

Outcomes and treatment patterns in primary and secondary plasma cell leukemia: insights from a large US cohort study

Shagun Singh,^{1*} Supriya Peshin,^{2*} Betsy C. Wertheim,³ Ashley Larsen,⁴ Iloabueke Chineke,⁵ Douglas W. Sborov,⁶ Damian Green,⁷ Michaela Liedtke,⁸ Marie Okoniewski,⁹ Mohammed Wazir,¹⁰ Omar Nadeem,¹¹ Levanto G. Schachter,¹² Dominique DeGraaff,¹³ Victoria A. Vardell,¹⁴ David G. Coffey¹⁵ and Krisstina Gowin¹⁶

¹Internal Medicine, Banner University Medical Center, Tucson, AZ; ²Norton Community Hospital, Ballad Health, Norton, VA; ³University of Arizona Cancer Center, Tucson, AZ; ⁴Department of Medicine, University of Arizona, Tucson, AZ; ⁵Rocky Mountain Oncology, Casper, WY; ⁶Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; ⁷University of Miami, Miller School of Medicine, Miami, FL; ⁸Stanford Medicine, Department of Hematology, Palo Alto, CA; ⁹University of Kansas Cancer Center, Kansas City, KS; ¹⁰UMass Memorial Medical Center, Division of Hematology/Oncology, Worcester, MA; ¹¹Harvard Medical School, Dana-Faber Cancer Institute, Boston, MA; ¹²UCLA Health, Hematology Oncology, San Luis Obispo, CA; ¹³University of Washington, Department of Oncology and Hematology, Seattle, WA; ¹⁴University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; ¹⁵Division of Myeloma, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL and ¹⁶Department of Supportive Care Medicine, Hematology/HCT, City of Hope, CA, USA

*SS and SP contributed equally as first authors.

Correspondence: K. Gowin
kgowin@coh.org

Received: December 12, 2024.
Accepted: April 9, 2025.
Early view: April 17, 2025.

<https://doi.org/10.3324/haematol.2024.287158>

©2025 Ferrata Storti Foundation

Published under a CC BY-NC license



Abstract

Plasma cell leukemia (PCL) is a rare and aggressive plasma cell disorder with a short survival duration despite the use of novel therapeutics. PCL remains an understudied disease for which there is no current standard of care treatment. Knowledge on optimal novel drug sequencing, including the role and timing of hematopoietic stem cell transplant as primary and salvage therapy is needed. We conducted a large retrospective analysis of 153 PCL patients, using the new definition of $\geq 5\%$ circulating plasma cells, including clinical features and treatment outcomes across seven academic centers in the United States. This is, to the best of our knowledge, the largest multicenter study conducted in the US of this rare disease. Disease presentation, clinical and genetic characteristics, and treatment patterns of 93 patients with primary PCL and 57 with secondary PCL are described. Additionally, associations between patient characteristics and mortality were investigated using Cox proportional hazards regression models. Secondary PCL was associated with a worse prognosis, with a median overall survival of 3.2 months compared to 36.6 months for primary PCL ($P < 0.001$). Receipt of a transplant was associated with a survival advantage in both primary PCL (Hazard Ratio [HR] 0.16, $P < 0.001$) and secondary PCL (HR 0.20, $P = 0.001$). No significant difference in outcomes was observed between proteasome inhibitor-based triplet regimens and the VTD-PACE like regimen. The presence of extramedullary disease and high-risk cytogenetics was not associated with survival in the primary PCL group.

Introduction

Plasma cell leukemia (PCL) is a rare and aggressive malignancy, constituting only 0.1–0.6% of all plasma cell disorders in the United States.¹ There are two variants of PCL: primary plasma cell leukemia (pPCL) arises *de novo*, and secondary plasma cell leukemia (sPCL) develops from multiple myeloma

(MM).² Both subtypes carry a poor prognosis, but sPCL is often more aggressive.³ Clinically, PCL patients present with more severe symptoms and biological abnormalities as compared to MM. Disease manifestations include thrombocytopenia, renal impairment, concomitant extramedullary disease (EMD), and high-risk cytogenetic abnormalities contributing to poor performance and a high mortality rate.^{3,4}

Until recently, a PCL diagnosis required $\geq 20\%$ circulating plasma cells or an absolute plasma cell count of $\geq 2,000/\text{mm}^3$, as defined by Kyle *et al.*⁵ The International Myeloma Working Group (IMWG) expanded the definition of PCL in 2021 to include patients with $\geq 5\%$ circulating plasma cells, after several studies found these patients to have similarly poor outcomes.⁶ PCL remains an understudied disease for which there is no current standard of care treatment. Novel treatments for PCL have been introduced in recent years, including CD38 targeted antibodies, proteasome inhibitors (PI), immunomodulatory drugs used during induction and maintenance phases, hematopoietic stem cell transplantation (HSCT), and cellular therapies such as chimeric antigen T-cell receptor (CAR-T) therapies.⁷⁻⁹ Despite these advancements, overall survival (OS) has remained limited, with only incremental gains observed between 2005 and 2020, ranging from 13 months to 18.3 months in pPCL and 1.2-3.5 months in sPCL.^{10,11} One study reported one-month, one-year, and three-year survival rates as 97.0%, 68.9%, and 36.1% for pPCL and 57.6%, 7.6%, and 3.8% for sPCL, respectively.¹¹ Elucidating optimal novel drug sequencing, including the role and timing of HSCT as primary and salvage therapy, is critically important.

