original reports abstract

Real-World Data on Adult T-Cell Leukemia/Lymphoma in Latin America: A Study From the Grupo de Estudio Latinoamericano de Linfoproliferativos

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PURPOSE Adult T-cell leukemia/lymphoma (ATLL) is an aggressive disease caused by the human T-cell leukemia virus type 1. Real-world data of ATLL in Latin America are lacking.

PATIENTS AND METHODS We analyzed patients with ATLL (acute, lymphomatous, chronic, and smoldering) encountered in 11 Latin American countries between 1995 and 2019. Treatment response was assessed according to the 2009 consensus report. Survival curves were estimated using the Kaplan-Meier method and log-rank test.

RESULTS We identified 253 patients; 226 (lymphomatous: n = 122, acute: n = 73, chronic: n = 26, and smoldering: n = 5) had sufficient data for analysis (median age 57 years). Most patients with ATLL were from Peru (63%), Chile (17%), Argentina (8%), and Colombia (7%). Hypercalcemia was positively associated with acute type (57% *v* lymphomatous 27%, $P = .014$). The median survival times (months) were 4.3, 7.9, 21.1, and not reached for acute, lymphomatous, chronic, and smoldering forms, with 4-year survival rates of 8%, 22%, 40%, and 80%, respectively. First-line zidovudine (AZT)-interferon alfa (IFN) resulted in an overall response rate of 63% (complete response [CR] 24%) for acute. First-line chemotherapy yielded an overall response rate of 41% (CR 29%) for lymphomatous. CR rate was 42% for etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone versus 12% for cyclophosphamide, vincristine, doxorubicin, and prednisone–like regimen ($P < .001$). Progression-free survival at 1 year for acute type patients treated with AZT-IFN was 67%, whereas 2-year progression-free survival in lymphomatous type patients who achieved CR after chemotherapy was 77%.

CONCLUSION This study confirms Latin American ATLL presents at a younger age and has a high incidence of lymphomatous type, low incidence of indolent subtypes, and worse survival rates as compared with Japanese patients. In aggressive ATLL, chemotherapy remains the preferred choice for lymphomatous favoring etoposide-based regimen (etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone), whereas AZT-IFN remains a good first-line option for acute subtype.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) is a mature, peripheral T-cell neoplasm caused by the human T-cell leukemia virus type 1 (HTLV-1).[1,2] HTLV-1 infects up to 10 million people worldwide and it is predominantly transmitted via breastfeeding, blood transfusion, sharing of needles, and sexual intercourse.[3] The virus is endemic in southwestern Japan, the Caribbean Basin, South America, Western and Central Africa, and central Australia.[3,4] In Latin America, the highest prevalence is found in the Dominican Republic, Brazil, and Peru.[4,5]

ATLL is a generally incurable disease where CD4+ T cells carry clonally integrated copies of the HTLV-1 genome.[6] The cumulative lifetime risk of developing ATLL is estimated as 4%-7% among HTLV-1 carriers, with most cases presenting during the sixth decade of life in Japan and during the fifth decade in the Hispanic and Afro-Caribbean population.[5,7-9] Clinically, the disease is classified by the Shimoyama[10]

CONTEXT

Key Objective

Does adult T-cell leukemia/lymphoma (ATLL) present differently in Latin America than other parts of the world?

Knowledge Generated

Latin American ATLL overwhelmingly presents at a younger age and with aggressive disease, characterized by higher incidence of lymphomatous type, low incidence of indolent types, and low survival outcomes compared with Japanese patients.

Relevance

In aggressive ATLL, etoposide-based regimen (etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone) is a reasonable first-line choice over cyclophosphamide, vincristine, doxorubicin, and prednisone–like chemotherapy, whereas combination of zidovudine with interferon alfa-2b is a good option for nonbulky acute ATLL subtype.

criteria into four subtypes: acute, lymphomatous, chronic, and smoldering. The acute and lymphomatous are the most common and are often grouped as aggressive ATLL. The chronic and smoldering have a less aggressive course and are grouped as indolent ATLL.[5,7,10,11]

ATLL carries a dismal prognosis despite modern intensive therapies, with shorter survival rates compared with other peripheral T-cell lymphomas.[12] The treatment of ATLL remains challenging with no clearly established standard of care at the present time. To date, clinicoepidemiologic studies evaluating the incidence and management of ATLL in endemic and nonendemic areas for HTLV-1 infection in Latin America are lacking. Cognizant of this, the Grupo de Estudio Latinoamericano de Linfoproliferativos developed a clinical data registry of patients diagnosed with ATLL in Latin America. Herein, we describe the group's analysis and provide an in-depth insight into the epidemiology, clinical features, treatment, and disease outcome of patients with ATLL encountered collectively over the past 25 years in participating sites.

PATIENTS AND METHODS

Patients

We conducted a retrospective analysis of patients diagnosed with ATLL between January 1995 and December 2019. Twenty-four centers from 11 Latin American countries participated in the ATLL database query (Appendix Table A1). Patient demographics and clinical data were obtained from available medical records. Each Institutional Review Board approved this study.

Diagnosis, Disease Classification, and Risk Stratification

The diagnosis of ATLL was based on serologic evidence of HTLV-1 by enzyme-linked immunosorbent assay. Confirmation by reflex Western blot was performed in most cases, but not in some because of unavailability or high cost. In all cases, identification of clonal CD4+ CD7– CD25+/– T cells in peripheral blood and/or tissues was determined by histology, immunophenotyping, and gene rearrangement studies. Patient cases were classified according to the Shimoyama[10] criteria. Two indexes were used for risk stratification in aggressive ATLL: the International Prognostic Index (IPI) and the Prognostic Index for Peripheral T-Cell Lymphoma (PIT).[13,14]

Therapy Approaches

The therapy approaches investigated were classified into first-line therapy with (1) zidovudine (AZT)-interferon alfa (IFN) alone, (2) multiagent chemotherapy alone, (3) combined chemotherapy with AZT-IFN, and (4) single-agent chemotherapy and/or regional therapy (ie, topical therapy and phototherapy). The centers that used parenteral AZT-IFN had a comparable therapy protocol on the basis of previously published data.[15] In general, the chemotherapy regimens used at any time included cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP)–like regimens; etoposide-based regimens (eg, etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone [CHOEP] and EPOCH), platinum-based regimens, other non–platinum-based regimens, single-agent chemotherapy, and allogeneic transplant (allogeneic hematopoietic stem-cell transplant [allo-HSCT]). Regimens were selected by the treating physician on the basis of ATLL subtype and according to local institutional practices (Table 1).

