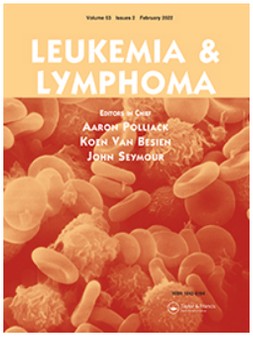

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ORIGINAL ARTICLE

An international, multicenter, retrospective study on the positive impact of cutaneous involvement on the clinical outcome of adult T-cell leukemia/lymphoma

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ABSTRACT

Adult T-cell leukemia/lymphoma (ATLL) is a largely incurable disease. Cutaneous involvement is common and could be first symptom of the disease. We analyzed 169 patients with ATLL of whom 63 had cutaneous involvement. Cutaneous involvement was found in 48, 27, 17, and 60% of acute, lymphomatous, chronic and smoldering ATLL cases, respectively. Eight cases had primary cutaneous tumoral variant. Erythroderma (24%) and plaques (22%) were the most frequent skin lesions. The presence of cutaneous involvement was associated with better overall survival compared to non-cutaneous involvement (aHR 0.55 [95% CI: 0.37–0.82], $p < 0.01$; 1-year OS 53 vs. 27%, respectively, $p = 0.012$). Combination zidovudine and interferon-alpha (AZT-IFN) yielded high response rates (overall response, OR = 100%, $n = 8$; complete response 62.5%) compared to chemotherapy (OR = 33.3%, $n = 12/36$). In conclusion, cutaneous involvement was associated with better survival in Latin American patients with ATLL. AZT-IFN demonstrated encouraging responses in ATLL patients with cutaneous involvement.

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Adult-T cell leukemia/lymphoma; ATLL; skin lymphoma; HTLV-1; interferon alpha; Latin America

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]. 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 [3,5].

Skin manifestations are frequent in HTLV-1 infection. ATLL affects the skin in 39 to 72% of cases and could be the first symptom of the disease [4,6,7]. Skin manifestations of ATLL vary and may consist of macules (or patches), plaques, multiple papules, tumoral nodules, erythroderma, or mixed lesions [6–9]. Most recently, primary cutaneous tumoral (PCT) has been recognized as a separate ATLL variant with unique clinical and prognostic features [10].

To date, data on the impact of cutaneous involvement on the clinical outcome of ATLL are limited [5,8,11–13]. Aside from Brazil, no data from other Latin American countries where HTLV-1 infection is known to be endemic exist [3]. Therefore, we performed a

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Supplemental data for this article can be accessed here.

retrospective review of ATLL cases diagnosed in four Latin American countries over the last 25 years. We analyzed the epidemiology, clinical features, treatment, and disease outcome of ATLL patients with cutaneous involvement and compared them to ATLL patients without cutaneous involvement.

Methods

Patients

We conducted a retrospective analysis of patients diagnosed with ATLL between January 1995 and December 2019. Six centers from four Latin American countries (Argentina, Chile, Colombia, and Peru) participated in the ATLL database query (Supplemental Table 1). We designed two cohorts: the first, ATLL patients with cutaneous involvement, and the second, matched cases without cutaneous involvement. Patient demographics and clinical data were obtained from available medical records. This study was approved by the Institutional Review Board at each participating institution.

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 (70%), but not in some due to availability or high cost. In all cases, identification of clonal CD4 + CD7 − CD25+/− T-cells in peripheral blood or tissues was determined by histology, immunophenotyping, and gene rearrangement studies. Patients were classified according to the Shimoyama criteria into acute, lymphomatous, chronic, and smoldering ATLL [14]. Patients with aggressive ATLL had at least one of the typical disease features, including blood-circulating pathognomonic flower-like cells with convoluted nuclei, elevated serum lactate dehydrogenase (LDH), generalized lymphadenopathy, hepatosplenomegaly, multi-visceral involvement, cutaneous lesions, and hypercalcemia. Patients with lymphoma features and absolute lymphocyte count (ALC) $<4 \times 10^9$/L were classified as lymphomatous type. Patients were classified as smoldering and chronic subtypes when presenting circulating ATLL cells (ALC $<4 \times 10^9$/L, or $\geq 4 \times 10^9$/L, respectively), normal or mildly elevated serum LDH (<1.5 or <2 times the upper limit of normal, respectively), and involvement of lung, skin, or liver (in chronic only), but no other extranodal sites and no hypercalcemia. Two indexes were utilized for risk stratification in aggressive ATLL: The International Prognostic Index (IPI) and the Prognostic Index for Peripheral T-cell Lymphoma (PIT) [15,16].

Skin assessment

We defined the different types of skin lesion as follow: patches as non-infiltrating erythema; plaque as infiltrating erythema; multipapular as multiple infiltrated papules with less than 1 cm in diameter that may be confluent forming large infiltrated papules; tumoral nodule as infiltrated elevated lesions with more than 1 cm in diameter; erythroderma as generalized erythema involving more than 80% of the body surface area; and mixed-lesions as two or more predominant skin lesions (Figure 1) [7,8]. The PCT ATLL variant was classified according to the 2019 International Revised ATLL Consensus [10]. PCT is characterized by tumoral nodule skin involvement as the sole manifestation of the disease, normal serum LDH and calcium levels in the absence of lymphocytosis. In most cases (74%), input from an expert dermatologist was needed to define the type of skin lesions.

