Received: 18 November 2023 | Revised: 3 March 2024 | Accepted: 3 May 2024

DOI: 10.1002/hon.3280

ORIGINAL ARTICLE

WILEY

Real-world data on diagnostics, treatment and outcomes of patients with hairy cell leukemia: The HCL-CLLEAR study

Anna Panovská[1] | Pavel Žák[2] | Tereza Jurková[3] | Tomáš Arpáš[1] | Yvona Brychtová[1] | Alžběta Vašíková[1] | Viera Hrabčáková[1] | Adéla Prchlíková[1] | Martina Filipová[1] | Michael Doubek[1,4]

[1]Department of Internal Medicine—Hematology and Oncology, University Hospital and Masaryk University, Brno, Czech Republic

[2]4th Department of Internal Medicine—Hematology, University Hospital and Charles University Faculty of Medicine, Hradec Králové, Czech Republic

[3]Institute of Biostatistics and Analyses, Ltd., Brno, Czech Republic

[4]Central European Institute of Technology, Masaryk University, Brno, Czech Republic

Correspondence
Michael Doubek, Department of Internal Medicine—Hematology and Oncology, University Hospital and Masaryk University, Jihlavská 20, 62500 Brno, Czech Republic.
Email: doubek.michael@fnbrno.cz

Pavel Žák, 4th Department of Internal Medicine—Hematology, University Hospital and Charles University Faculty of Medicine, Hradec Králové, Czech Republic.
Email: Zak@lfhk.cuni.cz

Funding information
EARTRIS-CZ; National Institute for Cancer Research (Program EXCELES), Grant/Award Number: LX22NPO5102; Czech CLL Study Group

Abstract

Hairy cell leukemia (HCL) and HCL-like disorders have to be distinguished because of their different biology and treatment response. Thus, we conducted a retrospective study on patients with HCL and hairy cell leukemia variant (HCLv) to assess diagnostic algorithms and treatment outcomes in a real-world setting. We analyzed 225 HCL and 26 HCLv patients with median follow-up of 67.9 months (HCL) and 20.1 months (HCLv). Median age at diagnosis was 56.2 (HCL) and 69.5 years (HCLv), male predominance was observed in both groups (76.0% vs. 73.1%). Diagnostics was mostly based on morphological evidence of hairy cells in the peripheral blood and bone marrow. At diagnosis, *BRAF V600E* mutation was detected in 94.7% of examined HCL patients and in no HCLv patient. Front-line treatment was indicated in 205 (91.1%) HCL and 18 (69.2%) HCLv patients. The majority of HCL patients were administered a cladribine-based regimen (91.2%). Overall response rate (ORR) was higher in cladribine-treated patients compared to those given other treatments (97.7% vs. 81.3%), the same applied with achieving Complete remission (CR) (91.2% vs. 62.5%). HCLv treatment was heterogeneous, but cladribine remained the most frequent option (44.4%) with ORR 81.3% and CR rates 43.8%. Second-line treatment was indicated in 52 HCL and 8 HCLv patients, 25.4% and 44.4% of those treated in first-line. In the whole HCL group, median time to next treatment (TTNT) was not reached and 10-year TTNT was estimated at 74.1%. HCLv patients who underwent first-line treatment had a median TTNT of 56 months. The median overall survival (OS) in HCL patients was not reached compared to HCLv with a median OS of 9.5 years. These data confirm an excellent prognosis for HCL patients treated with cladribine-based therapy. On the contrary, HCLv with its aggressive

behavior represents a group of patients in whom novel treatment approaches are needed.

KEYWORDS
*BRAF V600E*mutation, cladribine, hairy cell leukemia, hairy cell leukemia variant, overall survival, time to next treatment

1 | INTRODUCTION

Hairy cell leukemia (HCL) is a rare indolent B-cell lymphoproliferative disorder composed of characteristic hairy cells that usually involve the bone marrow (BM), peripheral blood (PB), and spleen. Its molecular pathology is associated with *BRAF V600*E somatic mutation, which tumorous cells bear in more than 95% of cases. The World Health Organization (WHO) has recognized HCL as an entity since 2008.[1] HCL appears more frequently in men than women (4:1) and accounts for approximately 2% of all leukemias. The worldwide incidence rate is 0.3–0.4/100,000 and it remains relatively stable over time.[2–4] The median age at diagnosis varies between 62 (in men) and 65 years (in women) and it rarely occurs in patients under the age of 30. At diagnosis, HCL is usually characterized by infections, splenomegaly, and a presence of cytopenias.[3,4]

Hairy cell leukemia (also known as classic HCL) has to be distinguished from other HCL-like disorders including splenic B-cell lymphoma/leukemia with prominent nucleoli, splenic diffuse red pulp small B-cell lymphoma and splenic marginal zone lymphoma which have a different pathobiology, clinical course and response to treatment. In the last (fifth) edition of WHO classification, the term hairy cell leukemia variant (HCLv) was replaced by splenic B-cell lymphoma/leukemia with prominent nucleoli which also covers CD5-negative B prolymphocytic leukemia from the fourth edition of WHO classification.[5,6] On the contrary, the International Consensus Classification for Mature Lymphoid Neoplasms published in 2022, still works with the term HCLv.[7] Diagnosis of HCL is based on morphologic evidence of hairy cells, typical HCL immunophenotype regarding CD11c, CD103, CD123 and CD25 expression and the presence of *BRAF V600*E somatic mutation.