One of the primary challenges in treating PCL is the limited data and lack of large, well-designed clinical trials. Most studies to date have been small, retrospective, or single center in nature, limiting the generalizability of their findings. The bulk of the literature has focused on pPCL, with comparatively fewer studies exploring the more aggressive sPCL type. The heterogeneity in clinical course and treatment responses between pPCL and sPCL further complicates the development of standardized treatment protocols.^{3,4,12}

This large, multicenter retrospective analysis aims to examine patient characteristics, disease features, and treatment-associated survival outcomes for both pPCL and sPCL patients. This is, to the best of our knowledge, the largest multicenter study conducted in the US of this rare disease. By identifying key factors that influence prognosis, this study seeks to inform future treatment strategies to improve survival outcomes for this rare but deadly malignancy.

Methods

Data from patients diagnosed with pPCL and sPCL between January 2010 and January 2021 were collected from electronic medical records at seven academic centers in the United States and entered into a study-specific REDCap database. The study protocol received approval from the Institutional Review Board of each participating institution. The inclusion criteria required a diagnosis of PCL defined by the presence of $\geq 5\%$ circulating plasma cells, as per the 2021 IMWG consensus guidelines,⁶ and sPCL patients were

required to have a prior diagnosis of MM. High-risk genetic features, as defined by the revised 2016 IMWG consensus guidelines, were defined by t(4;14), t(14;16), Del17p13, a non-hyper diploid karyotype and gain (1q).¹³ Response data were determined by each treating institution.

Patient characteristics were summarized descriptively. Kaplan-Meier survival curves were generated to assess OS, defined as the time from diagnosis to last follow-up or death. Patients that were lost to follow-up were censored at the date they were last known to be alive. Cox proportional hazards regression models were employed to test the associations between patient characteristics and survival, producing hazard ratios (HR) with 95% confidence intervals (CI), adjusted for PCL type and transplant status. All statistical analyses were performed using Stata 18, with two-sided *P* values and an alpha level of 0.05.

Results

Demographics and clinical characteristics

A total of 157 patients were initially identified, with 4 excluded due to unknown survival times, leaving 153 patients for analysis (96 with pPCL and 57 with sPCL). The median follow up-time was 13.1 months. The median time from initial MM diagnosis to sPCL progression was 21.2 months (range: 1-194.5 months). All patients in the data set met the inclusion criteria of $\geq 5\%$ circulating plasma cells. However, the data on actual percentage of circulating plasma cells were incomplete (Table 1). The median age at diagnosis was similar for pPCL and sPCL patients at 60.0 ± 10.8 years and 60.7 ± 9.2 years, respectively ($P=0.684$). Average creatinine levels were higher in pPCL patients (3.3 ± 0.8 mg/dL) compared to sPCL patients (1.7 ± 1.4 mg/dL) ($P=0.315$), while beta-2 microglobulin levels were significantly elevated in pPCL (12.6 ± 14.6 mg/L) compared to sPCL (7.0 ± 6.7 mg/L) ($P=0.001$). Conversely, LDH levels were higher in the sPCL cohort (838.8 ± 937.1 U/L) compared to pPCL (342.9 ± 235.2 U/L) ($P=0.144$). Albumin levels were similarly low in both groups, averaging 3.3 ± 0.8 g/dL in pPCL and 3.3 ± 0.6 g/dL in sPCL ($P=0.754$). EM disease was observed more frequently in sPCL patients (34.0%, 16/47) than in pPCL patients (20.5%, 17/83) ($P=0.098$). Among high-risk genetic features, del(17p) was more common in sPCL (42.9%, 12/26) compared to pPCL (34.4%, 21/61) ($P=0.484$), and t(4;14) was also slightly more frequent in sPCL (24.0%, 6/25) than in pPCL (21.1%, 12/57) ($P=0.778$). However, t(14;16) was observed more among pPCL patients (22.4%, 13/58) than in sPCL patients (4.3%, 1/23) ($P=0.059$). The t(11;14) translocation was observed more frequently at diagnosis (54.4%, 31/62) or at any time during the disease course (50.7%, 36/71) in pPCL patients compared to sPCL patients (40.9%, 9/22, and 48.3%, 14/29, respectively) ($P>0.05$).

In terms of staging, pPCL patients were primarily classified as International Staging System (ISS) stage III (81.2%,

Table 1. Patient characteristics.