Therapy approaches

The frontline therapy approaches were classified as follows: (1) AZT-IFN alone, (2) multiagent chemotherapy alone, (3) combined chemotherapy with AZT-IFN, and (4) single-agent chemotherapy and/or regional therapy (i.e. topical therapy, phototherapy) (Supplemental Table 2). The centers that used parenteral AZT/IFN had a comparable therapy protocol based on previously published data: high-dose AZT (1.5 g or 750 mg/m^2, twice daily) and interferon-alfa-2b (IFN; 5-10 million units twice daily) were used intravenously during the induction period and on an inpatient basis [17]. Patients who responded continued to receive oral AZT 600 mg twice daily and subcutaneous IFN 5 million units once or twice daily as outpatient. For those with prolonged clinical responses, drugs were eventually tapered down to as low as AZT 300 mg twice daily and subcutaneous IFN 3 million units three times weekly as maintenance therapy. In general, the chemotherapy regimens used at any time included cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP)–like regimens; etoposide-based regimens (e.g. CHOEP, EPOCH), platinum-based regimens, other non–platinum-based regimens, single-agent chemotherapy, and allogeneic hematopoietic stem cell transplantation (allo-HSCT).

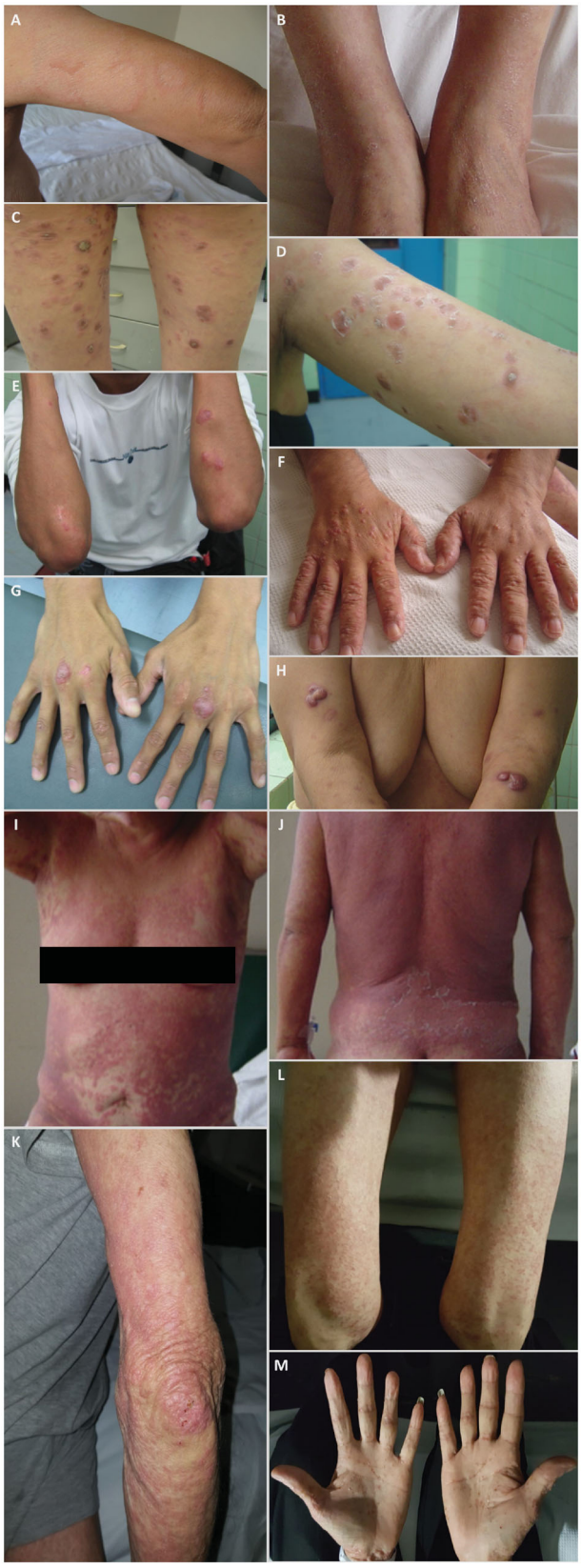

Figure 1. Types of ATLL skin lesions: patch-type (A, B); plaque-type (C,D); multipapular-type (F); tumoral nodule-type (E,G,H); erythrodermic-type (I, J); and mixed-lesions (K,L,M).

Regimens were selected by the treating physician based on ATLL subtype and according to local institutional practices.

Response criteria

Therapy responses were assessed according to the 2009 consensus report for ATLL [18]. The Cheson criteria were used to evaluate response through computerized tomography imaging [19]. Complete response (CR) required a decrease in the ALC to $<4 \times 10^9$/L with $<5\%$ of flower-like cells remaining along with 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 ALC $>4 \times 10^9$/L at any time, and/or $\geq 50\%$ increase in size of any nodal or extranodal lesions. Stable disease (SD) was defined as failure to attain CR/PR in the absence of PD. Responses (CR, PR, and SD) should persist for at least four weeks to be classified as such.

