bone marrow is hypocellular. The loss of haematopoeitic cells (especially granulocytes) can result in an incorrect diagnosis of aplastic anaemia. This is resolved by demonstrating the abnormal B cell infiltrate with immunohistochemical stains. This is because the hairy cell infiltrate in these cases may be difficult to demonstrate with routine stains [1]. Immunohistochemical stains for CD20, annexin A1, tartrate-resistant acid phosphatase (TRAP), DBA.44 and VE1 (a stain for BRAF V600E) are used to ascertain the degree of bone marrow involvement [8,10]. Hairy cell leukaemia cells stain positive for annexin A1. Annexin A1expresses high specificity for hairy cell leukaemia thus it is valuable for correct diagnosis [11].

Immunophenotyping by flow cytometry

Flow cytometry is performed on bone marrow aspirates/ peripheral blood samples collected in ethylenediaminetetra-acetic acid tubes. The immunophenotypic profile of the HCL cells is very important for confirming the diagnosis. When the mononuclear cells of the peripheral blood are characterised by immunophenotyping, immunoglobin light chain restriction of either kappa or lamda-expressing populations of Bcells are seen. The diagnostic features of classic hairy cell leukaemia cells are confirmed by bright expression/positivity of CD19, CD20, CD22, CD25, CD103, CD123,CD11c [11-13]. The neoplastic HCL cells stain negatively for CD27 antigen but are intensely stained for CD 200 [8].

Molecular diagnosis of hairy cell leukaemia using BRAF V600E mutation

The BRAF V600E mutation was identified in 2011 using whole-exome sequencing (WES) as the underlying genetic occurrence in the pathogenesis of hairy cell leukaemia [3]. The BRAF V600E is not always essential in the diagnosis of hairy cell leukaemia. It is however very essential when diagnosis is uncertain and early identification of BRAF V600E helps in more accurate monitoring when therapies that will eradicate the disease are administered [14].

Different techniques are used for detection of BRAF V600E mutation [14]. Highly sensitive techniques must be used to prevent false negative results. These include allele-specific polymerase chain reaction [15] and next generation sequencing, which may eventually become the technique of choice [16]. The less sensitive methods include Sanger sequencing, pyrosequencing and melting curve analysis. Addition of immunonological stains like VE1 to the bone marrow biopsy can help in the detection of BRAF V600E in the absence of adequate leukaemic cells or of highly sensitive molecular methods for genetic profiling [17,18].

Therapy for Classic Hairy Cell Leukaemia

In about 10% of asymptomatic hairy cell leukaemia patients, it is essential to adopt the watch- and- wait strategy [19]. Most of the agents used for treatment of hairy cell leukaemia are really efficacious but they are immunosuppressive. After therapy with a purine nucleoside analogue, there is additional decrease in neutrophils before recovery. It is therefore advisable to start therapy before the haematological parameters have decreased to a dangerous level or before a patient has an active infection [8].

First-line therapy for hairy cell leukemia

The indications for treatment of patients with hairy cell leukaemia include symptoms of the disease or decreasing haematological parameters. These haematological parameters include at least one of the following: haemoglobin < 11g/dl, platelet count < 100g/l and absolute neutrophil count < 1g/l. Symptomatic splenomegaly may also be an indication for therapy [20]. Other indications for treatment include recurrent infections and systemic symptoms. These parameters not only serve as an indication for therapy, they denote that bone marrow is compromised and requires therapy. Only 10% of newly diagnosed patients with hairy cell leukaemia do not have any indication to start therapy [8].

The standard first-line therapy for classic hairy cell

leukaemia is purine nucleoside analogues (PNA) either pentostatin or cladribine when used in monotherapy. Both drugs confer in most cases a long overall survival rate [21]. Treatment with PNA should not commence immediately on patients with renal impairment or active infection. The infection must be controlled first before administering PNAs [8]. Preliminary data advocate that administering rituximab at the same time with cladribine can lengthen complete remission [22]. Few asymptomatic patients whose blood counts are well conserved may not need to be treated immediately [9].