Characteristic	Total N=153	Primary PCL N=96	Secondary PCL N=57	P
Age at diagnosis, years, mean±SD	60.2±10.2	60.0±10.8	60.7±9.2	0.684
Lab measurements at diagnosis, mean±SD				
LDH (U/L)	503.6±606.5	342.9±235.2	838.8±937.1	0.144
Albumin (g/dL)	3.3±0.7	3.3±0.8	3.3±0.6	0.754
Creatinine (mg/dL)	3.3±13.2	4.5±17.3	1.7±1.4	0.315
Beta-2 microglobulin (mg/L)	10.3±12.2	12.6±14.6	7.0±6.7	0.001
Race, N (%)				1.000
Caucasian	132 (89.8)	82 (89.1)	50 (90.9)	
African American	8 (5.4)	5 (5.4)	3 (5.5)	
Asian	2 (1.4)	1 (1.1)	1 (1.8)	
American Indian / AK native	1 (0.7)	1 (1.1)	0 (0.0)	
Other	4 (2.7)	3 (3.3)	1 (1.8)	
Ethnicity, N (%)				0.725
Non-Hispanic	138 (93.9)	88 (94.6)	50 (92.6)	
Hispanic	9 (6.1)	5 (5.4)	4 (7.4)	
High-risk genetic feature, N (%)				0.507
No	40 (43.0)	26 (40.6)	14 (48.3)	
Yes	53 (57.0)	38 (59.4)	15 (51.7)	
Del17p, N (%)				0.484
No	56 (62.9)	40 (65.6)	16 (57.1)	
Yes	33 (37.1)	21 (34.4)	12 (42.9)	
t(4;14), N (%)				0.778
No	64 (78.0)	45 (78.9)	19 (76.0)	
Yes	18 (22.0)	12 (21.1)	6 (24.0)	
t(14;16), N (%)				0.059
No	67 (82.7)	45 (77.6)	22 (95.7)	
Yes	14 (17.3)	13 (22.4)	1 (4.3)	
Any transplant (auto, allo, or tandems), N (%)				< 0.001
No	60 (44.4)	28 (30.1)	32 (76.2)	
Yes	75 (55.6)	65 (69.9)	10 (23.8)	
Transplant timing, N (%)				< 0.001
Transplant at induction	69 (51.9)	61 (67.0)	8 (19.0)	
Delay transplant to relapse	4 (3.0)	2 (2.2)	2 (4.8)	
No transplant	60 (45.1)	28 (30.8)	32 (76.2)	
Extramedullary disease, N (%)				0.098
No	97 (74.6)	66 (79.5)	31 (66.0)	
Yes	33 (25.4)	17 (20.5)	16 (34.0)	
First line of chemotherapy, N (%)				0.003
Proteasome inhibitor triplet	49 (59.8)	40 (72.7)	9 (33.3)	
VTD PACE-like regimen	18 (22.0)	7 (12.7)	11 (40.7)	
Daratumumab quadruplet	3 (3.7)	2 (3.6)	1 (3.7)	
Other	12 (14.6)	6 (10.9)	6 (22.2)	
Best response to first line of chemotherapy, N (%)				0.126
Less than CR	29 (45.3)	15 (37.5)	14 (58.3)	
CR or better	35 (54.7)	25 (62.5)	10 (41.7)	
MRD negative (10 ⁻⁶) ever achieved, N (%)				0.109
Yes	11 (9.7)	10 (13.3)	1 (2.6)	
No	22 (19.5)	13 (17.3)	9 (23.7)	
Unknown	80 (70.8)	52 (69.3)	28 (73.7)	

Plasma cell leukemia (PCL) defined as malignant plasma cell disorder with ≥5% circulating plasma cells.⁶ P value for comparing primary PCL versus secondary PCL from Wilcoxon rank-sum test (continuous variables) or Fisher's exact test (categorical variables). High-risk genetic features, as defined by the revised 2016 IMWG consensus, include the presence of t(4;14), t(14;16), Del17p13, a non-hyper diploid karyotype and

Continued on following page.

gain (1q). Missing data for each characteristic (total): lactate dehydrogenase (LDH) (82), albumin (56), creatinine (65), beta-2 microglobulin (62), race (6), ethnicity (6), high-risk genetic feature (60), Del 17p (64), t(4;14) (71), t(14;16) (72), any transplant (18), transplant timing (20), extramedullary disease (23), first-line chemotherapy (71), best response to first line of chemotherapy (89), minimal residual disease (MRD) response (40). Missing data for each characteristic (primary PCL): LDH (48), albumin (38), creatinine (45), beta-2 microglobulin (43), race (4), ethnicity (3), high-risk genetic feature (32), Del 17p (35), t(4;14) (39), t(14;16) (38), any transplant (3), transplant timing (5), extramedullary disease (13), first-line chemotherapy (41), best response to first line of chemotherapy (56), MRD response (21). Missing data for each characteristic (secondary PCL): LDH (34), albumin (18), creatinine (20), beta-2 microglobulin (19), race (2), ethnicity (3), high-risk genetic feature (28), Del 17p (29), t(4;14) (32), t(14;16) (34), any transplant (15), transplant timing (15), extramedullary disease (10), first-line chemotherapy (30), best response to first-line of chemotherapy (33), MRD response (19). AK: Alaska Native; allo: allogeneic; auto: autologous; CR: complete response; N: number; SD: standard deviation; VTD PACE: bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphide-etoposide.

26/32), with smaller proportions at stages I (6.2%, 2/32) and II (12.5%, 4/32). In contrast, sPCL patients showed a more balanced distribution across ISS stages III (48.0%, 12/25), II (36.0%, 9/25), and I (16.0%, 4/25) ($P=0.027$). Revised (R)-ISS staging also reflected higher proportions of advanced disease in pPCL, with 64.0% (16/25) in stage III, 32.0% (8/25) in stage II, and 4.0% (1/25) in stage I, compared to 50.0% (9/18) in stage III, 33.3% (6/18) in stage II, and 16.7% (3/28) in stage I for sPCL patients ($P=0.421$). However, staging analysis was limited due to missing data.

Transplantation rates differed significantly between the groups, with 69.9% (65/93) of pPCL patients undergoing transplantation compared to only 23.8% (10/42) of sPCL patients. Among pPCL patients, 50.0% (45/90) received a single autologous (auto) transplant, 4.4% (4/90) a single allogeneic (allo) transplant, 1.1% (1/90) tandem auto-auto, and 11.1% (10/90) tandem auto-allo at induction. At relapse, transplantation included 2.2% (2/90) receiving a single autologous transplant, 4.4% (4/90) a single allogeneic transplant, 1.1% (1/90) tandem auto-auto, and 1.1% (1/90) tandem auto-allo. For sPCL patients, transplantation at induction included 14.3% (6/42) receiving a single autologous transplant, 2.4% (1/42) a single allogeneic transplant, and 2.4% (1/42) tandem auto-allo, while at relapse only 5.0% (2/40) underwent a single autologous transplant.

