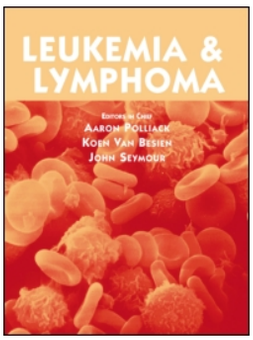

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

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To cite this article: Camila Peña, Eloísa Riva, Natalia Schutz, Aline Ramírez, Jule Vásquez, Daniel del Carpio, Cristian Seehaus, Paola Ochoa, Rosa Vengoa, Patricio Duarte, Humberto Martínez-Cordero, Yrving Figueredo, Rosa Oliday Ríos, Jhoanna Ramírez, Virginia Bove, Macarena Roa, Moisés Russo, Marcela Espinoza, Gloritza Rodriguez, Guillermina Remaggi, María Elvira Enciso, Mauricio Chandía & Dorotea FantlOn behalf of the Grupo de Estudio Latinoamericano de Mieloma Múltiple (GELAMM) (2023): Primary plasma cell leukemia in Latin America: demographic, clinical, and prognostic characteristics. A study of GELAMM group, Leukemia & Lymphoma, DOI: 10.1080/10428194.2023.2171266

To link to this article: https://doi.org/10.1080/10428194.2023.2171266

Published online: 25 Jan 2023.

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LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2023.2171266

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ORIGINAL ARTICLE

Primary plasma cell leukemia in Latin America: demographic, clinical, and prognostic characteristics. A study of GELAMM group

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ABSTRACT

Primary plasma cell leukemia (pPCL) is an infrequent and aggressive plasma cell disorder. The prognosis is still very poor, and the optimal treatment remains to be established. A retrospective, multicentric, international observational study was performed. Patients from 9 countries of Latin America (LATAM) with a diagnosis of pPCL between 2012 and 2020 were included. 72 patients were included. Treatment was based on thalidomide in 15%, proteasome inhibitors (PI)-based triplets in 38% and chemotherapy plus IMIDs and/or PI in 29%. The mortality rate at 3 months was 30%. The median overall survival (OS) was 18 months. In the multivariate analysis, frontline PI-based triplets, chemotherapy plus IMIDs and/or PI therapy, and maintenance were independent factors of better OS. In conclusion, the OS of pPCL is still poor in LATAM, with high early mortality. PI triplets, chemotherapy plus IMIDs, and/or PI and maintenance therapy were associated with improved survival.

ARTICLE HISTORY
Received 19 October 2022
Revised 5 November 2022
Accepted 16 January 2023

KEYWORDS
Latin America; plasma cell leukemia; proteasome inhibitors; immunomodulatory drugs

Background

Primary plasma cell leukemia (pPCL) is a rare plasma cell disorder whose incidence varies between countries, ranging from 0.4 to 1.2/million cases per year [1,2].

For decades, pPCL was defined by the presence of 20% plasma cells within the peripheral blood leukocyte count, or an absolute plasma cell count greater than 2×10^9/L, according to Kyle's criteria [3,4]. This definition has recently been changed by the International Myeloma Working group (IMWG) to 'the presence of 5% or more circulating plasma cells in peripheral blood smears in patients otherwise diagnosed with symptomatic multiple myeloma' [5].

The prognosis of pPCL is poor. The median overall survival has increased from four months in 2004 to 12 months in 2009 with conventional chemotherapy [6]. The advent of new therapies along with autologous stem cell transplantation (ASCT) improved survival in up to 36 months [7]. Nevertheless, the standard of care has not been established so far. Data on this disease are scarce in our region. This study aimed to describe demographic, clinical, and prognostic characteristics of newly diagnosed pPCL in Latin America (LATAM).

Methods

This is a retrospective, multicentric, international observational study. Patients from 9 countries of LATAM with a diagnosis of pPCL between 2012 and 2020 were included. Demographic and clinical data were collected from clinical records. pPCL was defined as per Kyle's criteria, with 20% or more plasma cells in

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peripheral blood at diagnosis or an absolute number of plasma cell count of 2×10^9/L. Secondary PCL was excluded. Response to pPCL treatment was evaluated according to the IMWG response criteria [4]. Four treatment groups were defined: treatment based on thalidomide (group 1), proteasome inhibitors (PI) triplets (group 2), chemotherapy plus immunomodulatory drugs (IMIDs) and PI (group 3) and other options (group 4). Descriptive analysis was used. Survival curves were estimated using the Kaplan–Meier method. Uni- and multivariable Cox proportional hazards models were used to assess risk factors.