Statistical analysis

Demographics, clinical features, and therapies received were summarized using descriptive statistics. The primary study outcome were treatment response and overall survival (OS). OS was defined as the elapsed time from diagnosis until death from any cause. Alive patients were censored at last follow-up in clinic or by telephone. The median follow-up was estimated with the reverse Kaplan-Meier method. We fit a multivariate cox regression model to evaluate the effect of cutaneous involvement on mortality. Different clinical variables (i.e. age <65 years, gender, performance status, presence of B symptoms, hypercalcemia, extranodal involvement >1, serum albumin <3.5 g/dL, serum LDH level, IPI and PIT scores) were used in the univariate analysis. However, only the variables that were statistical significant in the univariate analysis were included in our final model (i.e. B symptoms, hypercalcemia, serum albumin <3.5 g/dL, and the IPI score). We repeated our analyses for individuals with only cutaneous involvement to evaluate the effect of the type of skin lesion on mortality, controlling for the abovementioned predictors. We report our analysis with Hazard Ratios (HRs) and a 95% confidence interval. All the predictors and the overall model met the hazard assumption (p-value for global test: 0.170).

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. *p*-Values lower than 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 23.

Results

Epidemiological and clinical features

A total of 169 patients with ATLL were identified between January 1995 and December 2019. Demographic and clinical features of ATLL patients are shown in Table 1. Overall, the majority ($n = 138$, 81%) had aggressive ATLL (lymphomatous $n = 84$, 50%; acute $n = 54$, 31%), and 23 (14%) had indolent ATLL (chronic $n = 18$, 11%; smoldering $n = 5$, 3%). Sixty-three (37%) cases had cutaneous involvement at the time of diagnosis, of whom 8 (5%) had PCT ATLL variant. The remaining ($n = 106$, 63%) did not have cutaneous involvement at the time of diagnosis. The median age at diagnosis was 57 years in both groups, with a female predominance (56%). Most ATLL patients were from Peru ($n = 125$, 74%) followed by Chile ($n = 24$, 14%), Colombia ($n = 12$, 7%), and Argentina ($n = 8$, 5%).

The clinical features of ATLL patients are summarized in Table 1. Cutaneous involvement was most frequently found in acute (48%, $n = 26/54$) ATLL subtype compared to lymphomatous (27%, $n = 23/84$) and chronic/smoldering (26%, $n = 6/23$) ($p < 0.001$). The most commonly observed skin lesions were erythroderma (24%), plaques (22%), tumoral nodules (19%), macules (18%), multiple papules (11%), and mixed lesions (6%). In both, patients with cutaneous and non-cutaneous involvement, advanced stage (stage III–IV 90 versus 89%, respectively; $p = 0.53$), presence of B symptoms (70 versus 75%, respectively; $p = 0.72$), and ECOG performance status ≥ 2 (41 versus 45%, respectively; $p = 0.44$) were not different at the time of diagnosis. However, extranodal involvement of more than one site was frequent in patients with cutaneous involvement (51 versus 18%; $p < 0.001$). Hypercalcemia (43% versus 42%, respectively; $p = 0.86$), elevated LDH (78 versus 88%, respectively; $p = 0.18$), and high-intermediate/high-risk IPI and PIT scores (IPI: 80 versus 67%, respectively; $p = 0.09$; PIT: 81% versus 93%, respectively; $p = 0.09$) were not significantly different among patients with cutaneous and non-cutaneous involvement.

Comorbid co-infections were more frequently seen in patients with cutaneous involvement (14%) compared to patients with non-cutaneous involvement (2%); however, this was not statistically significant ($p = 0.308$). Overall, patients had infective dermatitis ($n = 3$), *Pneumocystis jirovecii* pneumonia ($n = 3$), pulmonary tuberculosis ($n = 3$), and strongyloidiasis ($n = 2$). Two patients with cutaneous involvement were also diagnosed with HTLV-1-associated myelopathy/tropical spastic paraparesis ($n = 2$).

Patient outcomes

With a median follow up of 32 months (95% CI: 23–54), the median OS times were 4.4 months, 6.9 months, and 22.6 months for acute, lymphomatous, and chronic ATLL, and median not reached for smoldering and PCT ATLL variant, respectively. The 2-year OS rates were 7, 27, 43, 80, and 63%, respectively (Figure 2).

The presence of cutaneous involvement at the time of diagnosis was associated with better OS rates compared to non-cutaneous involvement (1-year OS: 53%, median 13.1 months versus 27%, median 5.6 months, respectively; $p = 0.01$) (Figure 3(A)). This finding was also factual for patients with acute (1-year OS: 40%, median 6.5 months versus 6%, median 2.9 months, respectively; $p < 0.001$) and lymphomatous (1-year OS: 55%, median 13.1 months versus 31%, median 6.8 months, respectively; $p = 0.002$) ATLL subtypes (Figure 3(B,C), respectively). Patients presenting with plaques and multiple papules skin lesions had better OS rates than with other skin lesions (1-year OS: 65%, median 13.9 months versus 41%, median 5.1 months, respectively; $p = 0.03$) (Supplemental Figure 1A and Supplemental Figure 2). This finding was again factual for patients with aggressive ATLL subtypes (Supplemental Figure 1(B,C)).