The introduction of the purine nucleoside analogs (PNAs) pentostatin and cladribine significantly improved the outcome for HCL patients. These drugs demonstrate high Complete remission (CR) rates 80%–90% and 10-year overall survival (OS) rates of approximately 90%.[8–11] Some HCL patients still relapse and available published data support rechallenging with PNAs in the second line.[8,11] However, real-world data on the diagnostic processes, treatment selections and outcomes of these patients are limited.

Thus, we conducted a retrospective analysis of patients with classic HCL and HCLv to compare patients' profiles, diagnostic algorithms and treatment outcomes in a real-world setting.

2 | MATERIALS AND METHODS

2.1 | Patients and data collection

This study involves the secondary use of data from the registry database HCL-CLLEAR which gathers epidemiological and clinical data on diagnostics and treatment practices in HCL in the Czech Republic. So far, two leading hematology centers (The Department of Internal Medicine—Hematology and Oncology in Brno and The Department of Internal Medicine—Hematology in Hradec Králové) regularly contribute to this HCL database so it contains detailed data on every HCL patient regarding baseline demographic characteristics, diagnostic procedures, treatment regimens and other data according to requirements. Data from all patients who were diagnosed with either classic HCL or HCLv were included in the analysis and these data were extracted from the HCL-CLLEAR registry on 9 September 2022. The HCL and HCLv diagnosis was established by assessment of PB and/or BM including flow cytometry, *BRAF V600*E mutation examination and immunohistochemistry, as per WHO criteria.[1,5,6] All patients included in the analysis signed an Informed Consent (IC). All procedures were performed according to the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki.

2.2 | Treatment and response evaluation

First-line treatment was defined as the initial therapy administered after diagnosis. Single agent therapies included cladribine (pentostatin is not available in the Czech Republic), interferon alfa (INFα) and rituximab. Splenectomy was also considered a single agent treatment modality if not associated with adjuvant drug administration. Combined treatment was defined as more than one drug given within a period of 6 months. Second or further-line treatment was defined as any additional therapeutic intervention (including splenectomy) administered more than 2 months after the first-line therapy. Cladribine was administered either as a continuous intravenous infusion 0.1 mg/kg/day for 7 days, or 0.14 mg/kg/day subcutaneously for 5 days. Rituximab was given as an intravenous infusion 375 mg/m^2 once a week, in a total of 4 doses. Interferon alfa dosage varied depending on the drug form used (pegylated or non-pegylated) and the period of

administration. Response to treatment was assessed using standard response criteria.[10,12] CR required the morphologic absence of hairy cells in PB and BM aspiration and/or biopsy specimens and normalization of any organomegaly and cytopenia. Unconfirmed CR (CRu) was assigned to patients who had normalization of their PB count; however, BM biopsy was not performed to confirm CR. Partial remission (PR) was defined as normalization of a PB count associated with at least 50% reduction of organomegaly and BM hairy cells and less than 5% circulating hairy cells. All other outcomes were considered non-responses (NR). Relapse was defined as any new worsening cytopenia related to the detection of hairy cells in the PB and/or BM.

Although immunophenotyping of PB or BM biopsy is not generally required, one of the two hematology centers performs it as a routine part of both diagnostics and treatment response assessment including minimal residual disease (MRD). Our eight-color flow cytometric panel for HCL MRD detection comprises anti-CD3, CD11c, CD19, CD20, CD25, CD27, CD45, CD48, CD103, CD123, CD200, CD305 and anti-ROR1 antibodies (manuscript in preparation). Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

2.3 | Statistical analysis

Continuous demographic and clinical characteristics of the patients (e.g., age) were reported through the median with 5th and 95th percentiles, together with the total number of non-missing observations. Categorical parameters (e.g., gender, Overall response rate [ORR], CR or MRD negativity) were reported using absolute and relative frequencies. Time to next treatment (TTNT) is defined as time from a treatment termination to the start of a subsequent treatment. In the calculation of TTNT, we considered occurrences of death as a competing risk and, accordingly, utilized the cumulative incidence approach. Overall survival (OS) is defined as the time from diagnosis or from the first-line treatment to death from any cause. OS was computed through the Kaplan–Meier method. Median TTNT and OS accompanied with a 95% confidence interval was estimated for each subgroup and then compared across different treatment regimens (cladribine-based vs. non-cladribine regimen). Statistical analyses were performed using IBM SPSS Statistics (version 25.0) and R software (version 3.6.3).

3 | RESULTS

3.1 | Patients' characteristics

A total of 251 patients were included in the analysis: 225 patients diagnosed with classic HCL and 26 patients with HCLv. All patients were diagnosed between 1973 and 2021. The summary of patients' characteristics is listed in Table 1.