Results

Seventy-two patients from Chile, Argentina, Ecuador, Cuba, Perú, México, Paraguay, Colombia, and Uruguay were included. The median age was 57 years (range 28–92), and 53% were male. Performance status (PS) $\geq$ 2 was reported in 55% of the patients. Anemia was present in 79% at diagnosis, hypercalcemia in 45%, renal failure in 39%, thrombocytopenia in 57%, and bone lesions in 80%. High LDH was observed in 71% and hypoalbuminemia in 57%. The extramedullary disease was reported in 29% of patients, 2 with central nervous system involvement. The type of paraprotein was of light chain in 45% (55% Kappa), IgG in 36%, IgA in 12%, and not reported in 7% (Table 1). Flow cytometry was performed in 80% of patients, and Fluorescence *in situ* hybridization (FISH) in 28%. Of them, del (17p) was found in 25%, t(14;16) in 10%. The t(4;14) was not reported. The t(11;14) was investigated in 13 patients, and in two were reported as positive (15%).

Six patients died before receiving any specific treatment. From the 66 remaining patients, most (83%) were classified as eligible for transplant and received at least one treatment cycle. Treatment was based on thalidomide in 15% (group 1), proteasome inhibitors (PI) triplets in 38% (group 2), chemotherapy plus IMIDs and/or PI in 29% (group 3), and other options in 18% (group 4) of patients. The most used regimens were CyBorD (Bortezomib, cyclophosphamide, and dexamethasone) in 26%, VTD-PACE (Bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide) in 20%, VAD (Vincristine, doxorubicin, and dexamethasone) in 12%, and CTD (Cyclophosphamide, thalidomide, and dexamethasone) in 14%. One patient received daratumumab-KRd (Carfilzomib, lenalidomide, and dexamethasone) therapy. Forty patients (62%) received PI as part of the induction treatment.

Table 1. Demographic and clinical characteristics of the whole cohort.

Variable	% (range)
Age median (y)	57 (28–-92)
Male	53%
Clinical characteristics	
Extramedullary	29%
Anemia	79%
Hypercalcemia	45%
Renal failure	39%
Bone lesions	80%
High LDH	71%
CNS involvement	0.05%
Type of MC	
IgG	36%
IgA	12%
LC	45%

y: years; CNS: Central nervous system; MC: Monoclonal component; LC: Light chain.

Seventeen of 66 patients (26%) died during induction with a 3-month mortality rate of 30% (CI 95% 20–42), without significant differences between treatment groups. Per intention to treat analysis, the complete response (CR) rate or better was 0% in group 1, 24% in group 2, 28% in group 3, and 17% in group 4. ASCT was performed in 15 (23%) patients, including 6 in tandem auto-auto modality, and 1 auto-allo modality. One patient received a direct allogeneic transplant. Among patients that underwent transplantation, 33% were treated with PI-based triplets, 42% with new drugs plus polychemotherapy, and 0% patients were treated with regimens based on thalidomide or others ($p = .013$). Eighty-six percent of the patients who received ASCT continued with maintenance vs only 21% did it in the non-transplanted group.

Twenty-one patients received maintenance therapy with a duration range between 3 and 24 months. Maintenance regimens were heterogeneous, including lenalidomide monotherapy in 5 patients, bortezomib and lenalidomide in 4 patients, thalidomide and dexamethasone in 4 patients, and thalidomide monotherapy in 3.

With a median follow-up of 18 months, 38 patients (53%) died. Median overall survival (OS) was 18 months (CI 95% 9–28), 5 years OS was 20% (CI 95% 8–38). OS per the different groups of treatment are shown in Figure 1. The use of bortezomib as part of the induction treatment was associated with better overall survival (31 months vs 11 months, $p = .03$).

The median OS for patients achieving CR or better response was not reached in this study, with a 2-year OS of 80% (CI 95% 41–95) vs 28% (14%–44%) in patients with less than CR.

In the multivariate analysis, treatment within groups 2 and 3 and receiving maintenance therapy were independent factors of better OS (Table 2).