In the multivariate analysis, the presence of cutaneous involvement was an independent prognostic factor for improved survival compared to non-cutaneous involvement (aHR 0.55 [95% CI: 0.37–0.82], $p < 0.01$) (Table 2). The presence of B symptoms (aHR 1.78 [95% CI: 1.13–2.8], $p = 0.01$), hypercalcemia (aHR 1.59 [95% CI: 1.07–2.36], $p = 0.02$), and serum albumin less than 3.5 g/dL (aHR 1.56 [95% CI: 1.04–2.34], $p = 0.03$) were all associated with worse survival (Table 2). Among patients with aggressive ATLL and cutaneous involvement, the presence of hypercalcemia was an independent poor prognostic factor for survival (aHR 3.99 [95% CI: 1.39–11.45], $p = 0.01$) (Supplemental Figure 3). In the overall population, the IPI score was able to

Table 1. Clinical features of ATLL patients according to cutaneous involvement.

Category	Cutaneous involvement ($N = 63$)	No cutaneous involvement ($N = 106$)	Total ($N = 169$)	p-Value
Age, median years (range)	57 (18-95)	57 (20-91)	57 (18-95)	0.91
Gender, *n* (%)				0.424
Female	38 (60)	56 (53)	94 (56)	
Male	25 (40)	50 (47)	75 (44)	
Country, *n* (%)				
Argentina	5 (8)	3 (3)	8 (5)	
Chile	19 (30)	5 (5)	24 (14)	
Colombia	4 (6)	8 (8)	12 (7)	
Peru	35 (56)	90 (84)	125 (74)	
ATLL subtype, *n* (%)				<0.001
Acute	26 (41)	28 (26)	54 (31)	
Lymphomatous	23 (37)	61 (58)	84 (50)	
Chronic	3 (5)	15 (14)	18 (11)	
Smoldering	3 (5)	2 (2)	5 (3)	
PCT	8 (12)	–	8 (5)	
Type of skin lesion, *n* (%)[§]				
Macules	11 (18)	–	–	
Plaques	14 (22)	–	–	
Multiple papules	7 (11)	–	–	
Tumoral nodules	12 (19)	–	–	
Erythroderma	15 (24)	–	–	
Mixed lesions[+]	4 (6)	–	–	
Stage, *n* (%)[†]				0.532
I–II	5 (10)	10 (11)	15 (11)	
III–IV	44 (90)	79 (89)	123 (89)	
B symptoms, *n* (%)	44 (70)	79 (75)	123 (73)	0.718
Missing	1 (1)	0 (0)	1 (1)	
ECOG ≥ 2, *n* (%)	26 (41)	48 (45)	74 (44)	0.44
Missing	1 (1)	0 (0)		
Hypercalcemia, *n* (%)[†]	21 (43)	37 (42)	58 (34)	0.864
Missing	6 (12)	0 (0)		
LDH, *n* (%)				0.184
Normal	13 (21)	13 (12)	26 (15)	
Elevated	49 (78)	93 (88)	142 (84)	
Missing	1 (1)	–	1 (1)	
Extranodal involvement > 1, *n* (%)[*]	32 (51)	19 (18)	51 (30)	<0.001
Bone marrow[‡]	11 (17)	7 (7)	18 (11)	
Central nervous system	7 (11)	2 (2)	9 (5)	
Liver	5 (8)	5 (5)	10 (6)	
Lung	4 (6)	6 (6)	10 (6)	
Bone	1 (2)	6 (6)	7 (4)	
IPI score, *n* (%)[†]				0.086
Low risk	3 (6)	8 (9)	11 (8)	
Low-intermediate risk	7 (14)	21 (24)	28 (20)	
High-intermediate risk	18 (37)	32 (36)	50 (36)	
High risk	21 (43)	28 (31)	49 (36)	
PIT score, *n* (%)[†]				0.085
Low risk	3 (6)	2 (2)	5 (4)	
Low-intermediate risk	4 (8)	4 (5)	8 (6)	
High-intermediate risk	10 (20)	18 (20)	28 (20)	
High risk	30 (61)	65 (73)	95 (69)	
Missing	2 (4)	–	2 (1)	
Comorbidities, *n* (%)				0.308
Infective dermatitis	3 (5)	0	3 (2)	
HAM/TSP	2 (3)	0	2 (1)	
Strongyloidiasis	1 (2)	1 (1)	2 (1)	
Pneumocystis	3 (5)	0	3 (2)	
Tuberculosis (lung)	2 (3)	1 (1)	3 (2)	

HAM/TSP: tropical spastic paraparesis/HTLV-1–associated myelopathy; IPI: Lymphoma International Prognostic Index; LDH: lactate dehydrogenase; PIT: Prognostic Index for T-cell lymphoma.

[§]We defined the different types of skin lesion as follow: patches as non-infiltrating erythema, plaque as infiltrating erythema, multipapular as multiple infiltrated papules with less than 1 cm in diameter that may be confluent forming large infiltrated papules, tumoral nodule as infiltrated elevated lesions with more than 1 cm in diameter, erythroderma as generalized erythema involving more than 80% of the body surface area, mixed-lesions as 2 or more predominant skin lesions, and primary cutaneous tumoral (PCT) variant as skin involvement by tumors and as the solely manifestation of the disease (no organ involvement).

[+]Two patients had tumoral nodule with erythroderma and 2 patients had plaques with erythroderma.

[†]Applicable for patients with aggressive ATLL only (acute and lymphomatous).

[*]Only the most commonly involved extranodal sites are reported.

[‡]Patients with acute ATLL by definition have bone marrow involvement, thus we are only reporting those that underwent bone marrow biopsy.