TABLE 1 Baseline patients' characteristics.

	HCL (n = 225)	HCLv (n = 26)
Sex, *n* (%)		
Men	171 (76.0%)	19 (73.1%)
Women	54 (24.0%)	7 (26.9%)
Age at the diagnosis (years)		
Median (5th; 95th perc.)	56.2 (37.3; 76.3)	69.5 (50.7; 88.9)
B symptoms, *n* (%)		
Yes	42 (18.7%)	9 (34.6%)
ECOG at the diagnosis, *n* (%)		
n[a]	165	22
0–1	157 (95.2%)	22 (100.0%)
Creatinine level at the diagnosis, μmol/l		
n[a]	143	17
Median (5th; 95th perc.)	85.0 (59.0; 138.0)	89.0 (57.0; 195.0)
BRAF mutation testing, *n* (%)		
n[a]	56	10
Positive	53 (94.6%)	0 (0.0%)
Negative	3 (5.4%)	10 (100.0%)
Type of bone marrow collection, *n* (%)		
n[a]	141	14
Bone marrow aspiration	29 (20.6%)	3 (21.4%)
Bone marrow biopsy	112 (79.4%)	11 (78.6%)
Flow cytometry assessment, *n* (%)		
Yes	110 (48.9%)	16 (61.5%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCL, hairy cell leukemia; HCLv, hairy cell leukemia variant.

[a]number of patients with evaluable data.

The median age at diagnosis was lower in HCL patients (56.2 years, range 25–85) compared to HCLv (69.5 years, range 42–92). Male predominance was observed in both groups (76.0% vs. 73.1%). At diagnosis, the Eastern Cooperative Oncology Group (ECOG) status scale was evaluated in 165 HCL and 22 HCLv patients and most of them fulfilled the criteria for ECOG 0–1. B symptoms (night sweats, fever, weight loss and fatigue) were more frequent in HCLv patients (34.6% vs. 18.7%), which corresponds with the different biological behavior. Diagnosis of HCL and HCLv was mostly based on morphology assessment of hairy cells in the PB and BM. In the majority of patients a BM biopsy was performed (79.4% and 78.5%), while one fifth had only BM aspiration. The presence of *BRAF V600E* somatic mutation was assessed only in 56 HCL patients and 10 HCLv patients. Patients with classic HCL bore *BRAF V600E* mutation in 94.6% cases, whereas none of the patients in the HCLv group was positive. Flow cytometry assay of PB or BM aspirate was performed in 48.9% of HCL

patients and 61.5% of patients with HCLv at diagnosis. The median interval from diagnosis to first-line treatment initiation was approximately one month, with 5th and 95th percentile varying from 0.0 to 46.2 months in both groups - 1.1 month (0.0; 22.8) in HCL and 0.9 months (0.0; 46.2) in HCLv patients; only 8.9% of HCL patients never required treatment in contrast to 30.8% in the HCLv group. In both cohorts, the median of administered treatment lines was one (range 1–6 in HCL; 1–5 in HCLv).

3.2 | Treatment efficacy and safety

First-line treatment indications and types of regimen are summarized in Table 2. Median follow-up was 67.9 months (range 1.2–287.0) in the HCL cohort and 20.1 months (0.6–118.6) in the HCLv group. Two hundred and five patients with classic HCL and 18 patients with HCLv were indicated for the treatment initiation. The vast majority of HCL patients were administered a cladribine-based regimen (88.3% cladribine as a single agent and 2.9% cladribine in combination). Other drugs often used in first-line therapy were INFα (4.4%) and rituximab (1.5%), both as single agents. Splenectomy alone was indicated only in 2.4% of patients. Another 5.4% of HCL patients underwent a splenectomy after completing the first-line treatment. Treatment in the HCLv cohort was more heterogeneous. Cladribine as a single agent was administered in 44.4% of patients, rituximab in 27.8% and the other 27.8% patients were treated with various combinations including fludarabine, alkylating drugs and anthracyclines with or without rituximab.

The efficacy of the regimen was evaluated based on the best response to treatment (Table 3). For the purpose of our analysis, the HCL cohort was further divided into 2 subgroups - patients treated with a cladribine-based combination (170/187 evaluable pts.) and those treated with other types of regimen (16/18 evaluable pts.).

Second-line treatment was indicated in 52 HCL and 8 HCLv patients, 25.4% and 44.4% resp. of those treated in the first-line. Regarding HCL retreatment, 41 (78.8%) patients were retreated with a cladribine-based regimen, 9 (17.3%) patients were given rituximab as a single agent. Splenectomy as an adjuvant procedure was performed in 2 (3.8%) patients. Response rates were significantly higher in the cladribine-treated HCL subgroup (ORR 80.5%, CR/CRu 73.2%) in contrast to HCL patients treated with a non-cladribine regimen (ORR 45.5%, CR/CRu 27.3%).

