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Research paper

Outcomes and second neoplasms in hairy cell leukemia: A retrospective cohort

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ABSTRACT

Hairy cell leukemia (HCL) is a rare chronic B-cell lymphoproliferative disease which is treated on the basis of small studies, making the literature still scarce of reports, especially of those conducted in Latin America. Here we intend to describe clinical characteristics, rates of response, survival and second neoplasms in HCL patients treated in a reference center in Brazil. All patients diagnosed with HCL between July/1987 and Jun/2018 were included in this analysis. Fifty-four patients were included in this analysis. Median age at diagnosis was 55 years (range, 26–88), with 37% being above 60 years-old. Most patients were treated with cladribine in our cohort (n = 36; 68%), administered through intravenous continuous infusion. Remaining patients were firstly managed with splenectomy (n = 7; 13%), IFN (n = 6; 11%) and rituximab (n = 2; 4%). In a univariate analysis, platelet count and B2M level at diagnosis were statistically associated with CR achievement (p = 0.004 and p = 0.024, respectively). A median follow-up time of 9 years was calculated. Estimated 10-year overall survival was 91.1% (95% confidence interval, 77–97). In this cohort, 10 patients had any second neoplasm, diagnosed before or after HCL. Regarding the sites of cancer, 69% were of skin – 8/16 carcinoma-type and 3/16 melanoma-type. Our response and survival data are similar to those reported by literature, which reaffirms the role of purine analogs in current HCL management. With a very long follow-up we also have observed a high incidence of second neoplasm.

1. Introduction

Hairy cell leukemia (HCL) is a rare chronic B-cell lymphoproliferative disorder which usually presents with cytopenias and splenomegaly, with a predilection for males and white race [1,2]. Before the introduction of the purine nucleoside analogs (pentostatin and cladribine), HCL was treated mainly with splenectomy or alpha-interferon (IFN) [3]. The introduction of pentostatin and subsequently cladribine (2-CdA) in the 1980s and 1990s, respectively, has completely changed the HCL scenario, being those drugs considered current first-line therapies, achieving a complete response rate (CR) of 80–90% and a long-term survival of approximately 90% [4–6]. Due to the better control of disease and longer survival, other late complications such as relapse and second neoplasms have been described [7].

Given its rarity, HCL is treated on the basis of prospective reports conducted in Europe and United States, but literature is still scarce of reports from Latin America [7–11]. Differences in the incidence of the disease and patient's characteristics were already described in Mexico, where HCL seemed to be less frequent and irregularly distributed across the country [12]. Another multicenter study conducted in Israel also highlighted differences in the age of presentation among ethnic subgroups [13].

In this manuscript, we intend to describe clinical characteristics, rates of response, survival and second neoplasms in HCL patients treated in a reference center in Brazil.

2. Material and methods

2.1. Study design

This is a retrospective single-center study, conducted at Hospital das Clinicas, Faculty of Medicine, University of São Paulo (HCFMUSP), in

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Brazil. Clinical and laboratory data were obtained from the databases of Leukemia clinic of Discipline of Hematology.

2.2. Patients

All patients diagnosed with HCL between July/1987 and Jun/2018 in HCFMUSP were included in this analysis. HCL diagnosis was established based on WHO criteria, considering the presence of typical morphology lymphocytes in peripheral blood, associated with at least one of those tests: immunophenotype by flow cytometry (CD11c, CD20, CD25, CD103, CD123) or immunohistochemistry (DBA44, Annexin V and Cyclin D1 expression) of bone marrow (BM) trephine specimens [14]. BRAF mutation testing was not available at the time of diagnosis. Clinical variables were retrospectively collected through clinical chart review.

2.3. Treatment and response evaluation

All patients were treated following our local institutional protocol at the time when they were referred, ranging from splenectomy to intravenous continuous infusion for 7 days of cladribine (2-CdA), at 0.09 mg/kg/day, as previously published [5,15]. IFN was used in 3 million IU subcutaneous three times a week when indicated. Vemurafenib is not approved in our country for HCL and rituximab is not reimbursed by the public health system in Brazil for this disease, even though some patients may have received it by other means.