Cladribine and pentostatin impede deoxyribonucleic acid synthesis in resting and rapidly growing cells, obstructing their metabolism and causing apoptosis. In addition, both drugs exhibit a potent myelosuppressive effect and induce extended immunosuppression. To date, no randomized study directly comparing the potency of cladribine and pentostatin has been carried out. Nevertheless, both drugs appear to be equally effective [23]. Furthermore, cladribine can be administered as a second-line therapy in patients who exhibit initial resistance to pentostatin. In reality, cladribine is administered more frequently mostly because of easier dosing and reduced drug toxicity, particularly nephrotoxicity [24].

Splenectomy has been largely replaced by purine analogue (PA) therapy since PA therapy effectively reduces the size of the spleen. Interferon is poorly tolerated and less efficacious than PAs hence it is rarely used except in patients with serious infection and pancytopenia [9].

One of the difficulties encountered in the treatment of hairy cell leukaemia is symptomatic disease and febrile infection. The infection must be controlled first before commencing therapy with PNA. If controlling the infection is difficult, interferon-alpha can be administered briefly. Interferon-alpha can also be another option for pregnant women [20]. Vemurafenib has recently been discovered to have the ability to elevate peripheral blood counts and thus improve the control of infection. This discovery is very promising and needs to be substantiated in clinical trials for those patients with active infection [25].

Second-line therapy for classic hairy cell leukaemia

Published data show that about half of the patients relapse within the first five years after first line therapy despite the long-lasting remissions attained. Patients who are less than 40 years may have shorter remissions than those above 40 years. Patients who relapse after first-line treatment with purine nucleoside analogues are more challenging to treat. They are more prone to significant and impaired reduced overall survival [26,27].

The type of therapy administered depends on the period of first remission. For remissions greater than five years, chemotherapy with cladribine or pentostatin is efficient as a second-linetherapy [19,27]. Chemoimmunotherapy with cladribine or pentostatin combined with rituximab can be used for remissions between two and five years [27-29]. If the remission is less than two years, the hairy cell diagnosis must be confirmed by checking for BRAF V600E mutation and the risk factors assessed. The patients should be regarded as relapsed or refractory hairy cell leukaemia patients. A combination of bendamustine and rituximab has showed encouraging results in patients with relapsed HCL [30-32].

Novel drugs for therapy in relapsed or refractory classic hairy cell leukaemia

Hairy cell leukaemia is a rare disease. It is therefore vital for patients with relapsed or refractory HCL to be tested in clinical trials as some of them may benefit from new drugs [9]. In recent years, the efficacy of various novel drugs has been tested in patients with classic hairy cell leukaemia. These include moxetumobab pasudotox targeting the CD22 antigen, BRAF kinase inhibitors (vemurafemib and dabrafemib) and the Bruton kinase inhibitor, ibrutinib [23]. Studies on these drugs focused on patients who are refractory to purine nucleoside analogues [4].

Moxetumomab pasudotox is an immunotoxin. Immunotoxins are formed by the merging of a bacterial toxin with the variable region of a monoclonal antibody that is aimed at a specific cell surface target like CD22 in hairy cell leukaemia. Immunotoxins are a novel therapeutic option now accessible to HCL patients, with or without BRAF V600E. Clinical trials with anti-CD22 immunotoxins are in progress as hairy cell leukaemia cells demonstrate CD22 and CD25 at a high density. The initial results obtained with moxetumomab pasudotox in a phase I clinical trial in relapsed HCL patients are encouraging [20]. The clinical trial was conducted in two stages. In first stage, 86% of the patients responded to treatment with complete remission of 46%. In the second stage, 88% of the patients responded to treatment with 64% achieving complete response. The therapy was well tolerated with no dose-limiting toxicity. The overall adverse drug reactions included moderate haemolytic uremic syndrome, development of drug- inducing antibodies, peripheral oedema, nausea, infusion-related reactions, hypoalbunaemia and increased transaminases [4,10].