In the HCLv cohort treatment was heterogeneous again. Two patients were given cladribine, 2 rituximab monotherapy, 3 patients other chemotherapy combinations and 1 patient underwent splenectomy alone. Overall response rate was 62.5%, and only 1 patient achieved CR/CRu. Subsequent lines of treatment were initiated on 18 HCL and 7 HCLv patients, 34.6% and 87.5% resp. of those who underwent the second-line. Three HCL patients were given vemurafenib as a single agent or in combination with rituximab in subsequent lines of therapy and all achieved CR/CRu. Vemurafenib has been authorized for use in the Czech Republic since 2013 (primarily in patients with metastatic melanoma) and

TABLE 2 First-line treatment—indications and types of regimen.

	HCL (n = 205)	HCLv (n = 18)
Indications for treatment, *n* (%)		
Neutrophils <1.0 × 10^9/l	61 (29.8%)	5 (27.8%)
Hemoglobin <110 g/L	82 (40.0%)	9 (50.0%)
Thrombocytes <100 × 10^9/l	135 (65.9%)	10 (55.6%)
B symptoms presence	28 (13.7%)	8 (44.4%)
Symptomatic organomegaly	88 (42.9%)	13 (72.2%)
Recurrent infections	5 (2.4%)	0 (0.0%)
Other autoimmune manifestation	1 (0.5%)	0 (0.0%)
Type of treatment, *n* (%)		
Cladribine monotherapy	181 (88.3%)	8 (44.4%)
Interferon alpha monotherapy	9 (4.4%)	0 (0.0%)
Rituximab monotherapy	3 (1.5%)	5 (27.8%)
Cladribine-based combination	6 (2.9%)	0 (0.0%)
Splenectomy alone	5 (2.4%)	0 (0.0%)
Other	1 (0.5%)	5 (27.8%)

Abbreviations: HCL, hairy cell leukemia; HCLv, hairy cell leukemia variant.

TABLE 3 First-line treatment—response assessment.

	HCL (n = 205)		
	Cladribine-based regimen (n = 187)	Non-cladribine regimen (n = 18)	HCLv (n = 18)
Treatment response assessed, *n* (%)			
n[a]	170	16	16
ORR	166 (97.6%)	13 (81.3%)	13 (81.3%)
CR/CRu	155 (91.2%)	10 (62.5%)	7 (43.8%)
PR	11 (6.5%)	3 (18.8%)	6 (37.5%)
NR	4 (2.4%)	3 (18.8%)	3 (18.8%)
Cladribine dose reductions, *n* (%)			
Yes	17 (9.1%)	---	---
MRD evaluated, *n* (%)			
n	55	6	---
Negative	31 (56.4%)	3 (50.0%)	---

Abbreviations: CRu, complete remisson without bone marrow assessment; HCL, hairy cell leukemia; HCLv, hairy cell leukemia variant; CR, complete remission; MRD, measurable residual disease assessed by flow cytometry assay; NR, non responders; PR, partial remission.
[a]number of patients with evaluable data.

could also be indicated in patients with *BRAF V600E* mutated relapsed/refractory HCL.

Measurable residual disease was evaluated in 61 HCL patients (29.8%), either with immunohistochemical (IHC) stains or flow cytometry assay of PB or BM aspirate. Undetectable MRD was achieved in 31 patients treated with a cladribine-based regimen (56.4% from 55 evaluated pts.) and 3 patients who were administered non-cladribine therapy (50.0% from 6 evaluated pts.).

Hematologic adverse events (AE; all CTCAE grades) were recorded in 108 (57.8%) HCL patients treated with a cladribine-based regimen, 2 (11.1%) HCL patients given non-cladribine treatment and in 6 (33.3%) HCLv patients. Non-hematologic AEs were described in 45 (24.1%) HCL cladribine-treated patients, 3 (16.7%) patients with a non-cladribine regimen and in 3 (16.7%) patients with HCLv. The most frequent non-hematologic AEs in all analyzed cohorts were infections. Grade ≥3 infections requiring hospitalization were observed in 43 (23.0%) cladribine-treated HCL patients, in 1 (16.7%) HCL patient administered a non-cladribine regimen and 5 (27.8%) HCLv patients.

3.3 | TTNT and OS outcomes

Time to next treatment analysis and OS outcomes for HCL and HCLv patients are shown in Figure 1. In the whole HCL cohort, median TTNT was not reached and 10-year TTNT was estimated at 74.1% (95% CI; 81.5%–66.6%). On the contrary, HCLv patients who underwent the first-line treatment had a median TTNT of 56 months. The median OS in the HCL group was not reached compared to HCLv patients with a median OS of 9.5 years.

Furthermore, TTNT and OS outcome data were analyzed separately for cladribine and non-cladribine treated HCL patients (Figure 2). Ten-year estimated TTNT was significantly higher in cladribine-treated patients - 74.9% (95% CI; 82.7%–67.1%) compared to the non-cladribine treated subgroup - 58.6% (95% CI; 85.6%–31.6%). The median OS was not reached in both subgroups, the cladribine-treated cohort had 10-year estimated OS 85.0% (95% CI; 91.0%–78.9%) versus 88.9% (95% CI; 100.0%–73.9%) in patients who were given non-cladribine therapy. Additionally, we compared relative survival probability in HCL patients and the general Czech population (Figure S1).