We assessed response through inspection of hematologic parameters, complete physical examination, including an evaluation of spleen size, and then a BM biopsy after 4 months of therapy in those patients who accepted to perform it at discretion of the physician [2]. Complete response (CR) was defined as disappearance of the characteristic hairy cells from the bone marrow, along with near normalization of peripheral blood counts – hemoglobin > 11 g/dL, neutrophil count > 1×10^9/L and platelet count > 100×10^9/L in peripheral blood. Minimal residual disease (MRD) was not systematically evaluated. Partial response (PR) was defined as an improvement in blood counts similar to CR and a decrease of 50% in spleen size and BM infiltration after therapy. Early death (ED) was defined as death within 30 days of diagnosis. Relapse was defined, in our cohort, as an indication for retreatment in a patient who had already achieved any level of response (partial or complete).

2.4. Statistical analysis

Categorical variables were summarized with frequencies and percentages, while continuous variables with a median value and range. Comparisons between groups were made using the Student's *t*-test or Mann-Whitney test for continuous variables and Pearson's chi-square or Fisher's exact test for categorical data, depending on their distribution. Survival duration was calculated from the date of diagnosis to death or the date of the last follow-up. Progression-free survival (PFS) and overall survival (OS) curves were plotted using the Kaplan-Meier method and differences were compared by a log-rank test. Cumulative incidence of relapse (CIR) was calculated using competing risks analysis [16]. Median follow-up time was estimated by reversing the codes for the censoring indicator in the Kaplan-Meier analysis. Univariate analysis was performed using the following variables: age, sex, splenomegaly, lactate dehydrogenase (LDH), beta-2-microglobulin (B2M), blood counts, albumin, first-line treatment and response. Multivariable analysis was not performed due to the low number of events. All analyses were done using Statistical Software for Social Sciences (v22.0, Chicago, IL), R-statistical package (v 3.5.1, http://www.r-project.org/) and GraphPad Prism (v8.0.2, San Diego, CA). All p-values are two-sided and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patients

Fifty-four patients were included in this analysis. Median age at diagnosis was 55 years (range, 26–88), with 37% being above 60 years-old. A male:female ratio of 17:1 was found and 93% presented classical HCL, whereas 4 patients had variant HCL (vHCL). Regarding comorbidities evaluation, systemic arterial hypertension was the most frequent (28%) and 17% of patients had any previous or current smoking.

At the time of diagnosis, 30% of subjects did not have a palpable spleen at physical examination. Blood counts had at least one cytopenia in all patients, being neutropenia the most frequent (89%). Monocytopenia was detected in 65% of patients and B2M was abnormal in 50% of available results. 43% of patients presented with infection at diagnosis, which was defined as febrile neutropenia or any need for antibiotic at this time.

BM biopsy was performed in 87% of patients, showing a diffuse infiltration pattern in 60%. Immunophenotyping was typical in all cases, with no remarkable findings, allowing distinction between classical and vHCL. Baseline characteristics of this cohort are detailed in Table 1.

3.2. Treatment and response outcomes

Most patients were treated with 2-CdA in our cohort (n = 36; 68%), administered through intravenous continuous infusion at the previously published dose [5]. Remaining patients were firstly managed with splenectomy (n = 7; 13%) and IFN (n = 6; 11%). Two patients were treated with rituximab in monotherapy (4%), both with vHCL diagnosis. Two (4%) patients remained in "watch and wait" approach, since they were asymptomatic at the time of diagnosis (Table 1). IFN was reserved for those patients considered unable to receive 2-CdA due to advanced age or poor performance status. IFN was used in 2 patients (one with severe neutropenia and systemic infection, and another with religious belief against blood transfusion) [17]. In both cases, after hematologic recovery, 2-CdA was started. Among those 4 patients with vHCL, 2 received rituximab as monotherapy, one underwent splenectomy and one was initially put in "watch and wait", being treated with IFN some years after [18].

Regarding the 36 patients treated with 2-CdA, response evaluation was available in only 30 patients, among them 21 achieved CR (70%), 7 (23%) PR and 2 (7%) were refractory. Three patients refused to collect a BM specimen after treatment and three patients died before any BM assessment. There were 18 cases of treatment-related infection, all

Table 1
Patient's characteristics (n = 54).