Response Criteria

Therapy responses were assessed according to the 2009 consensus report for ATLL.[16] The Cheson criteria was used to assess response through computerized tomography imaging.[17] Complete response (CR) required a decrease in the absolute lymphocyte count to $< 4 \times 10^9$/L with $< 5\%$ of flower cells remaining along normalization of all nodal and extranodal lesions (including bone marrow); partial response (PR) was defined as $\geq 50\%$ disease reduction; and progressive disease (PD) as $\geq 50\%$ increase in the count of flower cells and absolute lymphocyte count $> 4 \times 10^9$/L at any time, and/or $\geq 50\%$ increase in size of any nodal and/or extranodal lesions. Stable disease (SD) was defined as a failure to attain CR or PR in the absence of PD. Responses

TABLE 1. Demographics and Clinical Features of Patients With Adult T-Cell Leukemia/Lymphoma

Category	Acute (n = 83)	Lymphomatous (n = 127)	Chronic (n = 26)	Smoldering (n = 5)	Undetermined (n = 12)	Total (N = 253)	*P*
Age, median (range), years	58 (20-80)	58.2 (20-95)	55.5 (18-78)	53 (50-66)	52	57 (18-95)	1
Sex, n (%)							.107
Female	47 (58)	61 (48)	13 (50)	5 (100)	0	126 (50)	
Male	33 (40)	64 (50)	13 (50)	0	1 (8)	111 (44)	
Unknown	3 (2)	2 (2)	0	0	11 (92)	16 (6)	
Country, n (%)							
Argentina	12 (14)	7 (6)	1 (5)	0	0	20 (8)	
Bolivia	1 (1)	1 (1)	0	0	3 (25)	5 (2)	
Chile	27 (33)	13 (10)	3 (11)	1 (20)	0	44 (17)	
Colombia	7 (9)	6 (5)	3 (11)	0	1 (8)	17 (7)	
Ecuador	0	0	0	0	6 (50)	6 (2)	
Mexico	0	0	0	0	1 (8.5)	1 (0.5)	
Paraguay	0	0	0	0	1 (8.5)	1 (0.5)	
Peru	36 (43)	100 (78)	19 (73)	4 (80)	0	159 (63)	
B symptoms, n (%)	61 (73)	92 (72)	15 (58)	1 (20)	1 (8)	170 (67)	.011
Stage III-IV, n (%)	83 (100)	101 (80)	26 (100)	5 (100)	—	215 (89)	
ECOG ≥ 2, n (%)	47 (57)	56 (44)	4 (15)	0	—	107 (42)	.039
Hypercalcemia, n (%)	33 (40)	34 (27)	0	0	—	67 (26)	.014
High LDH, n (%)[b]	69 (83)	96 (76)	18 (69)	3 (60)	—	186 (74)	.082
IPI score, n (%)							< .001
Low risk	2 (3)	15 (12)	6 (23)	4 (80)	1 (8)	28 (11)	
Low-intermediate risk	11 (13)	37 (29)	10 (38)	1 (20)	0	59 (23)	
High-intermediate risk	27 (33)	34 (27)	9 (35)	0	0	70 (28)	
High risk	36 (43)	36 (28)	1 (4)	0	0	73 (29)	
Unknown	7 (8)	5 (4)	0	0	11 (92)	23 (9)	
PIT score, n (%)							< .001
Low risk	2 (2)	6 (5)	2 (8)	0	1 (8)	11 (4)	
Low-intermediate risk	2 (2)	21 (16)	0	2 (40)	0	25 (10)	
High-intermediate risk	18 (22)	22 (17)	6 (23)	1 (20)	0	47 (18)	
High risk	50 (60)	72 (57)	16 (61)	1 (20)	0	139 (55)	
Undetermined	11 (14)	6 (5)	2 (8)	1 (20)	11 (92)	31 (13)	
Comorbidities, n (%)							
Infective dermatitis	3 (4)	1 (1)	—	—	—	4 (2)	
HAM/TSP	1 (1)	1 (1)	—	—	—	2 (1)	
Sjogren's syndrome	1 (1)	—	—	—	1 (8)	2 (1)	
Strongyloidiasis	2 (3)	2 (2)	1 (4)	—	—	5 (2)	
Pneumocystis	4 (5)	1 (1)	—	—	—	5 (2)	
Tuberculosis (lung)	1 (1)	2 (2)	—	—	—	3 (2)	
HIV	2 (3)	—	—	—	—	2 (1)	
Hepatitis B	—	1 (1)	—	—	—	1 (1)	
Neurocysticercosis	1 (1)	—	—	—	—	1 (1)	
Multiple myeloma	—	1 (1)	—	—	—	1 (1)	

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TABLE 1. Demographics and Clinical Features of Patients With Adult T-Cell Leukemia/Lymphoma (Continued)

Category	Acute (n = 83)	Lymphomatous (n = 127)	Chronic (n = 26)	Smoldering (n = 5)	Undetermined (n = 12)	Total (N = 253)	*P*
Extranodal involvement, n (%)							
Marrow[a]	34 (41)	29 (23)	5 (19)	1 (20)	1 (8)	70 (28)	
Skin	27 (31)	26 (20)	7 (27)	3 (60)	—	63 (25)	
Bone	4 (5)	7 (5)	—	—	—	11 (4)	
Lung	5 (6)	6 (5)	2 (7)	—	—	13 (5)	
Hepatic	17 (20)	4 (3)	2 (7)	—	1 (8)	24 (9)	
CNS	7 (8)	4 (3)	—	—	—	11 (4)	
Breast	—	2 (1)	—	—	—	2 (1)	
GI tract	6 (7)	6 (5)	1 (4)	—	—	13 (5)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HAM, HTLV-1-associated myelopathy; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PIT, Prognostic Index for Peripheral T-Cell Lymphoma; TSP, tropical spastic paraparesis.

[a]Patients with acute and chronic adult T-cell leukemia/lymphoma usually have bone marrow involvement. The above percentages represent patients tested only.

[b]Reported elevation of LDH in chronic and smoldering forms were ≤ 1.5 and ≤ 2 times the upper limit of normal, respectively.

(CR, PR, and SD) should persist for at least 4 weeks to be classified as such.

Statistical Analysis

Demographics, clinical features, and therapies received were summarized using descriptive statistics. The primary study outcomes were treatment response, progression-free survival (PFS), and overall survival (OS). Event-free patients were censored at the date of last clinical follow-up. Alive patients were censored at last follow-up in clinic or by telephone. Survival estimates were calculated by the Kaplan-Meier method and compared using the log-rank test. The Clopper-Pearson method was used to estimate the two-sided 95% CI in response rates. Statistical analysis was performed using IBM SPSS Statistics version 23.

RESULTS

Epidemiologic and Clinical Features

A total of 253 patients with ATLL were identified between January 1995 and December 2019. Demographic and clinical features of patients with ATLL are shown in Figure 1 and Table 1.

The majority (n = 211; 83%) had aggressive ATLL (lymphomatous: n = 127, 50%; acute: n = 83, 33%), and 31 (12%) had indolent ATLL (chronic: n = 26, 10%; smoldering: n = 5, 2%). Twelve cases (5%) were unclassifiable because of lack of laboratory or imaging information. The median age at diagnosis was 57 years, with a female predominance in acute (n = 47; 58%) and smoldering (n = 5; 100%) subtypes. Most patients with ATLL were from Peru (n = 159; 63%), Chile (n = 44; 17%), Argentina (n = 20; 8%), and Colombia (n = 17; 7%) (Fig 1). During the ATLL data query, participating centers from Guatemala, Uruguay, and Venezuela did not report ATLL cases during the past 10-15 years.

Hypercalcemia was associated with acute ATLL (40% *v* lymphomatous 27%, $P = .014$). The PIT score yielded a higher risk classification than the IPI score (high-risk PIT [n = 139, 55%] *v* high-risk IPI [n = 73, 29%], respectively; $P < .001$). Coinfections were seen in 7% (n = 17) of cases with strongyloidiasis (n = 5) and *Pneumocystis jirovecii* pneumonia (n = 5) as the most commonly observed.

Disease Outcome

Two hundred twenty-six patients (lymphomatous: n = 122, acute: n = 73, and chronic and smoldering: n = 31) had sufficient data for analysis. With a median follow-up of 12 months (range 1 month to 15 years), the median OS times were 4.3 months, 7.9 months, 21.1 months, and not reached for acute, lymphomatous, chronic, and smoldering ATLL ($P < .001$), with 4-year survival rates of 8%, 22%, 40%, and 80%, respectively (Fig 2).