4 | DISCUSSION

Hairy cell leukemia and other HCL-like disorders are rare B-cell malignancies with a low global incidence and, given its indolent nature, long-term follow-up data are crucial to improving our knowledge on its impact on survival. Therefore, real-world data analyses play an important role in this field. We retrospectively analyzed 225 HCL patients and 26 HCLv patients who were diagnosed between 1973 and 2021. Patients' baseline characteristics such as male predominance, median age, and performance status were similar to other previously published real-world studies.[2,3,10,13]

Regarding diagnostics, the period when the diagnosis was established had a strong impact on the type of procedures performed. Morphology assessment of hairy cells in the PB and BM remains the mainstay of the HCL/HCLv diagnostics. In the majority of patients BM biopsy was performed (79.4% and 78.6%), while one fifth had only BM aspiration. The presence of *BRAF V600E* somatic mutation was assessed only in a minority of patients, which might be explained by the limited availability of testing in the early years of analysis (until 2012). Examined patients with HCL bore *BRAF V600E* mutation in 94.6% cases, whereas none of the patients in the HCLv group was positive which corresponds with previously published data.[2,14] Since then, *BRAF V600E* mutation testing has become widely available in the Czech Republic. Currently, every patient with a suspicion of HCL will be tested for *BRAF V600E* mutation not only for appropriate diagnostics, but also for further treatment options including *BRAF* inhibitors. Flow cytometry assay of PB and/or BM aspirate was performed in 48.9% of HCL patients and 61.5% of patients with HCLv at diagnosis. In recent years it has been indicated more often in routine clinical practice, including in attempts for MRD monitoring. Based on available data, assessment of MRD status at the time of achieving response in HCL patients can be an indicator of the depth of response and potentially a predictor of remission duration. On the other hand, it can be debated if in an indolent disorder such as HCL, with the availability of highly effective initial therapy, MRD monitoring is essential.[15] Potentially, it could be beneficial in HCL patients with CRu. In our dataset, MRD was assessed in less than one third of HCL patients so these results should be interpreted with caution, as it does not reflect MRD status in the entire study population.

Two hundred and five (91.1%) of HCL patients were indicated to first-line treatment. The vast majority of them (91.2%) were administered a cladribine-based regimen with ORR exceeding 97% and a high rate of CR/CRu (91.2%). In the non-cladribine HCL cohort, ORR reached 81.3% with significantly lower CR/CRu (62.5%). Bone marrow biopsy for CR confirmation was performed only in a minority of patients. A single-institution report with a long-term follow-up described no significant difference in progression-free survival and OS between CR and CRu patients.[8,16] Given these data, routine BM biopsy to confirm CR after front-line treatment does not appear to be necessary and likely can be omitted in most patients.

In the HCLv cohort, 18 (69.2%) of patients initiated front-line treatment. As there is no established consensus concerning the treatment of HCLv, it was more heterogeneous. The most frequent choice was cladribine (44.4%) followed by rituximab (27.8%). The ORR reached 81.3% with lower CR/CRu rates (43.8%) compared to the HCL group.

Currently, the first-line option relies on rituximab in combination with purine analogs or bendamustine.[17] Chihara et al. published promising data on rituximab in combination with cladribine in