Age (years), median (range)	55 (26 – 88)
Gender (M:F)	17:1
Splenomegaly, % (n)	67 (33)
LDH (IU/L), median (range)	339 (148 – 530)
B2M (mg/L), median (range)	2.8 (1.5 – 7.5)
Albumin (g/dL), median (range)	4.1 (2.5 – 4.8)
Hemoglobin (g/dL), median (range)	8.2 (5.2 – 15.8)
Neutrophils (x10^9/L), median (range)	0.65 (0 – 4.9)
Lymphocytes (x10^9/L), median (range)	1.7 (0.3 – 32.6)
Monocytes (x10^9/L), median (range)	0.01 (0 – 0.4)
Platelets (x10^9/L), median (range)	55.5 (15 – 189)
BM infiltration pattern, % (n)	Diffuse: 60 (26) Interstitial: 37 (16) Nodular: 2 (1)
First-line treatment, % (n) (missing one patient)	2-CdA: 68 (36) Splenectomy: 13 (7) IFN: 11 (6) Rituximab: 4 (2) "Watch and wait": 4 (2)

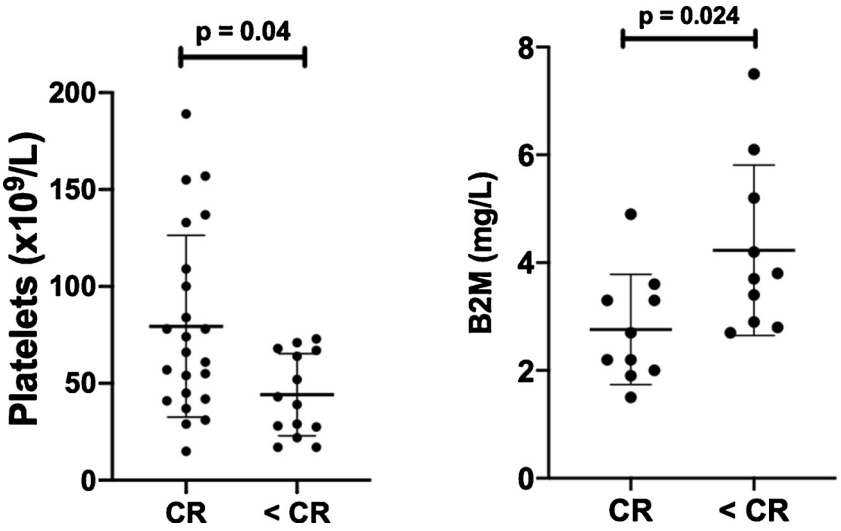

Fig. 1. Univariate comparison of platelet counts and B2M level for CR attainment (Student's *t*-test).

related to 2-CdA (18/36, 50%).

In the group of patients with available information treated with interferon (n = 5/6), splenectomy (n = 7) or Rituximab (n = 2), 5 patients had CR, 7 showed PR and 2 refractory disease. Overall, 11% were considered primary refractory patients, needing another second-line therapy. In a univariate analysis, platelet count and B2M level at diagnosis were statistically associated with CR achievement (p = 0.004 and p = 0.024, respectively) (Fig. 1).

3.3. Follow-up and survival data

A median follow-up time of 9 years (range, 0.03–24) was calculated. Estimated 10-year OS was 91.1% (95% confidence interval [CI], 77–97) and the median OS was not reached (Fig. 2). There were 4 deaths in our cohort – three from sepsis (all EDs) and another one from second neoplasm (prostate). All EDs occurred in patients after 2-CdA administration, despite using broad-spectrum antibiotics, intensive care and filgrastim. 10-year PFS was 67.9% (95% CI, 43–84) and 10-year CIR was 21.6% (95% CI, 6.8–41.7).

Among those relapsed patients (n = 8), a second line of treatment was required, with a median time to second treatment of 49 months (range, 3–162). Cladribine was used in 5 patients and splenectomy in 2, with a new transitory response. Univariate analysis of PFS and OS did not show any statistical significance for the tested variables.

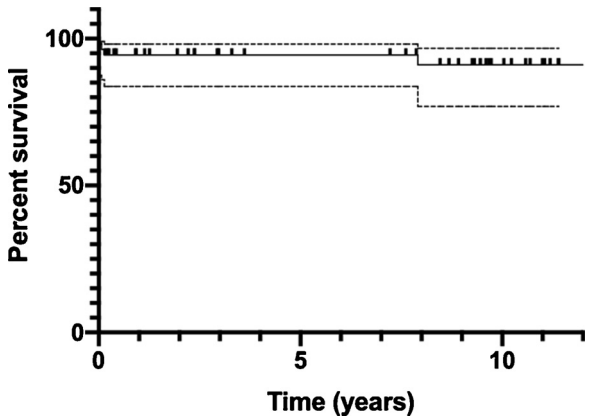

Fig. 2. Kaplan-Meier curve for OS of total cohort.

