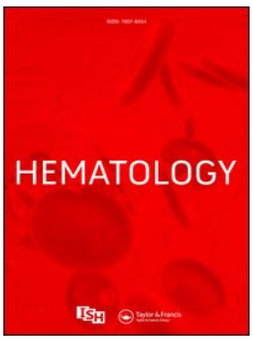

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Real-world analysis of treatment patterns and clinical outcomes in patients with newly diagnosed chronic lymphocytic leukemia from seven Latin American countries

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ABSTRACT

Objective: To describe chronic lymphocytic leukemia (CLL) treatment patterns and patient outcomes in Latin America.

Methods: This chart review study (NCT02559583; 2008–2015)evaluated time to progression (TTP) and overall survival (OS) outcomes among patients with CLL who initiate done (n = 261) to two (n = 96) lines of therapy (LOT) since diagnosis. Differences in TTP and OS were assessed by Kaplan-Meier analysis, with a log-rank test for statistical significance. Association between therapeutic regimen and risk for disease progression or death was estimated using Cox proportional hazard regression.

Results: The most commonly prescribed therapies in both LOTs were chlorambucil-, followed by fludarabine- and cyclophosphamide (C)/CHOP-based therapies. Chlorambucil- and C/CHOP-based therapies were largely prescribed to elderly patients (≥65 years) while fludarabine-based therapy was predominantly used by younger patients (≤65 years). In LOT1, relative to chlorambucil-administered patients, those prescribed fludarabine-based therapies had lower risk of disease progression (hazard ratio [HR] and 95% confidence interval [CI] 0.32 [0.19–0.54]), whereas C/CHOP-prescribed patients had higher risk (HR 95%CI 1.88 [1.17–3.04]). Similar results were observed in LOT2. There was no difference in OS between treatments in both LOTs.

Discussion: Novel therapies such as kinase inhibitors were rarely prescribed in LOT1 or LOT2in Latin America. The greater TTP observed forfludarabine-based therapies could be attributed to the fact that fludarabine-based therapies are predominantly administered to young and healthy patients.

Conclusion: Chlorambucil-based therapy, which has limited benefits, is frequently prescribed in Latin America. Prescribing novel agents for fludarabine-based therapy-ineligible patients with CLL is the need of the hour.

Trial registration: ClinicalTrials.gov identifier: NCT02559583.

KEYWORDS
Latin America; chronic lymphocytic leukemia; treatment pattern; real-world evidence; fludarabine; progression-free survival; chlorambucil; overall survival

Introduction

Important advances have recently been made in treating chronic lymphocytic leukemia (CLL) with the development of new treatments including immunotherapies [1–3] (alone or with chemotherapy), Burton tyrosine kinase inhibitors [4] and other novel therapies, which have improved clinical outcomes. However, the adoption of novel therapies in Latin America often lags behind that of other Western countries[5]. Furthermore, improving care for patients with CLL in this region is challenging as there are only limited data regarding CLL treatment patterns. Patient outcomes of disease progression that may be associated with treatment choices also remain unclear. To address this data gap, we conducted a medical chart review study in seven Latin American countries to provide insight into CLL treatment patterns and outcomes in this region.