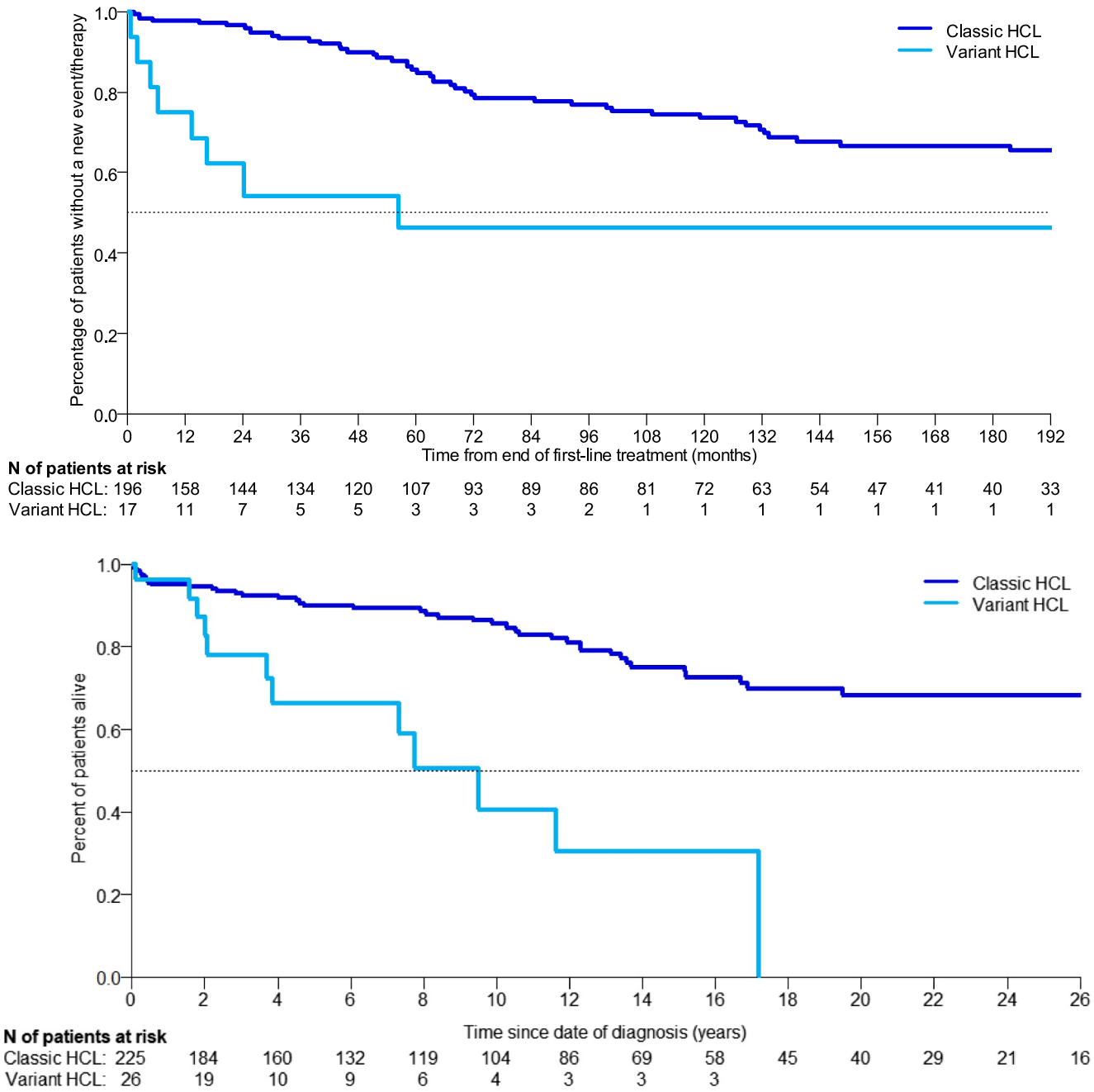

FIGURE 1 TTNT and OS in HCL and HCLv. HCL, hairy cell leukemia; HCLv, hairy cell leukemia variant; OS, overall survival; TTNT, time to next treatment.

treatment-naïve or relapsed HCLv patients (CR rates 95%). With a median follow-up of 69.7 months, the 5-year OS was 73.9%.[18] Recently published data also support ibrutinib as an alternative HCLv treatment either in the first-line or relapse.[19]

Regarding treatment safety, types of AEs and their incidence were comparable to previously published data.[8,9,11,13] As expected, hematologic AEs were most frequent in cladribine-treated HCL patients (57.8%). Infections represented the most common non-hematologic AE in all cohorts. Infections grade ≥3 were also the most frequent indication for hospitalization, except for drug administration itself.

Our study confirmed a favorable long-term prognosis of HCL. In the whole HCL cohort, 10-year TTNT was estimated at 74.1%. Cladribine-treated patients are expected to have longer TTNT compared to those treated with a non-cladribine regimen (10-year TTNT 74.9% vs. 58.6%). With a long-term follow-up, median OS was not reached in both HCL subgroups (cladribine and non-cladribine