3.4. Second neoplasms

In this cohort, 10 patients had any second neoplasm, diagnosed before or after HCL. Overall, there were 16 different sites of cancer, in which two patients had more than one diagnosis. Among those 16 cases, only three occurred before HCL diagnosis. The rest of the second neoplasms were diagnosed after the treatment for HCL. Regarding the sites of cancer, 69% were of skin – 8/16 carcinoma-type and 3/16 melanoma-type. Remaining cases comprise prostate (n = 2), thyroid (n = 1), bladder (n = 1) and diffuse large B-cell lymphoma (n = 1). There was no correlation between arising of second neoplasms and B2M levels (p = 0.961) or follow-up time (p = 0.247).

4. Discussion

Since very few data is available about HCL in Latin America, in this manuscript, we gathered and reviewed baseline and outcomes of those patients treated in a reference center. A long-term OS of 91% was found, even though only 68% of subjects were treated with the current standard-of-care, 2-CdA.

In our study, patients had a similar demographic profile than what was previously published in larger cohorts, with a median age of 55 years and a male prevalence, even though male:female ratio seemed to be higher in our cohort [19,20]. Overall, there is no difference in the health public system in Brazil that could justify this disparity, since we do not see this difference in other oncologic conditions. Recent cohort study from Pakistan encompassed 21 patients, all male [21]. In a recent report, Arab patients were younger at diagnosis of HCL than others from middle east ethnicity [13]. In contrast, in a large cohort of Swedish patients, median age at diagnosis was 62 years [22]. Table 2 describes characteristics and outcomes of patients with HCL in different countries. Currently, splenomegaly is not a ubiquitous finding in HCL, ranging from 60 to 100% since many patients are early diagnosed [2,15]. B2M was altered in 50% of available subjects, which was similar to preexistent literature [23].

We have found that platelet counts and B2M level were associated with CR status, which is considered a surrogate marker of long-term survival [6,24]. Prospective data published by Forconi et al. showed that although 59% of patients had an abnormal level of B2M, it did not reach statistical significance in univariate analysis [23]. This study also displayed leukocytosis, bulky spleen, unmutated status for Ig heavy chain variable region genes (IGHV) and TP53 dysfunction as clinical predictors of failure to purine analogs, despite the low number of patients [23,24]. Admittedly, B2M should be screened in HCL patients,

Table 2
Retrospective studies including large series of patients with HCL in different countries.

	USA[a] [19]	The Netherlands [20]	Brazil (Northeast) [10]	Mexico [9]	Turkey [27]	Israel [13,32]	Brazil (HCFMUSP)
n	749	1505	50	29	94	203	54
Median age (years)	56	59	54	62	55	54.3 (mean age)	55
Male proportion	77%	77%	84%	72%	70%	82%	94%
Median follow-up (years)	3	10	NR	2	2	5.2	9
First-line regimen: 2-CdA	76%	72%	54%	38%	90%	78.7%	68%
OS	92%	93%	NR	91%	96%	90%	94%
Second neoplasm	NA	18%	0%	NR	3%	11%[b]	25%[*]

NR = not reported.
[*] included all skin cancers.
[a] United States of America.
[b] previous report of 181 patients of this cohort.

even though its prognostic role in HCL has never been hitherto proved [15,24–26].

The degree of cytopenias has already been recognized as a clinical predictor of response by previous reports. Else et al. showed, in a retrospective cohort involving 233 patients, that response to treatment, hemoglobin and platelet counts remained significantly associated with PFS in a multivariable Cox model [6]. Platelet count also had a marginal impact on prognosis in a Turkish cohort of 96 patients [27].