The results derived from phase I clinical trials were corroborated by a phase III clinical trial in 80 patients with refractory and relapsed hairy cell leukaemia [33]. Some of the patients that partook in the study had received at least two lines of treatment, including one with purine analogue. Haematological remission was obtained in 80% of the patients and complete response

of 41%. The adverse drug reactions which were similar to those observed in phase I study, disappeared when the treatment was stopped [34].

Moxetumomab pasudotox was endorsed by the Food and Drug Administration (FDA) in 2018 as therapy for relapsed and refractory hairy cell leukaemia. The patient must have received two or more systemic treatments, including one with a purine nucleoside analogue [33]. It is given intravenously after the patient has been hydrated and administered with anti-allergic drugs. The FDA also approves of retreatment with moxetumomab pasudotox within 3-12 years after completing the first treatment [4]. Combined therapy of moxetumomab pasudotox and rituximab is still in the first phase of clinical trial [35].

BRAF kinase inhibitors

Identification of BRAF V600E mutation and the fundamentally active BRAF-MEK-ERK pathway in hairy cell leukemia cells formed the scientific basis for the use of BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib) for treatment in patients with relapsed or refractory hairy cell leukaemia [3]. The BRAF mutation results in constitutive activation of the MAP kinase pathway and regulates the survival of the leukaemic cells. The BRAF kinase inhibitors, vemurafenib and dabrafemib were used for the first time in 2014 to treat patients with refractory and recurrent hairy cell leukaemia [36]. In addition, the BRAF inhibitors were used in patients with contraindications to purine analogues, agranulocytosis and active infections [37].

Data imply that using BRAF or MEK inhibitors to block the RAF-MAPK/ERK kinase (MEK) pathway results in loss of HCL-specific gene expression profile characteristic, reverses the morphology of the cell from “hairy” to “smooth”, and triggers apoptosis [38,39]. The BRAF kinase inhibitors have proved to be efficacious in the therapy of classic HCL. The problems associated with their use are that only some patients reach complete remission and the average time from discontinuation of vemurafenib to relapse is just 14 months [40,41].

Vemurafenib was initially approved for malignant melanoma therapy [4]. It was tested in relapsed or refractory BRAF positive HCL patients in a phase II clinical trial conducted in Italy and United States of America (USA). The overall response rates were 96% and 100% and complete response rates were 35% and 42% respectively after 8 and 12 weeks. Vemurafenib is generally well tolerated with reversible side effects and no myelotoxicity [40].

Twenty seven patients treated with BRAF inhibitors, vemurafenib and dabrafenib outside clinical trials all achieved complete haematological response. The final response of the patients did not depend on the dose, duration of treatment or number of previous lines. Vemurafenib increases platetelet counts > 100 g/l after two weeks, neutrophils > 1.5 g/l after four weeks, and haemoglobin level > after eight weeks [41]. The best response is obtained when highest, well-tolerated doses of BRAF inhibitors (vemurafenib and dabrafenib) are administered to patients than lower doses [4].

Combination of BRAF inhibitors with rituximab increases their efficacy. This combination was administered to thirty patients enlisted in a study. The patients had refractory or recurrent hairy cell leukaemia. Ten of them were resistant to chemotherapy, five were resistant rituximab and seven patients were resistant to BRAF inhibitors. Twenty six (87%) of the patients achieved complete remission [4,42]. Combination of vemurafenib and rituximab is effective in treating patients with relapsed and refractory HCL including those previously treated with moxetumomab pasudotox [43]. Toxicity is mainly grade 1-2 and similar to when either drug is used alone. There is no myelotoxicity in this combination [9].

Vemurafenib can be administered in combination with a MEK inhibitor, cobimetinib to patients who are resistant to BRAF inhibitors [44]. Relapsed patients may be effectively retreated with vemurafenib [40]. Nevertheless, the period of response after repeated therapy is shorter than after the initial therapy [4]. There is rapid improvement in haematological parameters after repeated therapy in most patients [41].