Treatment regimens also varied between the groups. PI-based triplet regimens were more commonly used in pPCL patients (72.7%, 40/55) compared to sPCL patients (33.3%, 9/27) ($P=0.003$), whereas VTD-PACE-like (bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphide-etoposide) regimens were more frequently utilized in sPCL patients (40.7%, 11/27) compared to pPCL patients (12.7%, 7/55) ($P=0.003$). Daratumumab-containing quadruplets were infrequently used in both groups (3.6% in pPCL vs. 3.7% in sPCL; $P=0.003$). Clinical outcomes showed that more pPCL patients achieved a complete response (CR) or better (62.5%, 25/40) compared to sPCL patients (41.7%, 10/24) ($P=0.126$). Minimal residual disease (MRD) negativity was observed in 13.3% (10/75) of pPCL patients, compared to 2.6% (1/24) of sPCL patients ($P=0.109$).

Survival

The median OS for the entire cohort was 20.4 months; 68.0% of patients died during the study period. Notably, patients with pPCL demonstrated a significantly longer median OS

of 36.6 months compared to sPCL, whose median OS was only 3.2 months ($P<0.001$). An exploratory analysis was conducted to evaluate high-risk genetic features as defined by the revised 2016 IMWG consensus guidelines, which include the presence of t(4;14), t(14;16), Del17p13, a non-hyperdiploid karyotype, and a gain (1q) (13). However, the small sample size limits definite conclusions. In this exploratory analysis, high-risk genetic features were not significantly associated with worse survival across the entire cohort (HR 1.10, $P=0.749$). Furthermore, the presence of the t(11;14) translocation did not demonstrate a significant survival benefit (HR 0.65, $P=0.203$) (*Online Supplementary Tables S1, S2*). EM disease, as defined by the treating institution (it is uncertain whether true EM disease or para-medullary disease), was non-significantly associated with worse survival as well (HR 1.57, $P=0.919$) (Table 2, Figures 1, 2).

Receipt of any transplant, irrespective of type (auto, allo or tandems) significantly improved survival across the entire cohort and both PCL subtypes ($P<0.001$). The median OS for the entire cohort was 48.7 months for those who underwent transplantation, compared to 5.9 months for those who did not ($P<0.001$). For pPCL patients, the median OS with transplantation was 49.5 months, compared to 12.5 months without ($P<0.001$). In sPCL patients, transplantation ($N=10/42$) resulted in a median OS of 16 months compared to 3.4 months without any transplant ($P=0.005$). Allogeneic transplantation did not show a superior survival over autologous HSCT (49.5 vs. 37.9 months, $P=0.348$). Patients who underwent transplantation were generally younger, with a median age of 56.4 ± 9.0 years compared to 64.8 ± 10.0 years for non-transplanted patients ($P<0.001$). pPCL patients were more likely to receive transplants than sPCL patients ($P<0.001$). MRD negativity was more frequent in the transplant group (16.1%, 9/38) compared to the non-transplant group (2.5%, 1/76) ($P<0.001$). However, there were no significant differences between the transplant and non-transplant cohorts in baseline levels of LDH, creatinine, beta-2 microglobulin, albumin, or the prevalence of EM disease. Similarly, no significant differences were observed in the frequency of high-risk genetic features, t(11;14), type of chemotherapy or novel regimens, and CR rates between the two groups (*Online Supplementary Table S3*).

Among treatment modalities, no significant differences were observed between PI-based triplet therapies and VTD-PACE-like regimens across the entire cohort or by

Table 2. Associations with survival.

Characteristic	Group	Age-adjusted HR (95% CI)	Multivariate ¹ HR (95% CI)	P
Secondary PCL	Total, N=153	4.54 (3.01-6.83)	2.37 (1.47-3.84)	<0.001
Any transplant (auto, allo, or tandems)	Total, N=153	0.12 (0.06-0.21)	0.16 (0.08-0.29)	<0.001
Extramedullary disease	Total, N=153	1.57 (0.99-2.48)	0.97 (0.57-1.66)	0.919
Any transplant	Primary PCL, N=96	0.16 (0.07-0.37)	0.16 (0.07-0.37)	<0.001
Extramedullary disease	Primary PCL, N=96	1.26 (0.64-2.49)	1.09 (0.55-2.18)	0.797
Any transplant	Secondary PCL, N=57	0.20 (0.07-0.54)	0.20 (0.07-0.54)	0.001
Extramedullary disease	Secondary PCL, N=57	1.79 (0.94-3.42)	1.12 (0.48-2.62)	0.791

Plasma cell leukemia (PCL) defined as malignant plasma cell disorder with ≥5% circulating plasma cells.⁶ auto: autologous; allo: allogeneic; CI: confidence interval; HR: hazards ratio; N: number. ¹Further adjusted for PCL type and any transplant (auto, allo, or tandems).

PCL type. The median OS for the overall cohort with PI-based triplet therapy was 28.2 months compared to 12.6 months with VTD-PACE like regimen (*P*=0.212). In pPCL patients, the median OS with PI-based triplet therapy was 36.6 months and that with VTD-PACE like regimen was 31.8 months (*P*=0.734). While for sPCL patients, median OS with PI-based triplet therapy was 7.4 months compared to 6.6 months with VTD-PACE like regimen (*P*=0.654) (Figure 3).