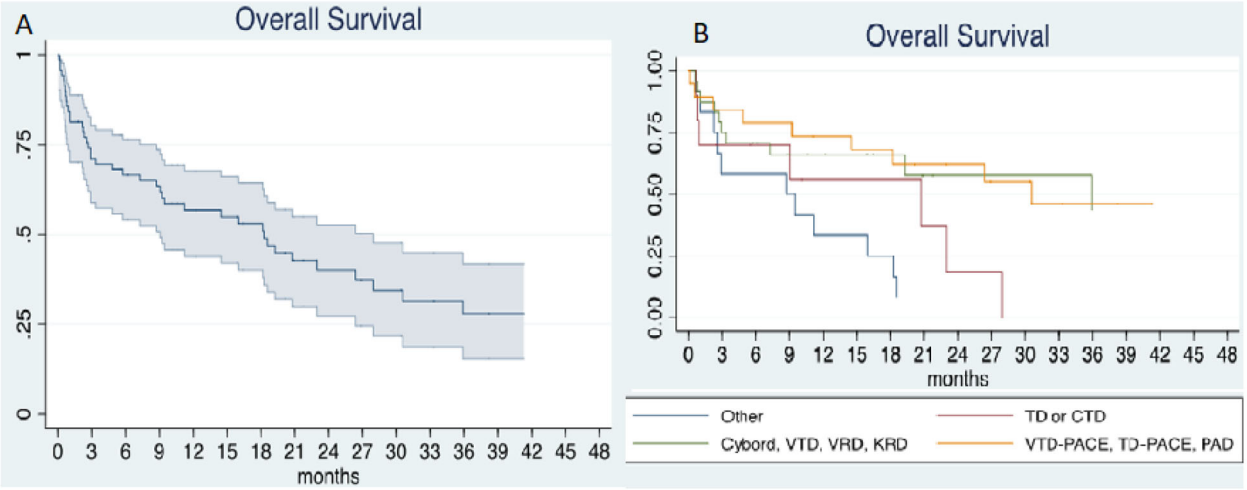

Figure 1. (A) Overall survival of the whole cohort. (B) Overall survival of the different treatment groups. CyBorD: Bortezomib, cyclophosphamide and dexamethasone; VTD: Bortezomib, thalidomide and dexamethasone; VRD: Bortezomib, lenalidomide and dexamethasone; KRD: Carfilzomib, lenalidomide and dexamethasone; TD: Thalidomide and dexamethasone; CTD: Cyclophosphamide, thalidomide and dexamethasone; VTD-PACE: Bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide; TD-PACE: Thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide; PAD: Bortezomib, doxorubicin and dexamethasone.

Table 2. Uni and multivariate analysis of factors associated with overall survival.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.02	0.99–1.04	.090	1	0.96–1.03	.997
Female sex	1.45	0.79–2.63	.224			
PS ECOG > 2	1.53	0.63–3.69	.345			
Extramedullary disease	2.78	1.34–5.76	.006	1.07	0.41–2.78	.883
Renal failure (Cr > 2 mg/dL)	1.09	0.57–2.07	.780			
Anemia (Hb < 10 g/dL)	2.55	0.90–7.20	.070	1.76	0.44–7.06	.420
PC in peripheral blood > 20,000/mm^3	1.37	0.62–3.00	.431			
Platelets < 100,000/ mm^3	1.44	0.74–2.78	.275			
Calcium > 11 mg/dL	1.21	0.64–2.25	.548			
High LDH	1.8	0.85–3.77	.119			
Albumin < 3.5 g/dL	2.91	1.46–5.78	.002	2.21	0.70–6.96	.172
Type of treatment						
CTD or TD	0.75	0.29–1.92	.551	1.85	0.46–7.12	.387
PI triplets (CyBord, VTD, VRD or KRD)	0.34	0.14–0.78	.012	0.33	0.10–1.04	**.050**
PI or IMiDs + Polychemotherapy (VTD-PACE, DT-PACE, PAD)	0.27	0.11–0.66	.004	0.30	0.09–0.91	**.034**
ASCT	0.11	0.03–0.40	.001	0.28	0.06–1.26	.099
Maintenance treatment	0.23	0.10–0.52	.000	0.23	0.08–0.66	**.006**
CR or better	0.24	0.07–0.79	.019	0.24	0.24–1.09	.065