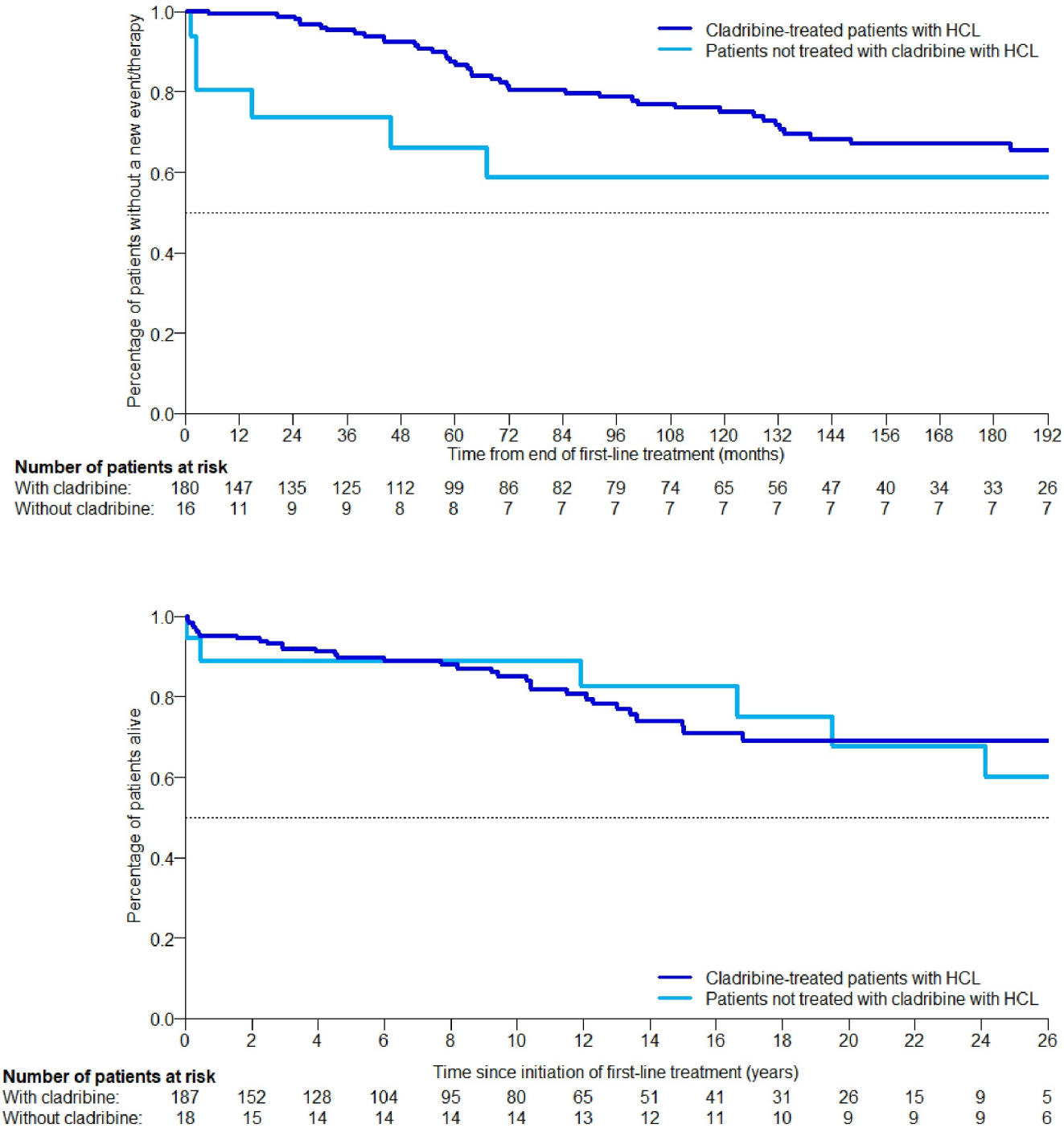

FIGURE 2 TTNT and OS in HCL—cladribine-based versus non-cladribine regimen. HCL, hairy cell leukemia; OS, overall survival; TTNT, time to next treatment.

treated), 10-year OS was estimated at 85.0% and 88.9%. Our results are in accordance with previously published data. In Else et al., a study comprising 233 patients with long-term follow-up, the 15-year OS was 78%.[10,20,21] German colleagues published 12-year follow-up data on 44 HCL patients treated with cladribine and estimated 12-year OS to be 79%.[13] On the contrary, in HCLv patients who underwent first-line treatment the median TTNT was 56 months and the median OS 9.5 years.

5 | CONCLUSION

Hairy cell leukemia was first described in 1958 and at that time median OS was only 4 years. The purine analogs, introduced in the 1980s, transformed this prognosis. Our data confirm an excellent prognosis for patients with classic HCL not only after first-line but also after cladribine readministration. Moreover, in recent years the combination of the *BRAF* inhibitor vemurafenib and rituximab has become

another highly effective treatment approach for those with relapsed/refractory HCL.[14,22] On the contrary, the OS observed in our HCLv cohort remains similar to data published by Matutes and colleagues in 2001.[21] With its aggressive behavior and recurrent relapses, HCLv represents a group of patients in whom novel treatment approaches are needed.

AUTHOR CONTRIBUTION

Michael Doubek, Pavel Žák, Anna Panovská designed the study; Michael Doubek, Pavel Žák, Anna Panovská, Adéla Prchlíková, Tomáš Arpáš, Yvona Brychtová, Martina Filipová, Alžběta Vašíková, Viera Hrabčáková collected data; Anna Panovská, Pavel Žák, and Michael Doubek wrote the manuscript; Tereza Jurková performed the statistical analyses.

ACKNOWLEDGMENTS

The study was supported by the Czech CLL Study Group; the Czech Leukemia Study Group—for Life; the National Institute for Cancer Research (Programme EXCELES, ID Project No. LX22NPO5102) - Funded by the European Union—Next Generation EU; and partially carried out with the support of research infrastructure EATRIS-CZ, ID number LM2023053, funded by MEYS CR.

Open access publishing facilitated by Fakultni nemocnice Brno, as part of the Wiley - CzechELib agreement.