Discussion

Plasma cell leukemia remains a highly aggressive malignancy with poor survival, characterized by early relapse and high mortality rates, even in the current era of novel therapeutic agents and HSCT.^{10,11} Survival outcomes in PCL have been reported to be influenced by various factors, including PCL subtype, high-risk genetic features, clinical parameters, and response to treatment.^{3,14-18} The median OS for pPCL reported in prior studies varies widely, from 18 months to over 30 months.^{19,20} This variability is likely attributable to the lack of standardized diagnostic criteria and treatment protocols for this rare malignancy and differences in median follow-up durations, which complicate direct comparisons of outcomes among novel agents and transplantation. Given the high tumor burden in PCL, there is an urgent need for rapid disease control, and both PI-based therapies as well as HSCT have demonstrated deeper response rates compared to conventional therapies such as alkylating agents (melphalan, cyclophosphamide, cisplatin) and anthracyclines (mitoxantrone, cytarabine, adriamycin) in combination with vincristine and etoposide.^{18,21} In our study, the median OS of pPCL patients was 36.6 months. Among this cohort, 47.0% received PI-based treatment, and 69.9% underwent any transplantation, with 50.0% receiving single autologous transplantation. These findings are comparable to the 36.3-month median OS observed in a small prospective study by Royer *et al.*, where 64.1% (25/39) underwent transplantation and 89.0% (35/39) of patients received PI-based induction.²⁰ Pagano *et al.*¹⁸ noted that receiving any transplant improves survival in pPCL,¹⁵ consistent with our findings (HR

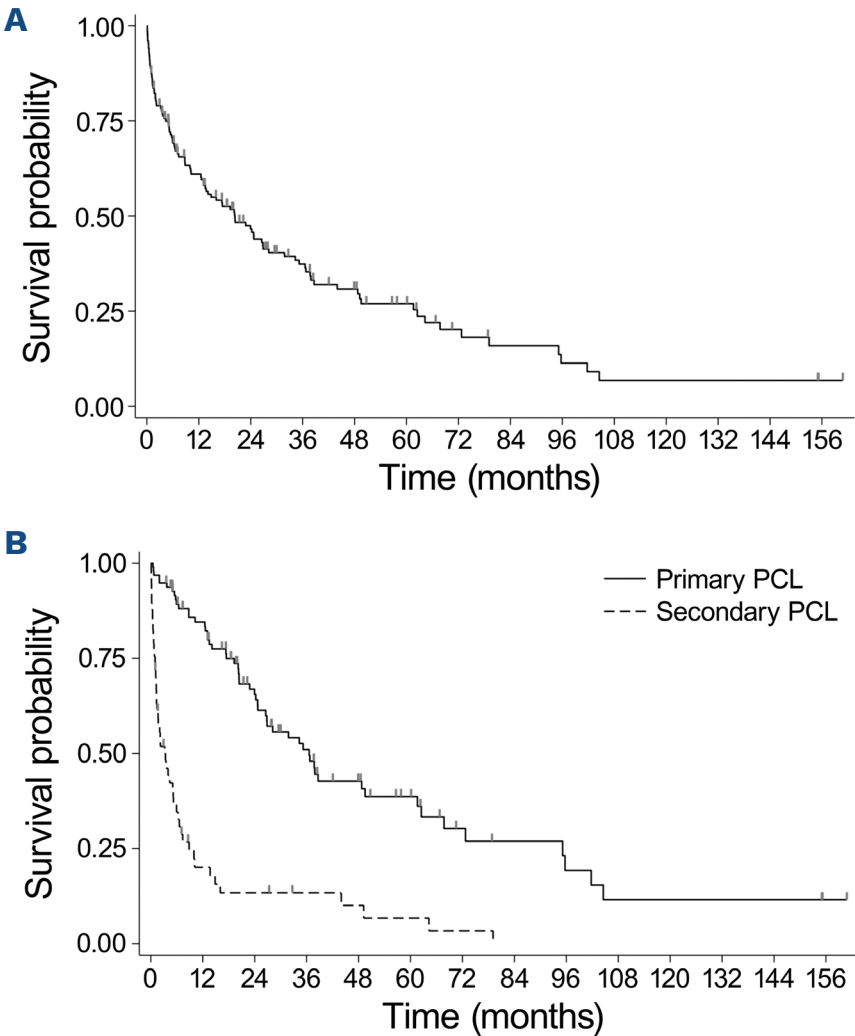


Figure 1. Overall survival for patients with plasma cell leukemia. (A) Death occurred in 104 of 153 (68.0%) plasma cell leukemia (PCL) patients. Median (95% Confidence Interval [CI]) survival was 20.4 (13.1-26.8) months. (B) Stratifying by PCL type, median (95% CI) survival was 36.6 (24.7-61.6) months for primary PCL (solid line) and 3.2 (1.3-5.2) months for secondary PCL (dashed line) (*P*<0.001).