PS: Performance status; Cr: Creatinine; Hb: Hemoglobin; PC: Plasma cells; CyBorD: Bortezomib, cyclophosphamide and dexamethasone; VTD: Bortezomib, thalidomide and dexamethasone; VRD: Bortezomib, lenalidomide and dexamethasone; KRD: Carfilzomib, lenalidomide and dexamethasone; TD: Thalidomide and dexamethasone; CTD: Cyclophosphamide, thalidomide and dexamethasone; VTD-PACE: Bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide; TD-PACE: Thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide; PAD: Bortezomib, doxorubicin and dexamethasone; ASCT: autologous stem cell transplant; CR: complete response.

Discussion

This study corresponds to the largest cohort of patients with pPCL from LATAM.

Of notice, our pPCL definition was planned before the new definition established by the IMWG in 2021 [5], so only patients with 20% or more plasma cells in peripheral blood smears were included.

As reported internationally, Latin American patients with pPCL were younger than myeloma (MM) patients, with a median age at diagnosis of 57 years. The median age varies according to studies between 52 and 65 years, ten years younger than the median age of patients with MM [8]. The clinical presentation of pPCL is aggressive, given the leukemic nature of the disease, with frequent extramedullary involvement (lymph nodes, spleen, pleura, soft tissues, central nervous system, and other organs). This is reported in up to 20% of cases at diagnosis [9]. In the present study, we found almost 30% of extramedullary involvement at diagnosis, however, this situation did not affect the

OS. pPCL is characterized by high tumor burden, high prevalence of anemia, thrombocytopenia, hypercalcemia, renal failure, elevated LDH, and elevated B2 microglobulin, as was shown in our patients. Bone lesions are less frequent than in MM, reported in about 35% of cases [8]. Interestingly, we found a higher than expected number of patients with bone lesions, maybe because of more advanced disease at the time of diagnosis. According to the type of M protein, the most frequently described is IgG (30%), followed by IgA, IgD, and IgE. However, 35%–40% produce only light chains (LC), and 8% are non-secreting [8], similar to our cohort, where kappa was the most frequently LC involved.

The cytogenetic alterations are more frequent in pPCL than in MM, which may explain its aggressive behavior [10]. The karyotype of pPCL is frequently non-hyperdiploid [11]. In addition, chromosomal translocations involving the immunoglobulin Heavy Chain (IgH) gene are frequently observed (up to 87% of cases). The presence of the t (11;14) translocation is common (70% of cases). Other common alterations are del(13q) (85%), del(17p) (37%), del(1p21), and 1q21 amplification [12]. The del(17p) together with TP53 mutations lead to allelic inactivation of TP53 in up to 56% of pPCL cases [13]. We highlight that only 28% of our patients had reported cytogenetics and FISH studies, confirming a suboptimal utilization of this test in LATAM, as shown in other GELAMM studies [14,15]. The most frequent alteration found in our cohort was del(17p). Nevertheless, there is data that shows that the presence of conventional high-risk cytogenetic abnormalities in pPCL may not exert a relevant prognostic effect [16]. It is important to mention that t(11;14) may be an exception to this rule. Recently, Cazaubiel et al. showed that these patients had significantly fewer other adverse cytogenetic abnormalities and a better OS when compared with pPCL without t(11;14) (39.2 months vs 17.9 months) [17]. We only had t(11;14) done by FISH in 13 patients because it is not considered in the basic FISH panel, which is meant to look for high-risk abnormalities in MM patients. We think that reporting this abnormality is crucial considering the promissory results of Venetoclax in this population [18].

Worldwide, the introduction of novel agents such as IMIDs and/or PIs has considerably increased the survival of MM patients. Their use in pPCL has also improved OS, that was only four months prior them [6]. In the most recent SEER evaluation [7], the OS was improved to 12 months between 2006 and 2009, probably because of the introduction of novel agents. Although suboptimal, our results are in this line: 18 months of median OS, PI triplets and chemotherapy plus IMIDs and/or PI are essential factors of better survival. Other studies, mostly retrospective, showed the same trend. Katodritou et al. [19] showed in a retrospective Greek cohort of 50 patients an OS of 18 months. 80% of this cohort received novel agents, and 40% were transplanted. Usmani et al. also reported an OS of 18 months in a cohort of the total therapy protocols [20]. Jurczyszyn et al. [21], in a cohort of 117 patients, showed an OS of 23 months, 98% of patients received novel agents, and 64% were transplanted, reinforcing the role of these two factors.