Therapy Approaches and Responses

The therapy approaches used during the first two lines of therapy are summarized in Table 2. The median number of treatment regimens administered in all patients was 1 (range 1-3). Sixteen (6%) patients did not receive first-line treatment and had best supportive care because of very poor performance status led by a rapid disease progression. No biologic agents were used in our cohort mainly because of lack of access to these agents. Data on patients managed for CNS involvement are presented in Appendix Table A2.

AZT-IFN–Based Regimen

Table 3 summarizes the response rates in patients with ATLL according to treatment regimen. Of the evaluable patients, 44 received either AZT-IFN alone (n = 20) or in combination with multiagent chemotherapy (n = 24). First-line AZT-IFN alone (n = 17) resulted in an overall response rate (ORR) of 71% and CR of 42% (acute: n = 8, ORR 63%,

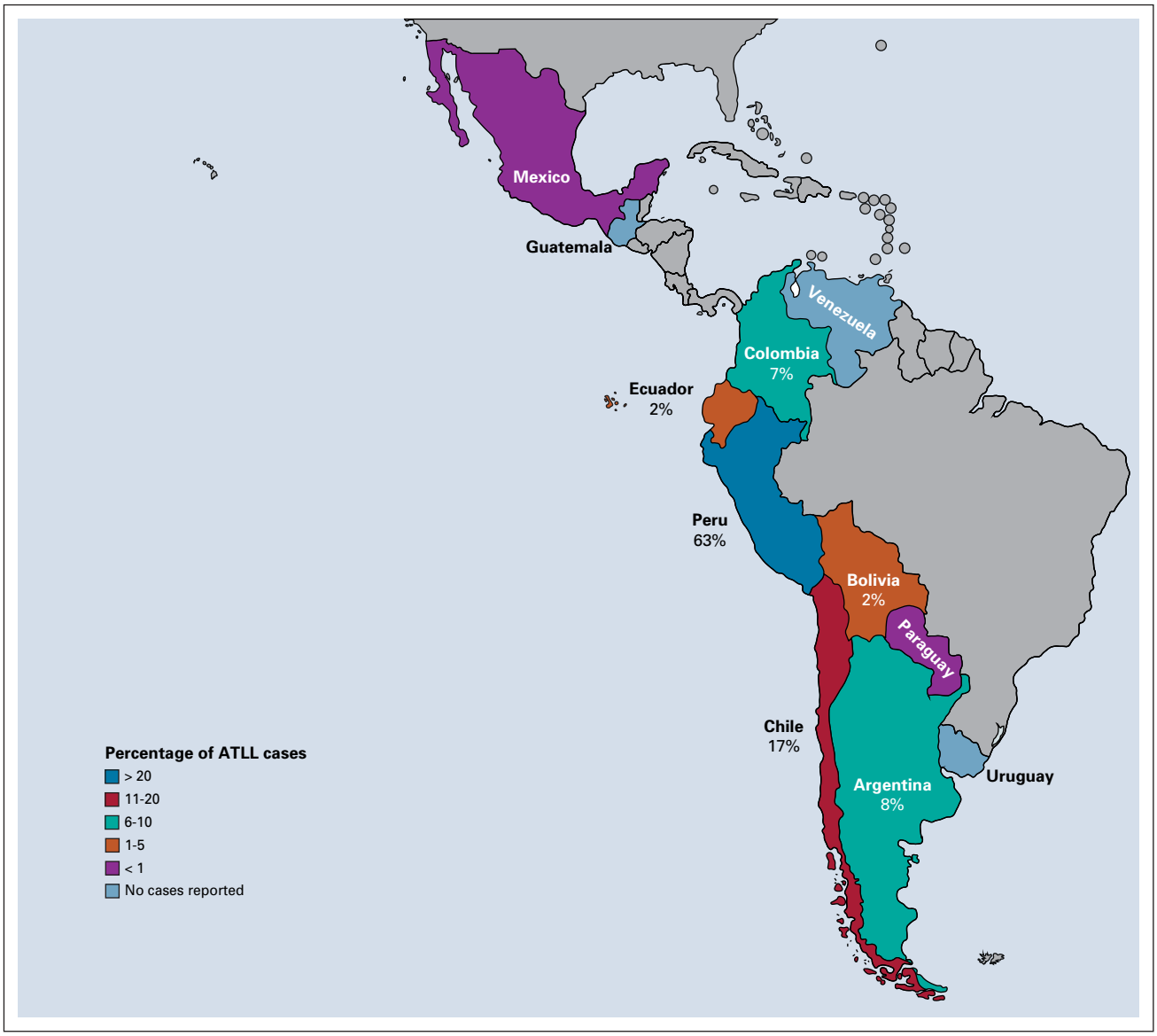

FIG 1. Geographical distribution map of patients with ATLL encountered in Latin America in Grupo de Estudio Latinoamericano de Linfoproliferativos cohort (N = 253). ATLL, adult T-cell leukemia/lymphoma.

CR 24%; lymphomatous: n = 8, ORR 75%, CR 50%; and smoldering: n = 1, CR 100%). First-line combination of AZT-IFN with multiagent chemotherapy (either concurrent or sequentially) resulted in an ORR of 67% and a CR of 17% (acute: n = 11, ORR 54%, CR 27%; lymphomatous: n = 11, ORR 73%, CR 9%; chronic: n = 1, PR 100%; and smoldering: n = 1, PR 100%). Second-line AZT-IFN alone (n = 3) yielded an ORR of 67% and a CR of 33% (one acute PR, one chronic CR, and one lymphomatous SD).

Chemotherapy-Based Regimen

A total of 187 patients received multiagent chemotherapy either as first line (n = 154) or as second line (n = 33). First-line chemotherapy resulted in an ORR of 32% and a CR of 21% (acute: n = 38, ORR 21%, CR 8%; lymphomatous: ORR 41%, CR 29%; chronic: n = 21, ORR 10%, CR 10%; and one with unknown ATLL subtype had CR). Second-line chemotherapy resulted in an ORR of 9% and a CR of 6% (acute: n = 6, ORR 17%, CR 17%; lymphomatous: n = 20, ORR 5%, PR 5%; chronic: n = 6, ORR 0%; and one with unknown ATLL subtype had CR). The most commonly used first-line regimens were CHOP or CHOP-like regimen (n = 117, 59%) and CHOEP regimens (n = 40, 20%) with an ORR of 29% (CR 12%) and 60% (CR 42%), respectively ($P < .001$) (Table 3). LSG-15–like regimen was used in four patients with an ORR of 0% (SD, n = 2, 50%) and hyperCVAD in four patients with one patient achieving CR (SD, n = 2, 50%).