0.16, *P*<0.001). Pagano *et al.* also further added that transplant showed a significant decrease in risk of death by 69.0% and risk of relapse by 88.0%.¹⁸ Our pPCL cohort demonstrated a considerably longer median OS of 49.5 months with any transplant. Previous literature suggests that tandem auto-allo transplant may contribute to prolonged survival in pPCL. For instance, Lebovic *et al.* reported that pPCL patients undergoing tandem auto-allo achieved OS beyond 40 months.²² Lawless *et al.*²³ also iden-

tified a significant 100-day progression-free survival (PFS) benefit with tandem auto-allo, with a median OS of 34.6% for allogeneic transplant recipients and 31.3% for autologous transplant recipients at 60 months. In their cohort, 16.2% of patients received tandem auto-allo, closely aligning with our cohort's rate of 14.6% for tandem auto-allo.²³ Mahindra *et al.* further reported a 3-year median OS of 84.0% in pPCL patients treated with tandem auto-allo.²⁴ However, a larger study by Dhakal *et al.* involving only 0.08% of patients undergoing tandem auto-allo transplantation demonstrated a lower median OS of 28.0% with autologous and 31.0% with allogeneic transplantation at four years.²⁵ Therefore, additional prospective studies are warranted to elucidate the potential benefits of upfront tandem autologous-reduced intensity conditioning allogeneic transplantation in pPCL. Consistent with previous literature, our study did not suggest a superior survival advantage of initial allogeneic transplantation over autologous transplantation, likely due to high rate of non-relapse mortality (NRM) ranging from 17% to 41.0% with allogeneic transplantation in various studies,²³⁻²⁵ perhaps due to lack of power to find such a difference. Furthermore, the numbers were too small to identify a potential benefit among patients undergoing allogeneic transplant from a match-related donor, although this population is known to experience lower rates of NRM.

While PI-based therapies have shown superior responses in pPCL compared to conventional chemotherapy combinations,^{21,26} our study did not observe a significant survival difference between PI triplet regimens over conventional chemotherapy combinations such as VTD-PACE, potentially due to missing data in 43.0% of pPCL cohort. However, Katodritou *et al.* reported improved survival with the bortezomib-lenalidomide-dexamethasone (VRd) regimen compared to bortezomib-dexamethasone-cyclophosphamide (VCd), bortezomib-anthracycline-dexamethasone (PAD), vincristine-doxorubicin-dexamethasone (VAD), and melphalan prednisone (MP).²⁷ Similarly, a single center study noted survival advantage of bortezomib or carfilzomib over the VTD-PACE regimen.¹⁰ The influence of treatment response may be modulated by immune type or cytogenetics, as bortezomib has been shown to be effective in patients with CD27-positive plasma cells, a subset that comprised 37.0% of the Katodritou study cohort.^{27,28} While immune modulatory drugs like lenalidomide are involved in cyclin D1 dysregulation,²⁹ which is coded by CCND1 and was noted to be a commonly associated 14q32 translocation frequently present among pPCL.³⁰ Therefore, missing data regarding immune-phenotype and immunoglobulin high chain (IGH) translocation data in our study may have limited our ability to draw conclusions in this regard. Survival improvements for sPCL with novel agents and transplantation have been modest. In our sPCL cohort, the median OS of 16 months with transplantation observed here mirrors the 17.5 months reported by Wang *et al.*³¹ Despite these efforts, sPCL survival remains significantly lower than that of pPCL, and the underlying mechanisms remain poorly understood.