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Materials and methods

The Hemato-Oncology Latin America Observational Study (clinicaltrials.gov identifier: NCT02559583) was a retrospective, medical chart review study that assessed patients newly diagnosed with selected hematologic malignancies between 2008–2015, who received care at 30 clinical sites in seven countries: Argentina, Brazil, Chile, Colombia, Mexico, Panama, and Guatemala. Sites were selected based upon their experience in providing clinical care for patients with CLL, geographic and practice type representativeness, and willingness to comply with study requirements. All eligible patients at participating centers were included regardless of patient demographics, prior or current treatments for disease, or clinical outcome. Each clinical site selected and prepared files for the abstractor to review; the Principal Investigator provided clarification in case of doubt. Referred patients were eligible if they had a complete referral note that included diagnosis, clinical first symptoms and previous treatments and the year of follow up at the center, unless he/she died before this period. The patient outcomes of interest in the present study were based on the clinician's assessment, and included: objective responses to treatment (e.g. complete or partial response), stable disease, disease progression, and survival. All information on each patient was collected during a one-time abstraction. The study protocol has been described in greater detail in an earlier report [5]. In the present analysis, only CLL patients who initiated treatment were included and assessed for up to two lines of therapy (LOTs). LOT1 was defined by the treatment received after disease diagnosis and before first disease progression and LOT2 was defined as the treatment received after first progression and prior to second progression. Time to Progression (TTP) and overall survival (OS) outcomes were calculated from the time of initiation of each LOT to the earliest occurrence of one of the following events: end of study follow-up, progression date (for TTP outcomes); and end of study follow-up or death date (for OS outcomes). Treatments regimens were grouped into one of the following four categories: chlorambucil-based therapy (± prednisone); cyclophosphamide (C)- or cyclophosphamide, adriamycin, vincristine, prednisone (CHOP)-based therapy (± rituximab); fludarabine-based therapy (± cyclophosphamide, rituximab) and other therapies. Difference in TTP and OS among treatment regimens in each LOT group was assessed by Kaplan-Meier analysis, with a log-rank test for statistical significance. The multivariable Cox proportional hazard regression with adjustment for baseline confounders was used to estimate the association between therapy choice in the first and second LOTs and risk for disease progression or death, comparing patients with chlorambucil-based therapy with other therapies. All statistical analyses were performed using SAS Enterprise Guide 7.1 (Cary, NC).

Results

A total of 261 patients initiated LOT1 at a median of 3.3 months (range: 0.03–83) following CLL diagnosis. Patient and treatment characteristics are shown in Table 1. The median age at diagnosis was 65 years, with 55% male and 45% female patients. More than 50% of the patients had a history of cardiovascular-related disease (as defined by each investigator) and >10% of patients had ≥3 morbidities prior to CLL diagnosis. Binet staging was available in 64% of patients, with >50% of them at stages A or B. Following treatment initiation, the median follow-up time in these patients was 26 months (range: 0.03–95).

In LOT1, the three most commonly used therapies, accounting for 96% of patients, were: chlorambucil-based therapy (± prednisone) (50.1%; $n = 132/261$); cyclophosphamide (C)- or cyclophosphamide, adriamycin, vincristine, prednisone (CHOP)-based therapy (± rituximab) (13.0%; $n = 34/261$); and fludarabine-based therapy (± cyclophosphamide, rituximab) (33.0%; $n = 86/261$). Nine of 261 patients (3.4%) received other therapies, including bendamustine + rituximab ($n = 3$), molecule target therapy ($n = 2$), alemtuzumab ($n = 1$), and unknown ($n = 3$).

Median time from diagnosis to treatment initiation was similar across the three most commonly used treatment categories; 4.0, 1.1, and 3.0 months for chlorambucil-, C/CHOP-, and fludarabine-based therapies, respectively. Notably, the median age of patients receiving fludarabine-based therapy (58 years) was lower than those receiving chlorambucil- and C/CHOP-based (median age of 67 and 69 years in chlorambucil and C/CHOP therapies). In addition, fewer patients initiating treatment with fludarabine had a prior history of cardiovascular events or ≥3 comorbidities, as compared with most other patients. Overall, 53% of patients with available Binet staging information were at Stage A. Among patients who received LOT1, 36.8% ($n = 96/261$) progressed to receive LOT2. The three most commonly used LOT1 options were used in a similar pattern for LOT2: chlorambucil-based therapy (± prednisone) (45.8%; $n = 44/96$); cyclophosphamide (C)- or cyclophosphamide, adriamycin, vincristine, prednisone (CHOP)-based therapy (± rituximab) (18.8%; $n = 18/96$); and fludarabine-based therapy (± cyclophosphamide, rituximab) (28.1%; $n = 27/96$).

Within LOT1, the estimated TTP rate at year 1, 2, and 3 was 75%, 60%, and 47%, respectively. There were statistically significant differences in TTP among the LOT1 regimens (overall difference: $p < 0.001$;

Table 1. Baseline characteristics of CLL patients by LOT.