Dabrafenib is an oral BRAF inhibitor [4]. In a study involving 10 patients, two of which were initially treated with vemurafenib. Dabrafenib was observed to be very effective. The response rate was 80%. Platelet count was elevated after 15 days, neutrophils after 35 days and haemoglobin after 51 days. The common side effects were joint pain, flushing of the face, skin changes, elevated levels of transaminases and pancreatic enzymes [40]. Combination of dabrafenib, a strong and selective BRAF inhibitor, and trametinib, a MEK inhibitor is currently being assessed in clinical trial in relapsed/refractory hairy cell leukaemia. This combination of a BRAF and a MEK inhibitor forms a double vertical inhibition within the MAPK pathway [20].

Ibrutinib is the B cell receptor pathway-associated Bruton’s tyrosine kinase inhibitor. It impedes survival and multiplication of hairy cells *in vitro* [45]. B cell receptor signalling is effective in hairy cell leukaemia [46]. In a multi-centre phase II study, ibrutinib was administered to HCL patients. Twenty eight of them were newly diagnosed or had relapsed. Nine patients had HCL variant [44]. The response rate was 24% after 32 weeks and 36% after 48 weeks. The results show that ibrutinib is effective for the treatment of relapsed hairy cell leukaemia despite its adverse effects especially after several therapy lines. However, longer treatments will be required to get the best response. Drug toxicity associated with the dose has not been reported [9].

Conclusion

Hairy cell leukaemia is an incurable disease. The discovery of BRAF V600E in almost all patients with classic HCL brought a breakthrough in both diagnosis and treatment of classic HCL. Purine analogues induce durable complete remissions in many of the patients. However, about 50% of the patients relapse after a few years. This elicited investigation of new drugs during clinical trials for patients who are refractory to first-line therapy or who relapse after treatment with purine analogues.

The novel agents include moxetumomab pasudotox which was approved by the FDA in 2018 for the treatment of HCL, vemurafenib, dabrafenib and ibrutinib. They are highly effective in clinical trials. However, they are associated with adverse drug reactions, some of which were solved by dose reduction. Vemurafenib is very effective in controlling infection and needs further research during clinical trials.

Despite the success achieved with the novel reagents, further research in clinical trials is required to establish duration and dose of treatment especially in relapsed or refractory patients. Since HCL has no cure till date, more drugs should be investigated either in mono-therapy or in combination to find a cure for HCL. Stem cell transplant could also be a cure for HCL.

Sources of Funding

None

Conflict of Interests

The authors have none to declare.