CONFLICT OF INTEREST STATEMENT

All authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Pavel Žák https://orcid.org/0000-0003-4465-5343
Michael Doubek https://orcid.org/0000-0002-1269-6282

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/hon.3280.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. International Agency for Research on Cancer; 2008.
2. Troussard X, Maitre E, Cornet E. Hairy cell leukemia 2022: update on diagnosis, risk-stratification, and treatment. *Am J Hematol*. 2022;97(2):226-236. https://doi.org/10.1002/ajh.26390
3. Wörnmann B, Bohn JP, Dietrich S, et al. Hairy-cell leukemia [online]. In: *Onkopedia-guidelines DGHO*; 2022. [Cit. 2. 8. 2023]. Accessed September 20, 2023. https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/hairy-cell-leukemia/@@guideline/html/index.html
4. Robak T, Matutes E, Catovsky D, Zinzani P, Buske C. Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(S5):v100-v107. https://doi.org/10.1093/annonc/mdv200
5. Allagio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the world Health organization classification of the haematolymphoid tumours: lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720-1748. https://doi.org/10.1038/s41375-022-01620-2
6. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th Edition*. International Agency for Research on Cancer; 2017.
7. Campo E, Jaffe ES, Cook JR, et al. The international consensus classification of mature lymphoid Neoplasms: a report from the clinical advisory committee. *Blood*. 2022;140(11):1229-1253. https://doi.org/10.1182/blood.2022015851
8. Madanat YF, Rybicki L, Radivoyevitch T, et al. Long-term outcomes of hairy cell leukemia treated with purine analogs: a comparison with the general population. *Clin Lymphoma, Myeloma & Leukemia*. 2017;17(12):857-862. https://doi.org/10.1016/j.clml.2017.07.003
9. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. *Blood*. 1998;92(6):1918-1926. https://doi.org/10.1182/blood.v92.6.1918.418k33_1918_1926
10. Paillassa J, Cornet E, Noel S, et al. Analysis of a cohort of 279 patients with hairy-cell leukemia (HCL): 10 years of follow-up. *Blood Cancer J*. 2020;10(5):62. https://doi.org/10.1038/s41408-020-0328-z
11. Dearden CE, Else M, Catovsky D. Long-term results for pentostatin and cladribine treatment of hairy cell leukemia. *Leuk Lymphoma*. 2011;52(Suppl pl 2):21-24. https://doi.org/10.3109/10428194.2011.565093
12. Catovsky D, Quesada JR, Colomb HM, et al. Consensus resolution: proposed criteria for evaluation of response to treatment in hairy cell leukemia. *Leukemia*. 2003;1:405.
13. Jehn U, Bart L, Dietzfelbinger H, Haferlach T, Heinemann V. An update: 12-year follow up of patients with hairy cell leukemia following treatment with 2-chlorodeoxyadenosine. *Leukemia*. 2004;18(9):1476-1481. https://doi.org/10.1038/sj.leu.2403418
14. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med*. 2011;364(24):2305-2315. https://doi.org/10.1056/nejmoa1014209
15. Ravandi F, Kreitman RJ, Tiacci E, et al. Consensus opinion from an international group of experts on measurable residual disease in hairy cell leukemia. *Blood Cancer J*. 2022;12:165. https://doi.org/10.1038/s41408-022-00760-z
16. Rosenberg JD, Burian C, Waalen J, Saven A. Clinical characteristics and long-term outcome of young hairy cell leukemia patients treated with cladribine: a single-institution series. *Blood*. 2014;123(2):177-183. https://doi.org/10.1182/blood-2013-06-508754
17. Burotto M, Stetler-Stevenson M, Arons E, Zhou H, Wilson W, Kreitman RJ. Bendamustine and rituximab in relapsed and refractory hairy cell leukemia. *Clin Cancer Res*. 2013;19(22):6313-6322. https://doi.org/10.1158/1078-0432.ccr-13-1848
18. Chihara D, Arons E, Stetler-Stevenson M, et al. Long term follow-up of a phase II study of cladribine with rituximab with hairy cell leukemia. *Blood Adv*. 2021;5(23):4807-4816. https://doi.org/10.1182/bloodadvances.2021005039
19. Rogers KA, Andritsos LA, Wei L, et al. Phase II study of ibrutinib in classic and variant hairy cell leukemia. *Blood*. 2021;137(25):3473-3483. https://doi.org/10.1182/blood.2020009688
20. Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *Br J Haematol*. 2009;145(6):733-740. https://doi.org/10.1111/j.1365-2141.2009.07668.x
21. Matutes E, Wotherspoon A, Brito-Babapulle V, Catovsky D. The natural history and clinico-pathological features of the variant form of hairy cell leukemia. *Leukemia*. 2001;15(1):184-186. https://doi.org/10.1038/sj.leu.2401999

22. Tiacci E, Carolis LD, Simonetti E, et al. Vemurafenib plus rituximab in refractory or relapsed hairy cell leukemia. *N Engl J Med*. 2021;384(19):1810-1823. https://doi.org/10.1056/nejmoa2031298

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Panovská A, Žák P, Jurková T, et al. Real-world data on diagnostics, treatment and outcomes of patients with hairy cell leukemia: the HCL-CLLEAR study. *Hematol Oncol*. 2024;e3280. https://doi.org/10.1002/hon.3280