Comparing Therapy Regimens

There were no differences in PFS in patients with acute or lymphomatous ATLL receiving either first-line AZT-IFN

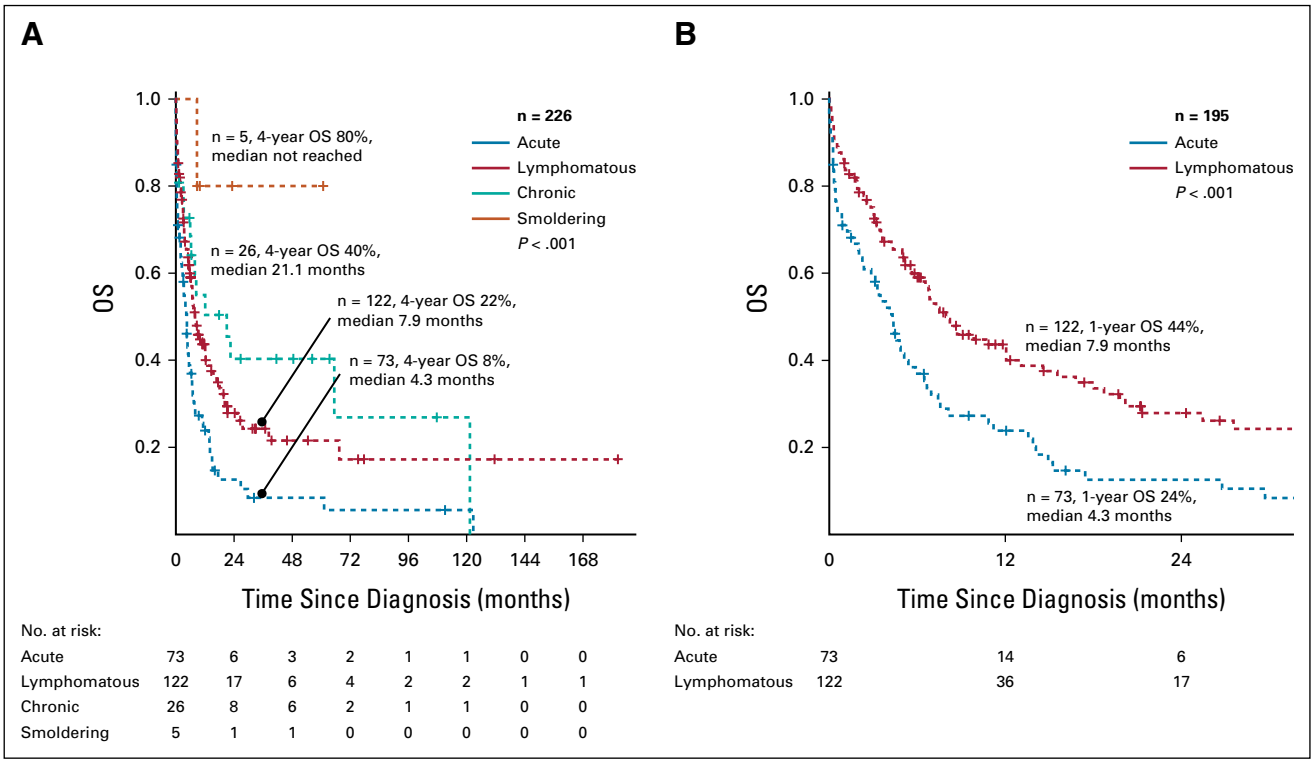

FIG 2. OS of patients with ATLL according to clinical subtype: (A) all ATLL and (B) aggressive ATLL. ATLL, adult T-cell leukemia/lymphoma; OS, overall survival.

alone, chemotherapy alone, or combination therapy (Appendix Fig A1). However, in patients with aggressive ATLL who achieved CR, first-line AZT-IFN (alone or in combination with chemotherapy) yielded a better PFS compared with chemotherapy alone in acute ATLL (AZT-IFN–based: n = 5, median 30.4 months, 1-year PFS 67% *v* chemotherapy-based: n = 3, median 2.8 months, 1-year PFS 0%). Chemotherapy resulted in improved PFS in patients with lymphomatous ATLL compared with AZT-IFN–based approach (AZT-IFN–based: n = 4, median 17.7 months, 2-year PFS 37% *v* chemotherapy-based: n = 26, median 67.1 months, 2-year PFS 77%) (Appendix Fig A1). However, these differences were not statistically significant.

Table 4 summarizes the therapy approaches and outcomes of patients with ATLL who achieved first complete remission.

TABLE 2. Approaches Used During the First Two Therapy Evaluations in All Patients

Therapy Approaches	Total (N = 414)	First-Line (n = 253)	Second-Line (n = 161)
AZT-IFN alone, n (%)	22 (5)	18 (7)	4 (2)
AZT-IFN plus chemotherapy, n (%)	25 (6)	25 (10)	0
Multiagent chemotherapy, n (%)	199 (48)	159 (63)	40 (25)
Single-agent chemotherapy, n (%)	13 (3)	5 (2)	8 (5)
Regional therapy, n (%)	5 (1)	5 (2)	0
Topical therapy (carmustine), n	3	3	—
Phototherapy plus topical therapy (clobetasol), n	2	2	—
Best supportive care, n (%)	124 (30)	16 (6)	108 (67)
Watch-and-wait approach, n (%)	2 (0.5)	2 (1)	0
Patient refused, n (%)	1 (0.5)	1 (1)	0
Consolidation with allogeneic stem-cell transplant, n[a]	2	1	1
Unknown, n (%)	23 (6)	22 (8)	1 (1)

Abbreviation: AZT-IFN, zidovudine-interferon alfa.
[a]Patients in this section are not included into the total number (N) of patients.

TABLE 3. Response Rates in Patients With Adult T-Cell Leukemia/Lymphoma According to Treatment Regimen

Treatment	Response Rate, n (%)				
	OR	CR	PR	SD	PD
AZT-IFN alone (n = 20)					
First-line (n = 17)	12 (71)	7 (42)	5 (29)	0 (0)	5 (29)
Acute (n = 8)	5 (63)	2 (24)	3 (38)	0 (0)	3 (38)
Lymphomatous (n = 8)	6 (75)	4 (50)	2 (25)	0 (0)	2 (25)
Chronic (n = 1)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Second-line (n = 3)	2 (67)	1 (33)	1 (33)	1 (33)	0 (0)
Acute (n = 1)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Lymphomatous (n = 1)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Chronic (n = 1)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Multiagent chemotherapy alone (n = 187)					
First-line (n = 154)	50 (32)	33 (21)	17 (11)	25 (16)	79 (52)
Acute (n = 38)	8 (21)	3 (8)	5 (13)	9 (24)	21 (55)
Lymphomatous (n = 94)	39 (41)	27 (29)	12 (12)	9 (9)	46 (50)
Chronic (n = 21)	2 (10)	2 (10)	0	7 (33)	12 (57)
Unknown (n = 1)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Second-line (n = 33)	3 (9)	2 (6)	1 (3)	6 (18)	24 (73)
Acute (n = 6)	1 (17)	1 (17)	0 (0)	2 (33)	3 (50)
Lymphomatous (n = 20)	1 (5)	0 (0)	1 (5)	2 (10)	17 (85)
Chronic (n = 6)	0 (0)	0 (0)	0 (0)	2 (33)	4 (67)
Unknown (n = 1)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Combination chemotherapy and AZT-IFN (n = 24)					
First-line (n = 24)	16 (67)	4 (17)	12 (50)	3 (13)	5 (20)
Acute (n = 11)	6 (54)	3 (27)	3 (27)	2 (19)	3 (27)
Lymphomatous (n = 11)	8 (73)	1 (9)	7 (64)	1 (8)	2 (19)
Chronic (n = 1)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Smoldering (n = 1)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Single-agent chemotherapy and/or regional therapy (n = 17)					
First-line (n = 10)	1 (10)	0 (0)	1 (10)	4 (40)	5 (50)
Acute (n = 1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Lymphomatous (n = 5)	0 (0)	0 (0)	0 (0)	1 (20)	4 (80)
Chronic (n = 2)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
Smoldering (n = 2)	1 (50)	0 (0)	1 (50)	1 (50)	0 (0)
Second-line (n = 7)	0 (0)	0 (0)	0 (0)	4 (57)	3 (43)
Acute (n = 3)	0 (0)	0 (0)	0 (0)	1 (33)	2 (67)
Lymphomatous (n = 3)	0 (0)	0 (0)	0 (0)	2 (67)	1 (33)
Chronic (n = 1)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
First chemotherapy line[a]					
CHOP or CHOP-like regimen (n = 117)	34 (29)	14 (12)	20 (17)	18 (15)	65 (56)
CHOEP (n = 40)	24 (60)	17 (42)	7 (18)	3 (7)	13 (33)
LSG-15 (n = 4)	0 (0)	0 (0)	0 (0)	2 (50)	2 (50)
HyperCVAD (n = 4)	1 (25)	1 (25)	0 (0)	2 (50)	1 (25)
ABVD (n = 2)	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)
DA-EPOCH (n = 2)	1 (50)	0 (0)	1 (50)	0 (0)	1 (50)