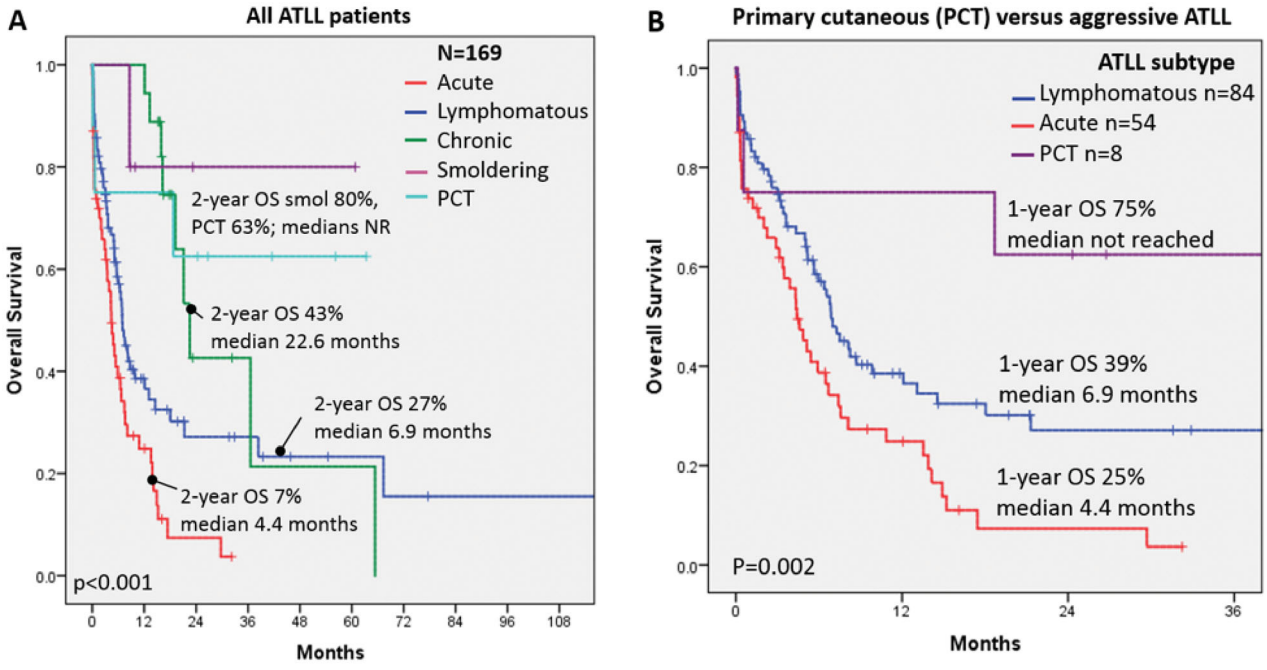

Figure 2. Overall survival of ATLL patients according to clinical subtype.

discriminate patients in low and high risk disease, but not in patients with cutaneous involvement only.

Therapy approaches and responses

The therapy approaches used during the first line of therapy are summarized in Supplemental Table 2. Most patients with cutaneous involvement ($n = 17$, 27%) received first-line AZT-IFN (either alone or in combination with chemotherapy) compared to patients with non-cutaneous involvement ($n = 6$, 6%). In contrast, most patients with non-cutaneous involvement ($n = 88$, 83%) received first-line multiagent chemotherapy compared to patients with cutaneous involvement ($n = 36$, 57%). Five patients with skin involvement received either topical carmustine ($n = 3$) or a combination of topical clobetasol with phototherapy ($n = 2$). Two patients with smoldering ATLL and non-cutaneous involvement had a watch-and-wait strategy, whereas six patients (3 on each group) did not receive treatment and had best supportive care. No biologic agents were used in our cohort of patients, mainly due to lack of access to these agents. Two patients (1 in each group) underwent allo-HSCT.

AZT-IFN-based regimen

Table 3 summarizes the response rates in ATLL patients with cutaneous involvement according to the treatment regimen, type of skin lesion and ATLL clinical subtype. First-line AZT-IFN alone ($n = 8$) resulted in an overall response rate (ORR) of 100% and a CR rate of 63%. Four lymphomatous ATLL patients had plaques ($n = 2$, CR 100%) and erythroderma ($n = 2$, CR 100%); and 3 acute ATLL patients had multiple papules ($n = 1$, PR 100%) and erythroderma ($n = 2$, PR 100%). The only PCT ATLL patient achieved CR after AZT-IFN. In ATLL patients with non-cutaneous involvement, AZT-IFN was given to 3 patients with acute ATLL and resulted in 2 CR and 1 PD (Supplemental Table 3).