	First LOT treatment regimen					Second LOT treatment regimen				
Parameters	Total ($n = 261$)	CH ($n = 132$)	CHOP/C ($n = 34$)	F ($n = 86$)	Other[a] ($n = 9$)	Total ($n = 96$)	CH ($n = 44$)	CHOP/C ($n = 18$)	F ($n = 27$)	Other[b] ($n = 7$)
Age, *n* (%)										
< 65 years	123 (47%)	48 (32%)	14 (41%)	64 (74%)	3 (33%)	37 (39%)	14 (32%)	7 (39%)	13 (48%)	3 (43%)
≥ 65 years	138 (53%)	90 (68%)	20 (59%)	22 (26%)	6 (67%)	59 (61%)	30 (68%)	11 (61%)	14 (52%)	4 (57%)
Female, *n* (%)	118 (45%)	73 (55%)	13 (38%)	28 (33%)	4 (44%)	38 (40%)	19 (43%)	8 (44%)	9 (33%)	2 (29%)
Comorbidities,*n* (%)										
Cardiovascular events	134 (51%)	79 (60%)	18 (53%)	31 (36%)	6 (67%)	48 (50%)	26 (59%)	7 (39%)	11 (41%)	4 (57%)
Infection disease	21 (8%)	9 (10%)	3 (9%)	9 (10%)	0	7 (7%)	3 (7%)	2 (11%)	2 (7%)	0
Number of comorbidities, *n* (%)										
0 – <3	227 (87%)	109 (83%)	32 (94%)	78 (91%)	8 (89%)	80 (83%)	34 (77%)	15 (83%)	25 (93%)	6 (86%)
≥3	34 (13%)	23 (17%)	2 (6%)	8 (9%)	1 (11%)	16 (17%)	10 (23%)	3 (17%)	2 (7%)	1 (14%)
Binet staging, *n* (%)										
A	88 (34%)	55 (42%)	6 (18%)	24 (28%)	3 (33%)	30 (31%)	18 (41%)	7 (39%)	5 (19%)	0
B	32 (12%)	14 (11%)	4 (12%)	14 (16%)	0	11 (11%)	3 (7%)	4 (22%)	3 (11%)	1 (20%)
C	47 (18%)	22 (17%)	8 (24%)	15 (17%)	2 (22%)	17 (18%)	5 (11%)	1 (6%)	7 (26%)	4 (80%)

[a]Including bendamustine + rituximab ($n = 3$), molecule target therapy ($n = 2$), alemtuzumab ($n = 1$), and unknown ($n = 3$).
[b]Including bendamustine + rituximab ($n = 3$), molecule target therapy ($n = 2$), and unspecified immunochemotherapy ($n = 2$). Abbreviations: CH – Chlorambucil; C/CHOP – Cyclophosphamide/Cyclophosphamide, Adriamycin, Vincristine, Prednisone; CLL – Chronic Leucocytic Leukemia; F – Fludarabine, LOT – Line of Therapy.

Figure 1a), with the highest median TTP for fludarabine-based therapy (>50 months), followed by chlorambucil (32 months), and C/CHOP (13 months) based therapies. Shorter median TTP was seen in all the LOT2 regimens, ranging from 5 months (C/CHOP) to 37 months (fludarabine) (overall difference: $p < 0.01$, Figure 1c). Relative to chlorambucil-based therapy, risk of disease progression in LOT1 was lower for fludarabine-based therapy (hazard ratio [HR] 95% confidence interval[CI]:0.32,[0.19–0.54]), but higher for C/CHOP therapy (HR 95% CI: 1.88 [1.17–3.04]). A similar pattern was also observed for risk of disease progression in LOT2; a lower progression risk, albeit not of statistical significance, for fludarabine therapy (HR 95% CI: 0.80 [0.37–1.74]) and higher risk for C/CHOP therapy (HR 95% CI: 2.34 [1.09–5.06]) were observed, relative to chlorambucil therapy.

Fifty-two (20%) patients died during the study period following LOT1 initiation. The 3-year OS rate was 77%withinthe LOT1 group; 85% and 69% in patients aged < 65 and ≥65 years, respectively. OS was not significantly different among LOT1 regimens ($p = 0.30$, Figure 1b). Following initiation of LOT2, the 3-year OS rate was 65% (74% and 60% in patients < 65 and ≥65 years). There was also no statistically significant difference in OS among the LOT2 regimen groups ($p = 0.08$, Figure 1d). In addition, there was no difference in risk for mortality between chlorambucil and other therapies for either LOT1 or LOT2 ($p \geq 0.20$).