Having prospective studies of a disease with a low incidence is difficult. Two publications showed an increase in survival with novel agents. In a prospective study of 40 pPCL patients who received bortezomib-based induction, the IFM [22] reported a median OS of 36 months. Musto et al. [23] investigated the role of lenalidomide and dexamethasone as induction. They reported 23 months of median OS in 23 patients.

Frontline therapies were heterogeneous in our cohort. It is known that pPCL has an aggressive behavior, so the goal of treatment should be rapid control of the disease. New guidelines recommend that patients who are transplant candidates should receive an intensive induction regimen, consisting of combination chemotherapy that includes a PI or IMIDs, like hyperCVAD-VTD (dexamethasone, cyclophosphamide, vincristine, doxorubicin, bortezomib, and thalidomide) or VTD-PACE [4]. In our study, 80% received treatment with novel agents, 60% of patients received a bortezomib-based induction, and 29% an intensive chemotherapy-based approach, and these regimens were associated with a better survival rate. It is known that next-generation drugs (carfilzomib, ixazomib, pomalidomide) and anti-CD38 monoclonal antibodies have exhibited high efficacy in MM, even among those with high-risk features. These drugs may have an important role in pPCL treatment in the near future [24,25].

Consolidation with autologous transplant has also increased survival in pPCL patients [26,27], although inferior to the results of patients with MM. Reasons for 77% of potential candidates not being transplanted in our cohort are not available and merit further analysis. The role of allogeneic transplants remains uncertain. In the largest cohort studying transplant in pPCL patients, the authors compared patients undergoing a single autologous transplant, a single allogeneic transplant, or a combined tandem approach with an allogeneic transplant following an autologous transplant (auto-allo) or a tandem autologous transplant

(auto-auto) as consolidation. They conclude that a tandem transplant approach of either auto-auto or auto-allo showed better outcomes [28].

Guidelines also recommend post-transplant consolidation chemotherapy regimens or that maintenance treatment could be considered [4]. Our patients did not receive consolidation, but maintenance was frequently used, especially in the post-transplant phase. Furthermore, its use was a prognostic factor of better survival.

Prognostic factors are inconsistent between various reports primarily due to retrospective studies' small sample size and heterogeneity. We found that treatment with PI/IMIDs with or without intensive chemotherapy and maintenance were prognostic factors. These results may be explained by the fact that patients who were probably fitter or in better shape to receive a more aggressive approach were the ones who received these intensive chemotherapy and maintenance treatments. Jurczyszyn et al. [21] showed age $\geq$60 years, platelet count $\leq$100,000 mm^{3,} and peripheral blood plasma cell count $\geq$2000 mm^3 as independent predictors of worse survival. In a Greek cohort of 50 patients, bortezomib-based therapy + ASCT predicted OS in univariate analysis. In multivariate analysis, achievement of $\geq$ VGPR and LDH $\geq$ 300 U/L were significant predictors for OS [19].

Early mortality was high in our cohort, with a mortality rate of 30% in the first 3 months. In this regard, in a large Dutch cohort, Brink et al. [29] showed a mortality rate within six months after diagnosis among patients aged $\leq$65 of 25%, and among those aged $\geq$66 years of 49%. This situation may reflect the disease's aggressiveness, reaffirming the fact that leukemia itself is the most frequent cause of death in this population [30].

Our study is limited by its retrospective nature. Patients were classified using archived records and laboratory reports. Similarly, response assessment was evaluated by each investigator, which is subjected to observer bias. Also, it must be considered that our countries have different regulations, treatment protocols, and drug access.

Conclusion

To our knowledge, this is the first study to provide real-world data on pPCL in Latin America. OS of pPCL is still poor in LATAM, especially with high early mortality, although in line with other reports. PI triplets, chemotherapy plus IMIDs, and/or PI and maintenance therapy are associated with improved survival. We need to further investigate the reason why the majority of patients who were defined as eligible to transplant didn't get one.

Acknowledgments

The authors thank Dr. Joseph Mikhael for the comments that greatly improved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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