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TABLE 3. Response Rates in Patients With Adult T-Cell Leukemia/Lymphoma According to Treatment Regimen (Continued)

Treatment	Response Rate, n (%)				
	OR	CR	PR	SD	PD
MTX (n = 2)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
ESHAP (n = 1)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
GDP (n = 1)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Flu (n = 2)	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)
Cy (n = 6)	1 (16)	1 (16)	0 (0)	1 (16)	4 (68)
Flu/Cy (n = 1)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AZT-IFN, zidovudine-interferon alfa; CHOEP, etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; Cy, cyclophosphamide; DA-EPOCH, dose-adjusted etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; Flu, fludarabine; GDP, gemcitabine, dexamethasone, and cisplatin; HyperCVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternated with high-dose cytarabine and methotrexate; LSG-15 (VCAP-AP-VECP), VCAP—vincristine, cyclophosphamide, doxorubicin, and prednisone; AP—doxorubicin and prednisone; VECP—vincristine, etoposide, carboplatin, and prednisone; MTX, methotrexate; OR, overall response; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Chemotherapy or agent was given as first-line up front alone or in combination with AZT-IFN.

DISCUSSION

To our knowledge, this study is the first international, multi-institutional study evaluating the epidemiology, diagnosis, therapy approaches, and outcomes of patients with HTLV-1–related ATLL encountered in different Latin American countries over the past 25 years. In this study, Latin American patients with ATLL were predominantly women and were diagnosed at a younger age (median 57 years, range 18-95), which is in line with previous Latin American and US reports describing that Hispanic and Afro-Caribbean patients are diagnosed approximately a decade younger than Japanese patients.[5,7,18-22]

HTLV-1 is commonly found in indigenous peoples of the Pacific Islands (Australia and Melanesia) and the Americas.[23-27] In Latin America, there are more than 400 indigenous groups, ranging from 45 to 50 million individuals.[28-30] The 2020 International Work Group for Indigenous Affairs reported Bolivia as the country housing the largest indigenous population in Latin America (48% of the population), followed by Guatemala (43.8%), Mexico (21.5%), Chile (12.8%), and Peru (12.5%).[28] In countries such as Venezuela, Paraguay, Brazil, El Salvador, and Uruguay, indigenous people comprise < 3% of the population.[28-30] Besides Brazil, HTLV-1 infection is predominantly presented in indigenous people living in the Andes of Peru (Quechua and Aymara), Chile (Mapuche and Rapa Nui), and Colombia (Paez); in the Peruvian Amazon (Shipibo-Konibo); and in the Chaco region (Qulla and Puná of northwestern Argentina).[3,26,27] The prevalence of HTLV-1 infection in countries of Central America and Mexico is poorly known; however, it is estimated to be low on the basis of few studies performed in blood donors.[25-27,31]

In our study, ATLL cases were primarily encountered in Peru, encompassing 63% of the studied patients. Chile, Argentina, and Colombia also reported numerous cases, most of them in indigenous people living in areas close to the mountains and where the virus has been reported as endemic. Participating centers from Bolivia, Ecuador, Mexico, and Paraguay reported very few cases, whereas centers from Venezuela, Uruguay, and Guatemala did not report any cases during the past 2 decades. Possible explanations to our findings are as follows: (1) some participating centers in this study are located far from known HTLV-1 endemic areas, which might have yielded to underreporting the number of ATLL cases; however, all participating centers are referral cancer centers in their countries, with ATLL as a common motive for referral; and (2) limited resources and lack of standardized protocols for HTLV testing in Latin America (countries particularly known for having large indigenous population such as Bolivia, Ecuador, and Mexico had screening rates of HTLV-1/2 in blood donors of 0%, 8%, and 0%, respectively, during 2016-2017).[31] Although our findings seem to correlate with what is known regarding the geographical distribution of HTLV-1 infection in Latin America, there is an unmet need to better understanding the current incidence and prevalence of HTLV-1 infection in this region of the world. Brazil, a known highly endemic country for HTLV-1 infection, was not included in this study because of its recent incorporation to the Grupo de Estudio Latinoamericano de Linfoproliferativos; nonetheless, data of ATLL in Brazil are well-established, whereas these same data are lacking in other Latin American countries.[32-35]

In our cohort, lymphomatous (50%) ATLL was most commonly encountered compared with acute (33%) ATLL. This finding correlates with what has been previously described in other Latin American and US studies[5,20,36] but is dissimilar to Japanese and some other US cohorts where acute ATLL was the most common subtype.[7,21,22] We

TABLE 4. Clinical Characteristics, Therapy Approach, and Outcome of Patients With Adult T-Cell Leukemia/Lymphoma Who Achieved First Complete Remission