Discussion

Our study is the first to report treatment patterns beyond the LOT1 from multiple Latin American countries. Although this study is not population based, it provides important insight into patterns of care and outcomes in this region during the study period (2008–2015).

The most commonly usedLOT1 in this Latin American cohort was chlorambucil-based therapy (50.1%). However, in a US registry of academic, community and government centers, chlorambucil based therapy (either in combination with immunotherapy or monotherapy) made up only 5.7% for first line treatment regimens [6]. Our findings are consistent with the results of a Brazilian CLL registry which included 1903 patients enrolled from 2004 to 2016 and reported that 65% of patients received chlorambucil at any point during their treatment, followed by fludarabine-based regimens (41%), rituximab in combination with other drug(s)(22%), and CHOP/CVP-like regimens (19%) [7]. Also, our results underscore the low utilization of novel therapies in the region such as biofunctional alkylating agents (e.g. bendamustine) or kinase inhibitors(e.g. ibrutinib and idelalisib), which were rarely seen in this study. In the three largest countries in Latin America (Mexico, Brazil, and Argentina),

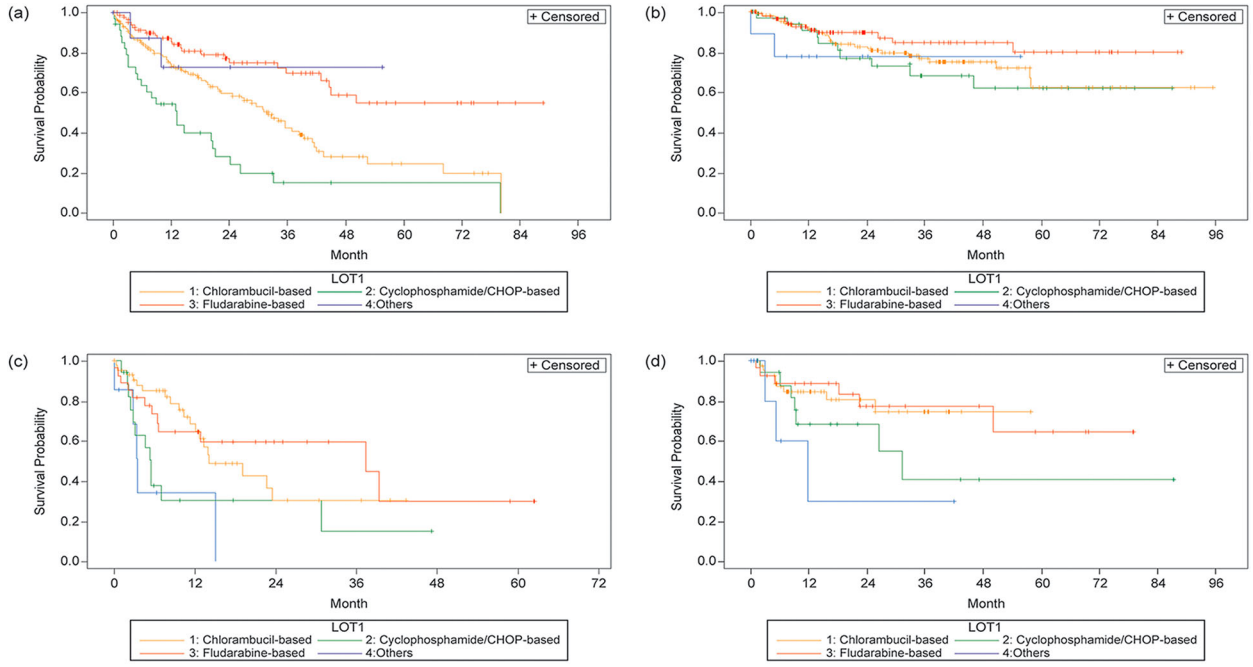

Figure 1. Kaplan-Meier curves (a) TTP and (b) OS in first LOT (c) TTP and (d) OS in second LOT. Abbreviations: LOT – Line OF therapy, OS – Overall Survival, TTP – Time to Progression.

bendamustine was approved in April 2016, December 2016, and July 2012, respectively, ibrutinib was approved in January 2015, July 2015, and November 2015, respectively while idelalisib has not yet been approved in these countries.