References

1. Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri SA, et al. (2017) WHO Classification of tumours of haematopoietic and lymphoid tissues. (4th edn), International agency for research on cancer, Lyon.
2. Grever MR, Blachly JS, Andritsos LA (2014) Hairy cell leukaemia: Update on molecular profiling and therapeutic advances. Blood Rev 28: 197-203.
3. Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, et al. (2011) BRAF mutations in hairy cell leukaemia. New England J Med 364: 2305-2315.
4. Janowska A, Janus A, Robak T (2021) New therapeutic options for hairy cell leukaemia. Acta Haematol Polonica.
5. Tadmor E, Polliack A (2015) Hairy cell leukaemia: Uncommon clinical features, unusual sites of involvement and some rare associations. Best Practice Res Clin Haematol 28: 193-199.
6. Else M, Dearden CE, Matutes E, Garcia-Talavera J, Rohatiner AZ, et al. (2009) 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 145: 733-740.
7. Dinmohamed AG, Posthuma EFM, Visser O, Kater AP, Raymakers RAP, et al. (2018) Relative survival reaches a plateau in hairy cell leukaemia: A population- based analysis in the Netherlands. Blood 131: 1380-1383.
8. Grever MR, Abdel - Wahab O, Andritsos LA, Banerji V, Barrientos J, et al. (2017) Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukaemia. Blood 129: 553-560.
9. Parry- Jones N, Joshi A, Forconi F, Dearden, et al. (2020) Guideline for the diagnosis and management of hairy cell leukaemia (HCL) and hairy cell variant (HCL-V). Br J Haematol 191: 730-737.
10. Kreitman RJ, Tallman MS, Robak T, Coutre S, Wilson WH, et al. (2018) Minimal residual hairy cell leukaemia eradication with moxetumomab: Phase 1 results and long-term follow-up. Blood 131: 2331-2334.
11. Xi L, Arons E, Navarro W, Calvo KR, Stetler-Stevenson M, et al. (2012) Both variant and IGHV4-34-expressing hairy cell leukaemia lack the BRAF V600E mutation. Blood 119: 3330-3332.
12. Gupta R, Sanjeev Y, Mittal N, Rahman K, Sharma A, et al. (2020) Clinicopathological spectrum of hairy cell leukaemia: A single- centre study with brief review of Indian literature. J Can Res Thera 16: 120-126.
13. Venkataraman G, Aguhar C, Kreitman RJ, Yuan CM, Stetler- Stevenson M (2011) Characteristic CD103 and CD123 expression pattern defines hairy cell leukaemia: Usefulness of CD 123 and CD 103 in the diagnosis of mature B-cell lymphoproliferative disorders. Am J Clin Pathol 136: 625-630.
14. Tiacci E, Pettirossi V, Schiavoni G, Falini B (2017) Genomics of hairy cell leukaemia. J Clin Oncol 35: 1002-1010.
15. Tiacci E, Schiavoni G, Forconi F, Santi A, Tentin L, et al. (2012) Simple genetic diagnosis of hairy cell leukaemia by sensitive detection of the BRAFV600E mutation. Blood 119: 192-195.
16. Cardus B, Colling R, Hamblin A, Soilleux E (2019) Comparison of methodologies for the detection of BRAF mutations in bone marrow trephine specimens. J Clin Pathol 72: 406-411.
17. Uppal G, Ly V, Wang ZX, Bajaj R, Solomides CC, et al. (2015) The utility of BRAF V600E mutation- specific antibody VE1 for the diagnosis of hairy cell leukaemia. Am J Clin Pathol 143:120-125.
18. Andrulis M, Penzel R, Weichert W, von Deimling A, Capper D (2012) Application of a BRAF V600E mutation- specific antibody for the diagnosis of hairy cell leukaemia. Am J Surg Pathol 36: 1796-1800.
19. Cornet E, Tomowiak C, Tanguy-Schmidt A, Lepretre S, Dupuis J, et al. (2014) Long- term follow- up and second malignancies in 487 patients with hairy cell leukaemia. Br J Haematol 166: 390-400.
20. Maitre E, Cornet E, Troussard X (2019) Hairy cell leukemia. 2020 update on diagnosis, risk stratification, and treatment. Am J Haematol 94: 1413- 1422.
21. Divino V, Karve S, Gaughan A, DeKoven M, Gao G, et al. (2017) Characteristics and treatment patterns among US patients with hairy cell leukemia: A retrospective claims analysis. J Comp Eff Res 6: 497-508.
22. Chihara D, Arons E, Stetler-Stevenson M, Yuan C, Zhou H, et al. (2019) Randomized phase II study of cladribine with simultaneous or delayed rituximab in patients with untreated hairy cell leukaemia. J Clin Oncol 37: 7003.
23. Pula A, Robak T (2021) Hairy cell leukaemia: A brief update on current knowledge and treatment prospects. Curr Opin Oncol 33: 412-419.

24. Falini B, Tiacci E (2019) New treatment options in hairy cell leukaemia with focus on BRAF inhibitors. Hematol Oncol 37: 30-37.

25. Dietrich S, Zenz T (2015) BRAF inhibitor therapy in HCL. Best Pract Res Clin Haematol 28: 246-252.

26. Rosenberg JD, Burian C, Waalen J, Saven A (2014) Clinical characteristics and long-term outcome of young hairy cell leukemia patients treated with cladribine: A single-institution series. Blood 123: 177-183.

27. Else M, Dearden CE, Catovsky D (2015) Long- term follow-up after purine analogue therapy in hairy cell leukaemia. Best Pract Res Clin Haematol 28: 217-229.

28. Chihara D, Kantarjian H, O'Brien S, Jorgensen J, Pierce S, et al. (2016) Long- term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: Update on a phase II trial. Br J Haematol 174: 760-766.