The most frequently employed first-line regimen was 2-CdA (68%), which is in line with previous retrospective published cohorts, illustrating the changes in the management over the decades [10,19,20]. Some patients were only followed without any treatment, also showing that few cases of HCL might indeed be managed in a "watch and wait" approach, as previously reported [28]. Probably due to the low number of subjects, this study was not able to demonstrate 2-CdA superiority over other strategies, since this therapy usually leads to a CR status, which may provide long-term survival and potential cure [7]. Three EDs from infection were found in this cohort, highlighting the role of IFN and more recently vemurafenib in cases presenting with infection or profound neutropenia [29,30]. Dinmohamed et al. demonstrated, in a population-based study carried out in The Netherlands, that relative survival (OS corrected for the life expectancy of general population) reached a plateau after two years since diagnosis among patients below 70 years who were diagnosed during 2001 to 2015 [20]. It shows that the majority of these patients can look forward to a normal life expectancy and this is arguably attributable to the use of purine analogs and better supportive care [20]. IFN is a reasonable option for those patients who present with infections or profound neutropenia, ideally as a bridge therapy to 2-CdA [17,28]. IFN is also a reasonable choice for those relapsed patients after 2-CdA [31]. In Table 2, the use of 2-CdA as a first-line treatment was 38% and 54% in a report from Mexico and Northeast of Brazil, respectively, which contrasts with more than 68% in our study and higher than 72% in other countries.

The reason for the arising of second neoplasms in HCL is still an unsolved issue. In larger, population-based studies, there appears to be an increased incidence of secondary cancers, varying from 5 to 31% [32–35]. Of note, the differences in the incidence of secondary cancers will depend on the type of cancers reported and importantly the time of follow-up of the patients as shown in Table 2. In our cohort, we detected an overall incidence of 25%, mostly from skin sites. Hisada et al. reported, in a large study involving 3104 patients from Surveillance, Epidemiology and End Results (SEER), found a cumulative probability of second cancer of 32% 25 years after the HCL diagnosis, especially enriched with Hodgkin and non-Hodgkin lymphoma and thyroid cancer [35]. It is worth mentioning that this study excluded nonmelanoma skin cancers from its analysis [35]. In a Swedish analysis encompassing 823 subjects, 18% had a secondary primary cancer, with non-Hodgkin lymphoma and melanoma being the most substantial correlations [22]. Recent survey seeking to report skin cancers incidence among 267 patients treated at Memorial Sloan Kettering Cancer Center, found an incidence of 11.3% [36]. Although it is still a controversial issue, the use of purine analogs does not contribute for the appearance of second cancers [6,33,37,38].

Recently, it was found that BRAF V600E mutation is the genetic hallmark of the vast majority of classical HCL, leading to phosphorylation of downstream molecules, as MEK and ERK, and eventually driving the morphologic and phenotypical findings of HCL [39]. This discovery has led to insights into the pathophysiology of HCL and second neoplasms, since BRAF mutations are widely found in other solid tumors, as melanomas, colorectal cancers, lymphomas and lung cancers, for instance [40]. In this analysis, we noticed a high incidence of skin cancer, which may be connected to environmental issues (tropical climate) and/or genetic aspects. This raises the question of whether underlying genetic predisposition, environmental factors and impairment of the immune system may play a role in these associations [7]. Unfortunately, we did not routinely perform molecular analysis in our cases, such as somatic hypermutation in IGHV, BRAF, CDKN1B, MAP2K1 or CCND3 mutations.

This study is the largest study published to date in patients with HCL in our country. Therefore, these results may indicate that at least the clinical course of Brazilian patients with HCL is similar to the results reported from developed countries.

In conclusion, this study confirmed the favorable prognosis of HCL patients in an emergent country, even when relapses have occurred, patients may be rescued with other treatments. We demonstrated that platelet count and B2M level may impact on CR rate, and this finding deserves further studies and larger series to be confirmed. Our response and survival data are similar to those reported by literature, which reaffirms the role of purine analogs in current HCL management. With a very long follow-up we also have observed a high incidence of second neoplasm. Whether this observation is associated to HCL itself or its treatment or it is due to a long survival period of the patients, should be further investigated.

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Conflict of interest

The authors declare that they have no conflict of interest.

Statement of human rights

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Contributions

1 W.F.S. performed the statistical analyses and wrote the manuscript.
2 A.C.N, I.A.S, L.I.R were in charge of acquisition of data from hospital charts.
3 E.D.R.P.V and G.D.A organized and reviewed the data.
4 V.B, V.R and E.M.R discussed and revised the manuscript critically.
5 All the authors approved the final version of the manuscript.

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