Patient Code	ATLL Subtype	High LDH	Hypercalcemia	Organ Involvement	WBC/ALC[a]	IPI/PIT	Regimen	Overall Outcome	PFS (months)
ATLL3	Acute	Yes	Yes	CNS	35/24.5	High-intermediate/high-intermediate	CHOEP plus IT chemotherapy	Deceased	7.0
ATLL15	Chronic	No	No	Skin	17.8/14	Low/unknown	AZT-IFN	Alive	50.7
ATLL18	Lymphomatous	Yes	No	Bone, hepatic	5.2/0.7	High/high	CHOEP	Alive	9.1
ATLL20	Lymphomatous	No	No	—	16/2.6	High-intermediate/high-intermediate	CHOEP × 6 cycles, then salvage therapy with DHAP followed by allo-HSCT	Deceased	First-line → 8.1; Second-line → 12
ATLL24	Lymphomatous	Yes	Yes	Hepatic, BM, parotid, skin	8/2.3	High-intermediate/high-intermediate	Hyper-CVAD	Alive	8.0
ATLL30	Acute	Yes	Yes	Hepatic, lung, skin, PB	5/1	High/high	ABVD	Deceased	2.0
ATLL40	Acute	No	No	CNS, skin	141/102	High-intermediate/high-intermediate	CHOP plus IT chemotherapy followed by AZT-IFN maintenance	Alive	30.4
ATLL67	Lymphomatous	Yes	Yes	GI	10.2/2.4	High-intermediate/high-intermediate	CHOP	Deceased	Unknown
ATLL68	Lymphomatous	No	No	—	7/3.5	Low-intermediate/low-intermediate	CHOP followed by AZT-IFN maintenance	Deceased	Unknown
ATLL79	Acute	Yes	Yes	BM, skin	287/191	High/high	CHOP followed by AZT-IFN maintenance	Alive	12.1
ATLL83	Lymphomatous	Yes	Yes	BM	1.9/0.5	Low-intermediate/high	CHOEP	Alive	12.3
ATLL88	Lymphomatous	Yes	Yes	—	13.8/2.8	Low-intermediate/high	CHOEP	Alive	5.2
ATLL110	Chronic	Yes	No	Skin	10.4/4.2	Low-intermediate/high	CHOEP	Alive	25.4
ATLL120	Acute	Yes	No	BM	164/131	High/high	AZT-IFN	Alive[b]	6.4
ATLL127	Acute	Yes	No	BM	3.9/3.5	High-intermediate/high	AZT-IFN	Alive[b]	0.9
ATLL138	Lymphomatous	Yes	No	—	6.9/1.6	High-intermediate/high	CHOP	Alive	44.1
ATLL151	Chronic	Yes	No	Hepatic, lung	12.4/4.9	High-intermediate/high	CHOEP	Deceased	19.6
ATLL171	Lymphomatous	Yes	Yes	—	6.4/1.5	Low/high-intermediate	CHOP	Alive[b]	30.5
ATLL189	Lymphomatous	No	No	—	5/2	Low/low	CHOP	Alive	181.6
ATLL194	Acute	Yes	Unknown	BM	296/—	High/high	Fludarabine plus cyclophosphamide	Deceased	2.8
ATLL196	Lymphomatous	No	Unknown	Skin	6.3/1.7	High-intermediate/high-intermediate	CHOP	Alive	39.4
ATLL197	Lymphomatous	Yes	Unknown	—	5.5/—	Low-intermediate/low-intermediate	CHOP	Deceased	14.9
ATLL198	Lymphomatous	Yes	Unknown	—	Unknown	High-intermediate/high-intermediate	CHOP	Alive	32.6
ATLL201	Lymphomatous	No	No	Bone, BM	6.9/1.1	High-intermediate/high-intermediate	CHOP	Deceased	67.1
ATLL202	Lymphomatous	Yes	Unknown	GI	16.9/0.8	High-intermediate/low-intermediate	CHOP	Alive	21.2
ATLL203	Lymphomatous	Yes	Unknown	BM, skin	1.1/0.8	High/high	AZT-IFN	Deceased	5.3
ATLL204	Lymphomatous	Yes	Unknown	—	45.3/—	Low-intermediate/low-intermediate	CHOP × 2 cycles, progressed, then ESHAP	Deceased	8.1
ATLL207	Lymphomatous	No	Unknown	BM, skin	4.8/1.8	Low-intermediate/low-intermediate	AZT-IFN plus phototherapy	Deceased	17.7
ATLL210	Lymphomatous	Yes	Unknown	—	14.4/1.2	High-intermediate/high-intermediate	CHOEP	Deceased	10.0

(Continued on following page)

TABLE 4. Clinical Characteristics, Therapy Approach, and Outcome of Patients With Adult T-Cell Leukemia/Lymphoma Who Achieved First Complete Remission (Continued)

Patient Code	ATLL Subtype	High LDH	Hypercalcemia	Organ Involvement	WBC/ ALC[a]	IPI/PIT	Regimen	Overall Outcome	PFS (months)
ATLL211	Lymphomatous	Yes	No	Skin	7.7/3.8	High/high-intermediate	CHOEP	Deceased	35.6
ATLL212	Lymphomatous	No	No	Skin	9.7/3.6	Low/low-intermediate	AZT-IFN followed by allo-HSCT	Alive	17
ATLL214	Lymphomatous	Yes	No	—	2.4/0.5	Low-intermediate/ high-intermediate	CHOP	Deceased	6.7
ATLL216	Lymphomatous	Yes	No	—	7.8/0.8	High-intermediate/ high-intermediate	CHOEP	Alive	31.3
ATLL217	Lymphomatous	No	Unknown	Skin	9.9/2.3	Low/low	CHOEP	Alive	51.9
ATLL221	Lymphomatous	No	Unknown	Bone, BM	12.8/4.2	Low-intermediate/low-intermediate	ABVD	Alive	13.8
ATLL226	Lymphomatous	No	No	CNS, BM	7.8/2.9	High-intermediate/ high-intermediate	CHOEP plus IT chemotherapy	Alive	5.2
ATLL227	Acute	Yes	Unknown	BM	31/14	High/high	CHOEP followed by AZT-IFN maintenance	Deceased	10.7
ATLL229	Lymphomatous	No	Unknown	—	5.9/1.6	Low/low	CHOEP	Alive	12.1
ATLL230	Lymphomatous	No	No	Skin	8.3/3.5	Low-intermediate/low-intermediate	CHOEP	Alive	15.9
ATLL232	Lymphomatous	No	Unknown	—	Unknown	Low/low	CHOEP	Deceased	19.4
ATLL234	Lymphomatous	Yes	No	Lung	4.5/1.6	High/high-intermediate	CHOP	Deceased	3.6
ATLL235	Lymphomatous	Yes	No	—	9.8/2.8	High/high	CHOEP	Alive	23.8
ATLL238	Lymphomatous	Unknown	Unknown	Skin	Unknown	Low/low	Tenofovir plus interferon alfa	Alive[b]	77.2

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ALC, absolute lymphocyte count; Allo-HSCT, allogeneic hematopoietic stem-cell transplant; ATLL, adult T-cell leukemia/lymphoma; AZT-IFN, zidovudine-interferon alfa; BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP, etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone; DHAP, dexamethasone, cytarabine, and cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; HyperCVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternated with high-dose cytarabine and methotrexate; IPI, International Prognostic Index; IT, intrathecal; LDH, lactate dehydrogenase; PB, peripheral blood; PIT, Prognostic Index for Peripheral T-Cell Lymphoma; PFS, progression-free survival.

[a]Unit for WBC and ALC is $\times 10^9$ cells.

[b]Lost to follow-up.

acknowledge that our patients were classified using archived records, therefore representing a potential risk for biases. However, there was a distinction between the acute and lymphomatous groups in our cohort, including higher rates of hypercalcemia and poorer outcomes in patients with acute ATLL. The 1-year OS rates of 24% for acute ATLL compared with 44% for lymphomatous ATLL ($P < .001$) are consistent with the natural history of ATLL (Fig 2B). A relative poorer survival has been reported in Hispanic and Afro-Caribbean patients as opposed to Japanese patients.[5,7,20-22,36] Although limited health care access in Latin American countries could ultimately influence patient outcome, our clinical findings suggest that Latin American patients with ATLL present with more aggressive clinical course than Japanese patients. Furthermore, a recent study reported that North American ATLL (mostly composed of patients of Caribbean descent) has a distinct genomic landscape with a high frequency of prognostic epigenetic mutations affecting p53 function and is consequently associated to chemorefractoriness.[37] This could potentially explain the differences in aggressiveness seen in American and Caribbean ATLL populations compared with Japanese population, despite sharing the same HTLV-1 serotype.