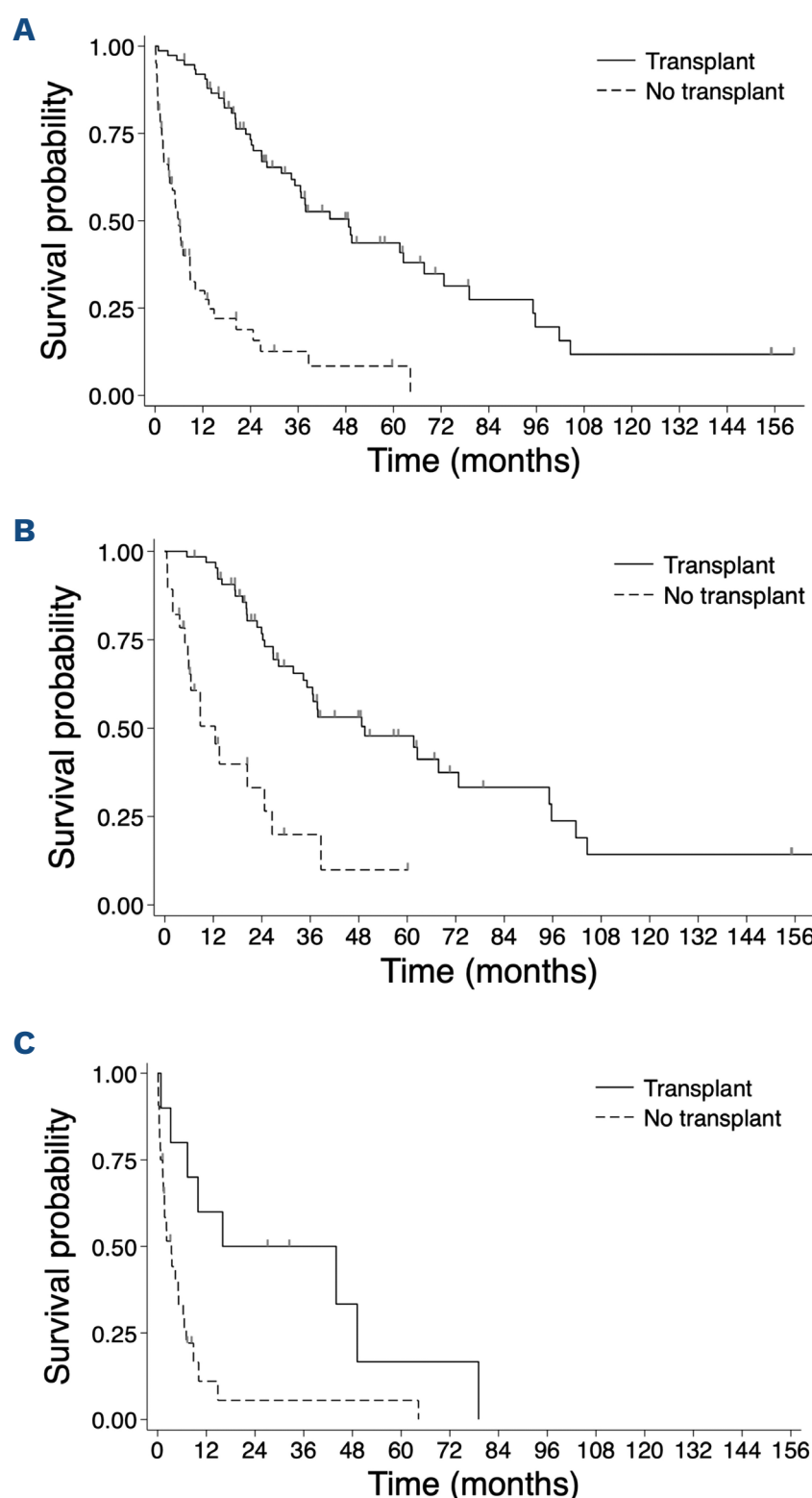


Figure 2. Overall survival for plasma cell leukemia patients with or without a transplant after diagnosis. Plasma cell leukemia (PCL) patients with (solid line) or without (dashed line) a transplant after their PCL diagnosis. (A) Median (95% Confidence Interval [CI]) survival for entire cohort of PCL patients was 48.7 (34.3-67.7) months with transplant and 5.9 (3.5-8.8) months without transplant ($P < 0.001$). (B) Median (95% CI) survival for primary PCL was 49.5 (34.3-72.7) months with transplant and 12.5 (5.7-24.7) months without transplant ($P < 0.001$). (C) Median (95% CI) survival for secondary PCL was 16.0 (0.8- not reached) months with transplant and 3.4 (1.3-6.3) months without transplant ($P = 0.005$).

This disparity is likely driven by differences in the treatment responses, molecular pathways, heavy disease pre-treatment during MM therapy, and drug resistance.¹² Skerget *et al.* identified high-risk proliferative gene expression in 83.3% of their sPCL cohort compared to 26.1% of pPCL cases, potentially explaining the more aggressive clinical behavior of sPCL at the molecular level.³² Moreover, response rates to PI-based

therapy are lower in sPCL (25-60%) as compared to >80.0% in pPCL.^{16,31} In addition, quality of response to PI-based regimens varies between pPCL and sPCL.¹⁹ The poor performance status of sPCL patients, often a consequence of extensive pre-treatment during the MM phase, further limits their ability to undergo salvage therapies.¹⁶

Despite advancement in treatment regimens, survival in PCL patients remains poor, with a median OS of the entire cohort in the current study of 20.4 months and with over 60% of patients succumbing within a few years of diagnosis. While deep initial responses are important, sustained remission remains the key goal. In the early 1990s, Sica *et al.* observed that, despite achieving clinical and laboratory remission in a PCL case, MRD often persists, which can hinder longer-term remission.³³ Kun-Huei Yeh *et al.* reported a case of PCL that remained in complete remission for up to 59 months with negative MRD.³⁴ Moreover, Kaiser *et al.* are currently exploring the impact of MRD on survival outcome in a prospective study. This study involves high-risk MM and PCL patients undergoing intensive induction therapy with daratumumab, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone (Dara-CVRd), followed by high-dose melphalan/autoSCT, bortezomib-augmented therapy, and Dara-VRD consolidation for 18 cycles, followed by Dara-R maintenance. The study has shown a decrease in MRD positivity from 41.0% post-induction to 14.0% 100 days post-ASCT, although survival outcomes have yet to be reported.³⁵ In our study, MRD status was unavailable for the majority of patients. However, treatments guided by MRD status, which can be reliably assessed via multi-parameter flow cytometry and next generation sequencing, could significantly influence survival outcomes.³⁶

Cytogenetic aberrations such as del1p21, t(4;14), and MYC translocations, are all associated with inferior survival outcomes.^{3,37,38} While the prognostic significance of t(14;16), amp1q21 remains unclear, t(11;14) has been associated with longer survival in some studies.³⁹ In the current pPCL cohort, we observed a non-significant adverse impact of del17p. However, this is to be interpreted with caution as there were few del17p events noted and 36.4% of the cohort had data missing, limiting the study's statistical power. Similarly, in independent studies, Tiedemann *et al.* reported no significant impact of del17p on pPCL survival.³ In contrast, Deng *et al.* and Li *et al.* observed significant survival associations with del17p.^{10,40} The negative prognostic implications of del17p are possibly attributed to TP53 inactivation.^{3,39} The discrepancies could stem from variations in cytogenetic assessment methods in retrospective studies, as conventional techniques may fail to detect sub-chromosomal mutations or RNA splicing variations. Further use of gene expression profiling and whole-genome sequencing is highlighting the presence of enriched MAF translocations, frequent copy number alterations, biallelic inactivation of TP53, driver gene