29. Else M, Dearden CE, Matutes E, Forconi F, Lauria F, et al. (2011) Rituximab with pentostatin or cladribine: an effective combination treatment for hairy cell leukaemia after disease recurrence. Leuk Lymphoma 52: 75-78.

30. Cornet E, Delmer A, Feugier P, Garnache-Ottou F, Ghez D, et al. (2014) Recommendations of the SFH (French Society of Haematology) for the diagnosis, treatment and follow-up of hairy cell leukaemia. Ann Haematol 93: 1977-1983.

31. Sadeghi N, Li HC (2018) MRD- negative complete remission in relapsed refractory hairy cell leukaemia with bendamustine and obinutuzumab. Ann Haematol 97: 723-724.

32. Burotto M, Stetler-Stevenson M, Arons E, Zhou H, Wilson W, et al. (2013) Bendamustine and rituximab in relapsed and refractory hairy cell leukaemia. Clin Cancer Res 19: 6313-6321.

33. JanusA, Robak T (2019) Moxetumomab pasudotox for the treatment of hairy cell leukaemia. Expert Opin Biol Ther 19: 501-508.

34. Kreitman RJ, Dearden C, Zinzani PL, Delgado J, Robak T, et al. On behalf of the Study 1053 investigators (2021) Moxetumomab pasudotox in heavily pre-treated patients with relapsed/refractory hairy cell leukaemia (HCL): long-term follow-up from the pivotal trial. J Hematol Oncol 14: 35.

35. Siddiqui R, Sardar M, Shahzad M, Jose J, Selene I, et al. (2021) Management of relapsed hairy cell leukaemia: a systematic review of novel agents and targeted therapies. Clin Lymph Myeloma Leuk 21: 659-666.

36. Andritsos LA, Grever MR (2015) Historical overview of hairy cell leukemia. Best Prac Res Clin Haematol 28: 166-174.

37. Robak T, Matutes E, Catovsky D, Zinzani L, Buske C, ESMO Guidelines Committee (2015) Hairy cell leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 26: 100-107.

38. Rolder T, Falini B, Dietrich S (2018) Recent advances in understanding and managing hairy cell leukaemia. F1000Res.

39. Pettirossi, V, Santi A, Imperi E, Russo G, Pucciarini A, et al. (2015) BRAF inhibitors reverse the unique molecular signature and phenotype of hairy cell leukaemia and exert potent antileukaemic activity. Blood 125: 1207-1216.

40. Tiacci E, Park JH, De Carolis I, Chung SS, Broccolli A, et al. (2015) Targeting mutant BRAF in relapsed or refractory hairy cell leukaemia. New Engl J Med 373: 1733- 1747.

41. Liebers N, Roider T, Bohn JP, Haberbosch I, Pircher A, et al. (2020) BRAF inhibitor treatment in classic hairy cell leukaemia; a long- term follow-up study of patients treated outside clinical trials. Leukaemia 34: 1454-1457.

42. Tiacci E, De Carolis L, Simonetti E, Capponi M, Ambrosetti A, et al. (2021) Vemurefenib plus rituximab in refractoryor relapsed hairy cell leukaemia. N Eng J Med 384: 1810-1823.

43. Robak T, Janus A, Jamroziak K, Tiacci E, Kreitman RJ (2021) Vemurafenib and rituximab in patients with hairy cell leukaemia previously treated with moxetumomab pasudotox. J Clin Med 10: 2800.

44. Caeser R, Collord G, Yao WQ, Chen Z, Vassilou GS, et al. (2019) Targeting MEK in vemurafenib- resistant hairy cell leukaemia. Leukaemia 33: 541-545.

45. Sivina M, Kreitman RJ, Arons E, Ravandi F, Burger JA (2014) The bruton tyrosine kinase inhibitor ibrunitib (PCI-32765) blocks hairy cell leukaemia survival, proliferation and B cell receptor signalling: a new therapeutic approach. Br J Haematol 166: 177-188.

46. Weston-Bell NJ, Forconi F, Kluin - Nelemans HC, Sahota SS (2014) Variant B cell receptor isotype functions differ in hairy cell leukaemia with mutated BRAF and IGHV genes. PLoS One 9: e86556.