Chemotherapy-based regimen

Thirty-six evaluable patients with cutaneous involvement received multiagent chemotherapy alone and nine patients received chemotherapy combined with AZT-IFN (Table 3). Multiagent chemotherapy alone resulted in an ORR of 33% ($n = 12/36$, CR 22%). However, in lymphomatous ATLL patients, the ORR was 47% ($n = 8/17$, CR 29%). Patients with plaque and multiple papules skin lesions had the highest response rates (plaque: ORR 62.5%, $n = 5/8$, all CR; multiple papules: ORR 50%, $n = 2/4$, all PR) compared to patients with other skin lesions. Combining multiagent chemotherapy with AZT-IFN yielded an ORR of 33% ($n = 3/9$, CR 22%). However, in acute ATLL patients with plaque skin lesions, the ORR was 67%, all CR ($n = 2$). Patients with erythroderma skin lesions had the lowest ORR regardless of the chemotherapy approach used (ORR: 17%, $n = 1/6$, and 0%, $n = 3$, with multiagent

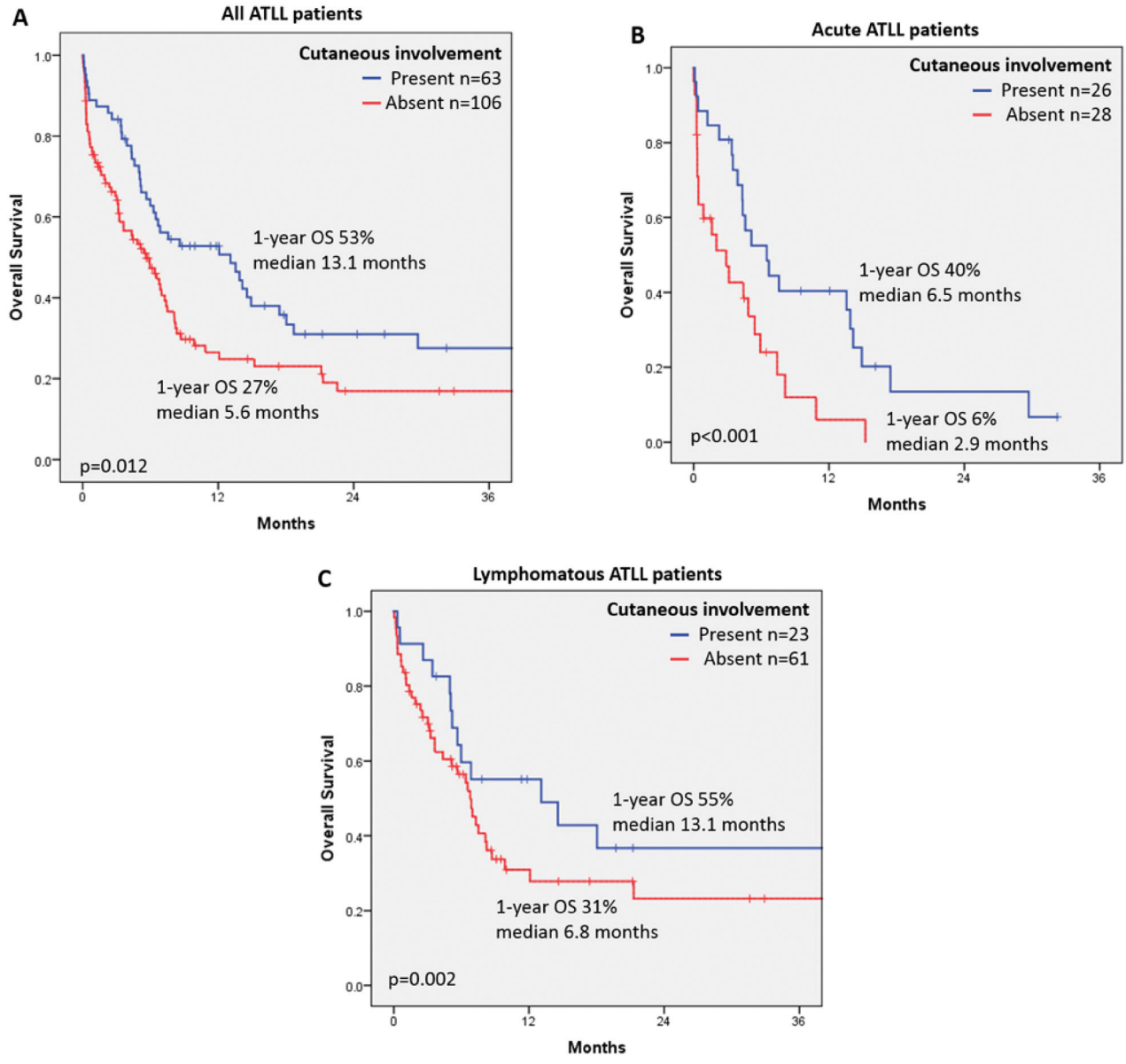

Figure 3. Overall survival of ATLL patients according to cutaneous involvement status.

chemotherapy alone, and combination with AZT-IFN, respectively). CHOP/CHOP-like regimen was the most common regimen used ($n = 17$), followed by CHOEP ($n = 9$). CHOEP yielded a higher ORR than CHOP (44 versus 26%, respectively; $p = 0.04$).

In ATLL patients with non-cutaneous involvement, multiagent chemotherapy alone yielded an ORR of 24% (CR 16%). In contrast, the combination of multiagent chemotherapy with AZT-IFN yielded an ORR of 100% ($n = 3$, all PR) (Supplemental Table 3). As with the cutaneous-involvement group, CHOP/CHOP-like was the most commonly used regimen ($n = 64$) followed by CHOEP ($n = 22$). CHOEP yielded a higher response rate compared to CHOP (ORR: 50% versus 19%, respectively; $p < 0.01$).