As expected, patients who received fludarabine-based therapy in these Latin American sites were younger than those treated with other therapies. This is consistent with practice patterns in other countries where fludarabine-based therapy is the standard of care for younger and healthier CLL patients [8–11]. As noted in this cohort, patients who received chlorambucil or cyclophosphamide-based regimens were more likely have a greater burden of cardiovascular disease or other comorbidities than those who received fludarabine-based therapies, suggesting that Latin American physicians also employ similar selection criteria in making treatment choices. However, these findings underscore the unmet need of older patients and comorbid patients who may not be a candidate for fludarabine-based therapy. We noted a shorter OS relative to other studies (77% of 3-year OS in HOLA vs. ≥80% of 5-year OS in other studies) [3,6]. The infrequent use of novel therapies in this cohort may have contributed to shorter OS.

The current study did not comprise patients who were administered the anti-CD20 monoclonal antibodies rituximab or obinutuzumab in combination with chlorambucil. However, evidence shows these combinations improve outcomes more than chlorambucil alone. The CLL11 study – a phase 3, randomized, open-label trial – showed a significant improvement in median progression-free survival (26.7 months with obinutuzumab–chlorambucil vs. 11.1 months with chlorambucil alone; HR [95% CI] for progression or death, 0.18 [0.13–0.24],$p < 0.001$; and 16.3 months with rituximab–chlorambucil vs. 11.1 months with chlorambucil alone; HR [95% CI], 0.44 [0.34–0.57],$p < 0.001$). Treatment with obinutuzumab–chlorambucil significantly improved OS compared with chlorambucil monotherapy (HR [95% CI] for death, 0.41 [0.23–0.74], $p = 0.002$). No significant benefit was observed with rituximab-chlorambucil over chlorambucil alone monotherapy (HR [95% CI] 0.66 [0.39–1.11], $p = 0.11$) [2].

Today, the treatment landscape of CLL in Latin America has changed slightly from the current study. Novel therapies such as Bruton Tyrosine Kinase inhibitors (ibrutinib) and B-cell Lymphoma 2 inhibitors (venetoclax) are nowadays prescribed in Latin America but are sometimes restricted to the private sector. Patients in the public sector are often treated only with standard chemotherapy as described in the current study due to limited access to advanced cancer medications [12]. Although initiatives to improve the current scenario have been undertaken, further efforts are required [13].

Our result should be put in the context of the study limitations. This was not a population-based sample, but instead drawn from a convenience sample of 30 clinics. Practice patterns and access to therapies likely differ by country. The included clinic sites might also not be representative within countries, since different clinics may employ different treatment approaches. In addition, these data were collected retrospectively rather than prospectively. It is possible that missing

or incomplete data could affect our results. If patients received treatment or experienced disease progression outside of the participating clinic, that data would not be available. In addition, if a patient's death was not reported to the participating center, this could lead to an over-estimation of overall survival. Therefore, it is important to interpret outcomes data in the context of this study. In addition, this was not a randomized study, so outcomes by treatment arms should not be interpreted as causal.

In summary, our study shows that chlorambucil-based therapy, which confers limited clinical benefit compared to novel therapies was frequently prescribed in Latin America during the study period. The incorporation of novel agents for CLL patients, especially among those ineligible for fludarabine-based therapy due to age and comorbidities, is urgently needed in this region.

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Author contributions

CP, AB, LPL, SSSA, DLCF, AG, KMGC, DGA, ETA, and CC enrolled the patients and acquired the data. GM and PB contributed to research design and data interpretation. JHL and YWC performed the data analysis and contributed to data interpretation. MM and LPR contributed to data interpretation and critical review of the manuscript. JHL drafted this manuscript with input from all other authors.

Data availability statement

The datasets are available from the corresponding author on reasonable request.

Disclosure statement

SSSA, AB, ETA, and DLCF report grants from Janssen Pharmaceuticals during the conduct of the study. DGA has been a paid speaker for Janssen Pharmaceuticals Inc. CC, CP, LPL, AG, and KMGC report no conflicts of interest. JHL, YWC, GM, MM, LPR, and PB are employees of Janssen Pharmaceuticals and own stock in Johnson and Johnson.

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