In this study, patients with acute ATLL who received first-line AZT-IFN either alone (n = 16) or in combination with chemotherapy (n = 22) had a tendency toward higher ORR (AZT-IFN alone: ORR 63% [CR 24%]; AZT-IFN combination: ORR 54% [CR 27%]) as compared with those treated with first-line multiagent chemotherapy (n = 132; ORR 21% [CR 8%]). This finding is in line with previous meta-analysis where patients with aggressive ATLL had an ORR of 66% and a CR of 35%.[38] Importantly, patients with acute ATLL who achieved CR after AZT-IFN had a longer PFS as compared with those who achieved CR after chemotherapy alone (30.4 months *v* 2.8 months, respectively) as only three of 38 acute type patients achieved CR after chemotherapy (Appendix Fig A1C). Previous studies have reported this positive outcome, suggesting that AZT-IFN is a good first-line option to attempt for patients with leukemic ATLL.[5,38] Although not formally studied in this cohort, a common disease feature we saw in responders to AZT-IFN was lymph node size of ≤ 3 cm in

patients with acute ATLL and mass ≤ 3.5 cm, suggesting that this therapy may only be effective in ATLL presenting with nonbulky disease. Despite the long-term responses seen with AZT-IFN, most patients will eventually experience disease progression, which confirms this therapy is suppressive but not curative, reason why patients in clinical remission should be evaluated for stem-cell transplantation or remain on maintenance therapy indefinitely, if deemed unfit for transplantation.[5,15,38]

In lymphomatous ATLL, although response rates were low in patients treated with first-line multiagent chemotherapy (ORR 41% and CR 29%), superior outcomes were observed in those who achieved a CR compared with first-line AZT-IFN (67.1 months *v* 17.7 months, respectively). However, this was not statistically significant because of the low number of patients treated (Appendix Fig A1D). This finding provides further evidence that chemotherapy should remain the standard first-line treatment of this subtype, as was observed in previous studies.[5,16,38] In this study, CHOEP regimen (n = 40) yielded higher response rates compared with CHOP or CHOP-like regimen (n = 117) (ORR 60%, CR 42% *v* ORR 29%, CR 12%, respectively; $P < .001$). Only four patients received the modified intensive regimen vincristine, cyclophosphamide, doxorubicin, and prednisone-doxorubicin and prednisone-vincristine, etoposide, carboplatin, and prednisone (known as LSG-15 regimen, vincristine, cyclophosphamide, doxorubicin, and prednisone-doxorubicin, ranimustine and prednisone-vincristine, etoposide, carboplatin, and prednisone), of whom two had SD and the other two PD. A previous study found no difference in outcomes between the above regimens, but this could have been related to the small sample size in the study.[5] Therefore, it would be reasonable to use CHOEP, or a similar regimen, in patients with aggressive ATLL who are good candidates for high-dose chemotherapy and allo-HSCT. In our study, only two patients with lymphomatous ATLL underwent allo-HSCT, one as second line after achieving CR with dexamethasone, cytarabine, and cisplatin (PFS 12 months, died from relapsed disease) and the other after achieving CR with first-line AZT-IFN (remains disease-free, PFS 17 months).

Finally, this study not only provides a comprehensive assessment of this rare and generally incurable disease but also offers a better understanding on the limitations the different participating institutions face during the initial and subsequent evaluation of patients with ATLL in Latin America. We identified disparities among countries in the following: (1) sophisticated imaging such as positron emission tomography and magnetic resonance imaging almost universally lacked in public or governmental institutions; (2) biologic agents (eg, interferon alfa-2b, mogamulizumab, and alemtuzumab) were not readily available for the management of ATLL in most Latin American countries, and if available, the cost was borne by the patient, which makes its use almost impossible; and (3) there was limited access to clinical trials for ATLL in Latin American countries (only two countries had mogamulizumab as a therapy option under a clinical trial in the past 25 years).

In conclusion, ATLL continues to carry a dismal outcome with conventional therapies, urging the development of novel approaches. Our study found that in Latin America, patients present at a younger age, with female predominance, high incidence of lymphomatous type, low incidence of indolent types, and worse survival rates as compared with previously reported Japanese patients. AZT-IFN produced durable responses in patients with acute ATLL who achieved CR as compared with chemotherapy alone. On the other hand, chemotherapy responses, especially after CHOEP, were more durable in lymphomatous type patients who achieved CR than the acute type. Our findings suggest that in the management of aggressive ATLL, chemotherapy remains the preferred first-line choice for lymphomatous type favoring the etoposide-based regimen CHOEP, whereas AZT-IFN is a good option to attempt for acute type up front, with consideration of allo-HSCT in those patients who achieve a good response to therapy. Further characterization of Latin American ATLL through genomic analysis is planned.

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APPENDIX

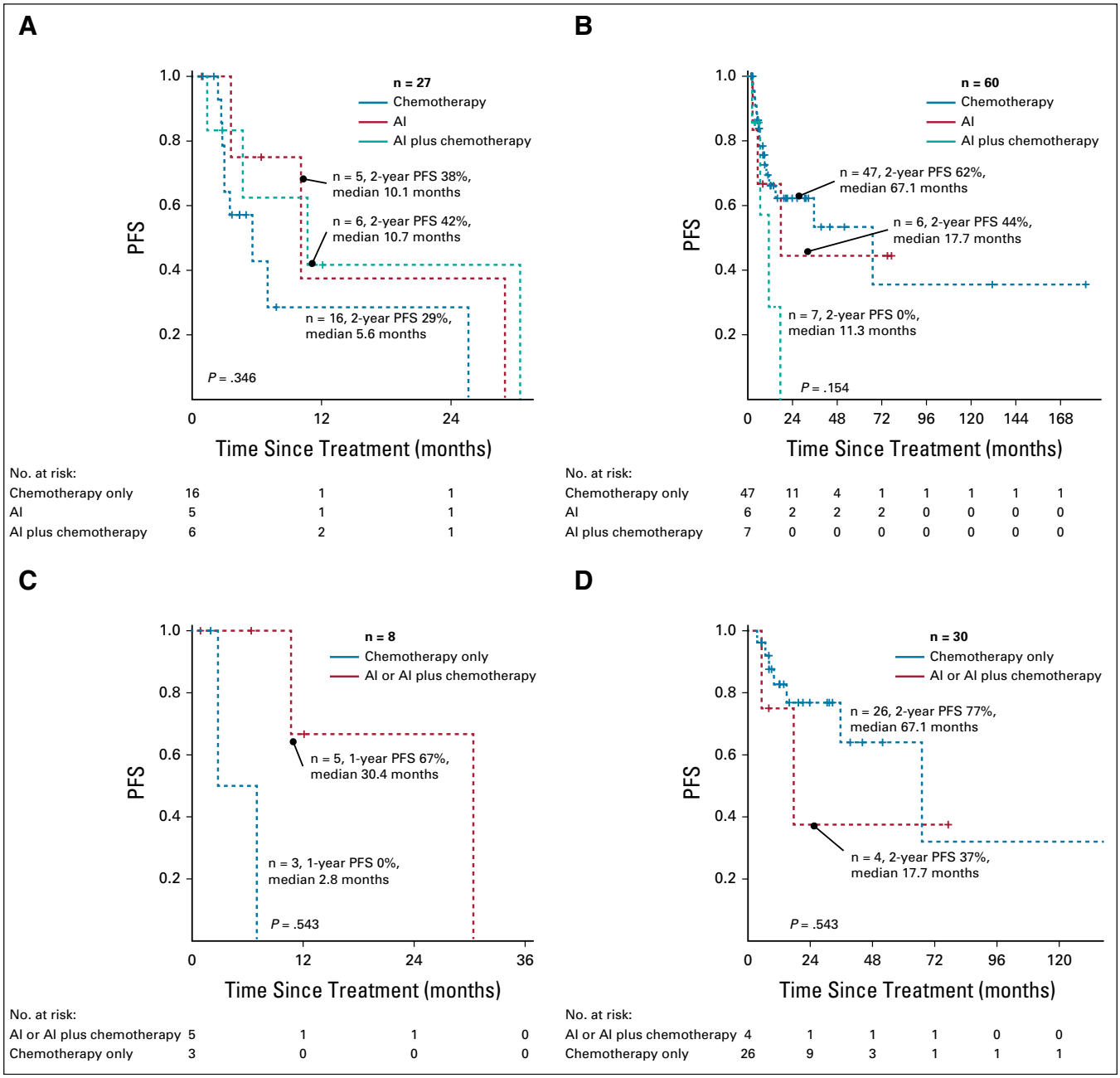

FIG A1. PFS of patients with aggressive ATLL after first-line therapy according to clinical subtype and treatment approach: (A) acute ATLL, (B) lymphomatous ATLL, (C) acute ATLL after CR, and (D) lymphomatous ATLL after CR. AI, AZT (zidovudine) with Interferon alpha 2b; ATLL, adult T-cell leukemia/lymphoma; CR, complete response; PFS, progression-free survival.