Discussion

This study indicates that cutaneous involvement is associated with improved survival in a cohort of Latin American patients with ATLL. The PCT subtype had higher survival rates than acute and lymphomatous ATLL but did worse than the smoldering subtype. Moreover, the aggressive ATLL forms that bear cutaneous involvement achieved higher response rates with the combination of AZT-IFN compared to chemotherapy. To our knowledge, this is the first Latin American study in endemic regions outside of Brazil to address the knowledge gap related to the outcomes of cutaneous involvement in ATLL patients.

Few reports have been dedicated to studying the impact of cutaneous involvement in ATLL [2,8,9,11–13,20].

Table 2. Multivariate cox regression analysis of clinical and laboratory variables associated to survival in ATLL patients.

Multivariate analysis		
Variable	HR (95% CI)	*p*-Value
Cutaneous involvement		
No	Ref	–
Yes	0.55 (0.37–0.82)	<0.01
B symptoms		
No	Ref	–
Yes	1.78 (1.13–2.8)	0.01
Calcium		
Normal	Ref	–
Elevated	1.59 (1.07–2.36)	0.02
Albumin		
Normal	Ref	–
<3.5 g/dL	1.56 (1.04–2.34)	0.03
IPI		
Low risk	Ref	–
Low-inter risk	2.47 (1.02–5.97)	0.05
High-inter risk	2.59 (1.09–6.14)	0.03
High risk	2.67 (1.08–6.59)	0.03

Our results suggest that cutaneous involvement is associated with improved survival compared to non-cutaneous involvement, including aggressive ATLL forms. This finding is consistent with a Brazilian study in which patients with lymphomatous, chronic and smoldering ATLL, but not acute ATLL, bearing skin lesions had better OS compared to those without it [12]. In contrast, in Japan, cutaneous involvement might be an adverse prognostic factor for those with acute, chronic and smoldering ATLL but not the lymphomatous subtype [13,21]. Other reports have shown no differences in survival in patients with cutaneous involvement [8,20]. With the above, this study supports what has been previously described that American patients with ATLL have distinct clinical characteristics and outcomes compared to Japanese patients [5,22–30]. A North American study reported that ATLL (mostly composed by Caribbean descent) has a distinct genomic landscape with a high frequency of prognostic epigenetic mutations affecting p53 function and consequently associated to chemorefractoriness, explaining the difference in outcome with the Japanese population [28]. Moreover, a recent study performed by the GELL group (Grupo de estudio Latinoamericano de Linfoproliferativos) found that Latin American ATLL is characterized by younger age, female predominance, high rate of lymphomatous type, low rate of indolent types, and worse survival compared to Japanese patients [30].

In this study, the presence of plaques and multiple papules were associated with improved outcomes compared to other skin lesions. In contrast, in Japan, bearing patches was associated to longer survival [13]. In addition, our cohort of PCT patients had better outcomes compared to acute and lymphomatous ATLL forms, but worse than the smoldering subtype. Similar results were found in Brazil where the median survival time for PCT was 21 months, compared to 4 and 9 months for acute and lymphomatous ATLL subtypes, respectively; while the smoldering subtype had a better survival time of 58 months [12].

In our cohort, patients with aggressive ATLL and cutaneous involvement managed with first-line AZT-IFN had an ORR of 100%. Despite the small number of patients, this study describes the potential benefit of AZT-IFN in patients with aggressive ATLL and skin involvement. A summary of these responders is presented in Supplemental Table 4. Previous studies, including a recent Latin American study, have demonstrated the potential benefit of AZT-IFN in patients with ATLL [5,29–31]. However, this benefit was mainly seen in patients with leukemic and indolent forms than lymphomatous subtype. In this study, both, patients with acute and lymphomatous ATLL with cutaneous involvement benefited from AZT-IFN therapy, thus we believe AZT-IFN might be a reasonable first-line option to try in this patient population whenever feasible. In this cohort, chemotherapy alone resulted in lower ORR in both ATLL patients with (ORR 33%, CR 22%) and without (ORR 24%, CR 16%) cutaneous involvement. Patients with lymphomatous ATLL and cutaneous involvement had better response rates to chemotherapy (ORR 47%) than the acute subtype (ORR 15%); those with erythroderma skin lesions had the lowest response rate to chemotherapy. CHOEP yielded a better ORR compared to CHOP regimen in both patients with and without cutaneous involvement.

Our study is limited by its retrospective nature. Patients were classified using archived records, laboratory and pathology reports. The absence of a centralized pathology review in this international study lays a risk for selection bias. Likewise, response assessment was evaluated by each investigator which might be subject to observer bias and variability. However, there was a clear distinction in outcomes between aggressive, indolent, and PCT ATLL groups, all consistent with the natural history of ATLL. Nonetheless, our main strength is the multi-institutional scale of this study which included patients seen at cancer centers in HTLV-1 endemic Latin American countries. Although our findings emerge as a clinical prognostic factor for ATLL patients, current prognostic models (e.g. IPI and PIT score) have not been prospectively validated in this population, and thus, incorporating population-specific factors might improve its prognostic value in future studies. We are currently expending our ATLL data registry to validate both the currently available and novel prognostic models for ATLL.

Table 3. Response rates to first-line therapy in ATLL patients with cutaneous involvement according to treatment regimen, type of skin lesion, and ATLL clinical subtype.