TABLE A1. Latin American Hospitals With Expertise in Cancer Services Participating in Adult T-Cell Leukemia/Lymphoma Database Query[a]

Country	City	Hospital Name	Affiliations	Query Date Range
Argentina	La Plata	Hospital Italiano La Plata	Universidad Nacional de La Plata	2000-2020
	Buenos Aires	Hospital Municipal Emilio Ferreyra	None	2000-2020
	Buenos Aires	Instituto de Investigaciones Biomédicas en Retrovirus y SIDA	Universidad de Buenos Aires	2000-2020
	Córdoba	Hospital Privado Universitario de Córdoba	Universidad Católica de Córdoba	2000-2020
Bolivia	La Paz	Hospital de Clinicas La Paz	Universidad Mayor de San Andres	2015-2020
	La Paz	Centro Medico Curare	None	1995-2020
	La Paz	Caja Nacional de Salud	Governmental National Health Center	2010-2020
Chile	Santiago de Chile	Hospital del Salvador	Universidad de Chile	2000-2020
Colombia	Cali, Valle del Cauca	Hospital Universitario del Valle	Universidad del Valle	2000-2020
Ecuador	Guayaquil	Hospital SOLCA	Instituto Oncológico Nacional Dr Juan Tanca Marengo, Sociedad de Lucha Contra el Cáncer del Ecuador	2000-2020
	Quito	Hospital de los Valles	Universidad San Francisco de Quito	2000-2020
Guatemala	Guatemala City	Instituto de Cancerología Hospital "Dr. Bernardo del Valle S." (INCAN)	Liga Nacional Contra el Cancer	2000-2020
Mexico	Mexico City	Instituto Nacional de Cancerologia	Universidad Nacional Autónoma de México	2000-2020
	Hermosillo, Sonora	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado de Sonora	Universidad del Valle de México, Campus Hermosillo, Sonora	2000-2020
Paraguay	Asuncion	Hospital Central Instituto de Previsión Social	Universidad Católica Nuestra Señora de la Asunción, Universidad del Norte	2000-2020
Peru	Lima	Hospital Nacional Edgardo Rebagliati Martins	Governmental National Health Center, Universidad de San Marin de Porres, Universidad Nacional Mayor de San Marcos	1995-2020
	Lima	Instituto Nacional de Enfermedades Neoplasicas	Governmental National Health Center, Universidad Cayetano Heredia, Universidad Nacional Mayor de San Marcos	1995-2020
	Lima	Hospital Nacional Guillermo Almenara	Universidad San Martin de Porres, Universidad Nacional Mayor de San Marcos	2000-2020
Uruguay	Montevideo	Hospital de Clinicas	Universidad de la Republica	2010-2020
Venezuela	Caracas	Instituto de Oncologia y Hematología	Universidad Central de Venezuela	2000-2020

[a]Hospitals offer transplant services in-house unless specified. Keywords used for data collection were standardized throughout all hospitals: adult T-cell leukemia lymphoma, leucemia/linfoma de celulas T del adulto, ATL, ATLL, and HTLV-1–associated T-cell lymphoma.

TABLE A2. Clinical Features and Outcome of Patients Diagnosed With ATLL and CNS Involvement (n = 11)

Patient Code	ATLL Subtype	Age/ Sex	High LDH	Hypercalcemia	WBC/ALC[a]	IPI/PIT	Diagnosis of CNS Involvement	Treatment	Overall Outcome
ATLL3	Acute	45/ F	Yes	Yes	35/24.5	High-intermediate/ high-intermediate	Positive CSF	CHOEP plus IT chemotherapy and with CR. Relapsed in CNS, received high-dose MTX alternating with high-dose cytarabine but progressed within 1 month	Deceased, PFS 7 months
ATLL25	Lymphomatous	31/ M	Yes	Yes	8.2/1.6	Low-intermediate/ high-intermediate	Positive CSF	CHOP plus IT chemotherapy with SD	Deceased, PFS 3 months
ATLL33	Lymphomatous	23/ M	No	Unknown	Unknown/ 0.4	High-intermediate/ high-intermediate	Positive CSF	LSG-15 plus IT chemotherapy with SD	Alive, PFS 2 months
ATLL38	Acute	65/ F	Yes	Yes	35.3/5.8	High/high	Positive CSF	AZT-IFN plus IT chemotherapy with PR. Relapses in CNS	Deceased, PFS 29 months
ATLL40	Acute	58/ F	Yes	No	141/102	High-intermediate/ high-intermediate	Positive CSF	CHOP plus IT chemotherapy followed by AZT-IFN maintenance with CR. Relapsed in CNS	Alive, PFS 30.4 months
ATLL41	Lymphomatous	58/ F	No	No	12.3/2.4	High-intermediate/ low-intermediate	Positive CSF	CHOP plus IT chemotherapy with PR. Relapsed in CNS	Deceased, PFS 4 months
ATLL60	Acute	47/ F	Yes	Yes	118/82.6	High-intermediate/ high-intermediate	Positive CSF	CHOP plus IT chemotherapy concurrent with AZT-IFN with PD	Deceased
ATLL62	Acute	59/ F	Yes	No	8.9/4.1	High-intermediate/ high-intermediate	Positive CSF	CHOP plus IT chemotherapy concurrent with AZT-IFN with CR. Relapsed in CNS	Deceased, PFS 17.4 months
ATLL78	Acute	27/ F	Yes	Yes	42.2/21.5	High/high	Presenting with headache, MRI with leptomeningeal disease, positive CSF	AZT-IFN plus IT chemotherapy with SD	Deceased, PFS 2.8 months
ATLL104	Acute	43/ M	Yes	No	4.8/0.7	High/high	Positive CSF	CHOEP plus IT chemotherapy with SD	Lost to follow-up, PFS 4.4 months
ATLL226	Lymphomatous	43/ F	No	No	7.8/2.9	High-intermediate/ high-intermediate	Positive CSF	CHOEP plus IT chemotherapy with CR	Alive, PFS 5.2 months

Abbreviations: ALC, absolute lymphocyte count; ATLL, adult T-cell leukemia/lymphoma; AZT-IFN, zidovudine-interferon alfa; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP, etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone; CR, complete response; IPI, International Prognostic Index; IT, intrathecal; LDH, lactate dehydrogenase; LSG-15 (VCAP-AP-VECP), VCAP: vincristine, cyclophosphamide, doxorubicin, and prednisone; AP: doxorubicin and prednisone; VECP: vincristine, etoposide, carboplatin, and prednisone; MRI, magnetic resonance imaging; MTX, methotrexate; PD, progressive disease; PFS, progression-free survival; PIT, Prognostic Index for Peripheral T-Cell Lymphoma; PR, partial response; SD, stable disease.

[a]Unit for WBC and ALC is $\times 10^9$ cells.