	Response Rate, *n* (%)				
Treatment	OR	CR	PR	SD	PD
AZT-IFN alone ($n = 8$)					
Plaques ($n = 2$)	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)
Lymphomatous ($n = 2$)	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)
Multiple papules ($n = 1$)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Acute ($n = 1$)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Tumoral nodule ($n = 1$)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
PCT ($n = 1$)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Erythroderma ($n = 4$)	4 (100)	2 (50)	2 (50)	0 (0)	0 (0)
Acute ($n = 2$)	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)
Lymphomatous ($n = 2$)	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)
Multi-agent chemotherapy alone ($n = 36$)					
Plaques ($n = 8$)	5 (62.5)	5 (62.5)	0 (0)	2 (25)	1 (12.5)
Acute ($n = 2$)	1 (50)	1 (50)	0 (0)	1 (50)	0 (0)
Lymphomatous ($n = 5$)	4 (80)	4 (80)	0 (0)	0 (0)	1 (20)
Chronic ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Macules ($n = 9$)	1 (11)	0 (0)	1 (11)	5 (56)	3 (33)
Acute ($n = 3$)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)
Lymphomatous ($n = 5$)	1 (20)	0 (0)	1 (20)	2 (40)	2 (40)
Chronic ($n = 1$)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Multiple papules ($n = 4$)	2 (50)	0 (0)	2 (50)	0 (0)	2 (50)
Acute ($n = 2$)	1 (50)	0 (0)	1 (50)	0 (0)	1 (50)
Lymphomatous ($n = 2$)	1 (50)	0 (0)	1 (50)	0 (0)	1 (50)
Tumoral nodule ($n = 7$)	3 (43)	3 (43)	0 (0)	2 (28.5)	2 (28.5)
Acute ($n = 2$)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)
Lymphomatous ($n = 1$)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
PCT ($n = 4$)	2 (50)	2 (50)	0 (0)	1 (25)	1 (25)
Erythroderma ($n = 6$)	1 (17)	0 (0)	1 (17)	2 (33)	3 (50)
Acute ($n = 2$)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)
Lymphomatous ($n = 4$)	1 (25)	0 (0)	1 (25)	1 (25)	2 (50)
Mixed lesion ($n = 2$)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)
Acute ($n = 2$)	0 (0)	0 (0)	0 (0)	1 (50)	2 (100)
Combination chemotherapy and AZT-IFN ($n = 9$)					
Plaques ($n = 3$)	2 (67)	2 (67)	0 (0)	0 (0)	1 (33)
Acute ($n = 3$)	2 (67)	2 (67)	0 (0)	0 (0)	1 (33)
Macules ($n = 1$)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Smoldering ($n = 1$)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Tumoral nodule ($n = 2$)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)
PCT ($n = 2$)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)
Erythroderma ($n = 3$)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)
Acute ($n = 2$)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
Lymphomatous ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Single-agent chemotherapy and/or regional therapy ($n = 6$)					
Plaques ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Smoldering ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Macules ($n = 1$)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Acute ($n = 1$)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Multiple papules ($n = 2$)	1 (50)	0 (0)	1 (50)	0 (0)	1 (50)
Lymphomatous ($n = 1$)	0 (0)	0 (0)	0 (0)	0 (0)	1(100)
Smoldering ($n = 1$)	1(100)	0 (0)	1(100)	0 (0)	0 (0)
Tumoral nodule ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
PCT ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Erythroderma ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Chronic ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Allogeneic stem cell transplant ($n = 1$)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Lymphomatous ($n = 1$)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
First chemotherapy line [‡]					
CHOP/CHOP like regimen ($n = 27$)	7 (26)	4 (15)	3 (11)	8 (30)	12 (44)
CHOEP ($n = 9$)	4 (44)	3 (33)	1 (11)	3 (33)	2 (23)
HyperCVAD ($n = 3$)	1 (33)	1 (33)	0 (0)	2 (67)	0 (0)
GDP ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
ABVD ($n = 1$)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Cyclophosphamide ($n = 1$)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AZT-IFN: zidovudine/Interferon alpha; CHOEP: etoposide, cyclophosphamide, vincristine, doxorubicin and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CR: complete response; GDP: gemcitabine, dexamethasone, cisplatin; HyperCVAD: cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternated with high-dose cytarabine and methotrexate; OR: overall response; PD: progressive disease; PR: partial response; SD: stable disease.

[‡]Chemotherapy/agent was given as first-line upfront alone or in combination with AZT-IFN.

In conclusion, this study identified the presence of cutaneous involvement as an independent prognostic factor for survival in ATLL patients across subtypes. Plaques and multiple papules skin lesions were associated with better OS compared to other lesions, and the PCT variant had better outcomes compared to acute and lymphomatous ATLL. The combination AZT-IFN yielded high response rates compared to chemotherapy, thus emerging as a reasonable option for ATLL patients with cutaneous involvement. Also, our findings further support the hypothesis that Latin American ATLL behaves differently than in Japanese patients. Further characterization of Latin American ATLL through genomic analysis is planned.

Author contributions

L.M., D.A.C. and B.E.B. designed the research; L.M., D.A.C., D.J.E., R.O-P., C.P., H.I., L.F., M.P., A.P., G.S., C.M., M.B. and B.E.B. searched data; L.M., D.A.C., D.J.E., R.O-P., C.P., H.I., L.F., M.P., B.V., A.P., G.S., C.M., J.J.C., L.V., J.C.R., M.B., and B.E.B. analyzed results and/or wrote the paper.

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