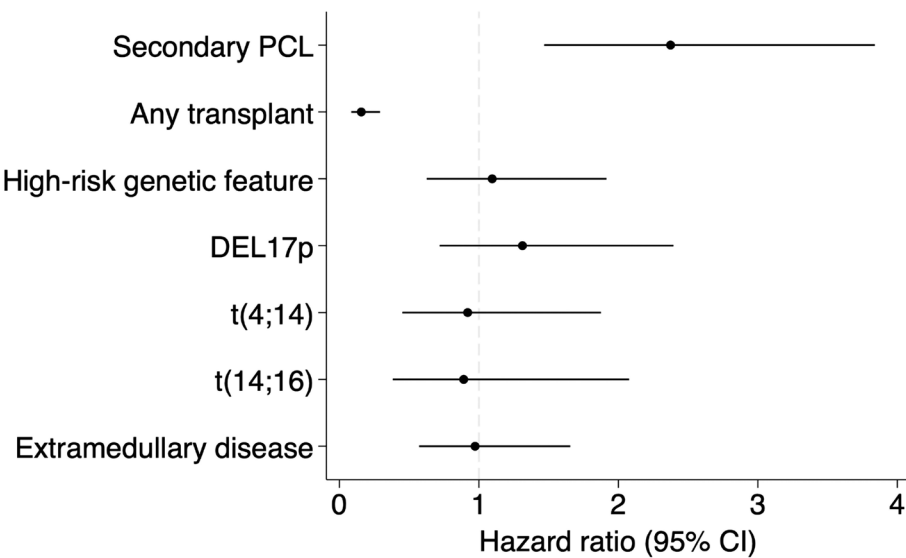


Figure 3. Associations with survival. Forest plot of plasma cell leukemia (PCL) patients with (solid line) or without (dashed line) a transplant after their PCL diagnosis. (See Table 2).

mutations in KRAS, ERAS, and NRAS, high-risk gene signatures, such as the GENE70 and GENE80 models, and an altered transcriptome involving lipid metabolism and adhesion molecules in pPCL compared to MM, conferring its aggressiveness.^{41,42} As high-throughput genomic technologies advance, we anticipate more precise molecular stratification of PCL, which may contribute to personalized treatment approaches. Similar to the current pPCL cohort, the substantial missing data on high-risk genetic features in the sPCL cohort (49.0%) limited our ability to draw definitive conclusion about its role on this sub-type. The t(11;14) translocation has been associated with improved survival outcomes in PCL patients, with a reported median OS of 39.2 months compared to 17.9 months in patients without this translocation.^{37,39} This favorable prognosis may stem from a more advantageous transcriptomic profile, a lower frequency of double-hit events, and the differential expression of *BCL2* family members linked to this translocation.³⁹ However, in the current analysis, no significant survival benefit was observed for patients with the t(11;14) translocation, likely due to missing data in over 40.0% of the cohort.

Clinical and biological parameters, such as elevated LDH, hypoalbuminemia, elevated beta-2 microglobulin, ISS stage III, and thrombocytopenia, have also been shown to negatively impact survival in PCL patients.^{14-18,26} In our study, we investigated the role of EMD on survival outcomes in PCL, recognizing that the evaluation of EMD at diagnosis and its response to treatment are critical components of PCL management, as per IMWG consensus guidelines.⁶ Extramedullary disease is observed with greater frequency in PCL compared to MM, with reported incidences in one study of 20.0% in pPCL, 28.0% in sPCL, and 8.0% in MM.⁴ The prevalence of EMD also varies between PCL subtypes. Tiedemann *et al.* documented high incidence of EMD in pPCL, while Pagano *et al.* observed lesser EMD involvement in pPCL, a finding corroborated

by Papadimitriou *et al.* and Li *et al.*^{3,4,10,18} The immature immune-phenotype of PCL plasma cells, often characterized by absence of CD56 and CD20 overexpression, likely contributes to the increased propensity for spread beyond the bone marrow microenvironment.^{14,43} In our cohort, EMD did not demonstrate an independent correlation with worse survival outcomes in either type. However, this may be attributed to incomplete data for 15.0% of patients, potentially limiting the significance of our findings. Nevertheless, Li *et al.* identified worse survival in both PCL types with EMD, with 47.0% of their cohort presenting EMD.¹⁰ Additionally, Jiminez-Zepada *et al.* suggested TP53 mutations and chromosome 1 alteration may drive EMD and its associated poor prognosis.⁴⁴ A dreadful complication of PCL is CNS involvement which is associated with significantly shorter survival.⁴⁵ Although the current cohort lacks sufficient data on CNS involvement, small scale case studies indicate a higher prevalence in sPCL, particularly among Caucasians and those treated with cyclophosphamide-dexamethasone.^{10,45} In our study, 3 patients had documented CNS disease: 2 with primary PCL and one with secondary PCL. The patients had missing data on most disease characteristics, but all patients had elevated LDH, and one had EMD. The 2 affected individuals were aged 70 and 88 years of age, while the younger patient, aged 45, had undergone a single autologous transplant at induction. Neuro-meningeal relapse has been noted in some studies involving transplantation of PCL patients, highlighting consideration of incorporating prophylactic intrathecal treatment.²⁰

Our study has several limitations. First, its retrospective design may introduce inherent biases. Additionally, there was a significant amount of missing data across key variables, including high-risk genetic features (missing in 39.0% of cases), first-line chemotherapy (46.0% missing), and treatment response (58.0% missing), which limits our ability to draw definitive conclusions. Moreover, the study population was predominantly white (90.0%), restricting our ability to explore racial and ethnic differences. Selection bias is a key limitation, as patients who were too ill or had uncontrolled disease were less likely to undergo transplantation or may have preferentially received PACE-based or other intensive regimens, confounding treatment outcome comparisons. Also, prior studies have demonstrated improved response rates, prolonged PFS, and enhanced OS with daratumumab-based quadruplets, but the low utilization in our cohort (approx. 4%) limited our ability to assess its impact on survival.^{10,30} Additionally, EM disease classification varied by institution, making it unclear whether cases reflected true EM or para-medullary involvement, limiting analytical precision. Furthermore, it is possible that t(11;14) did not appear to confer a survival benefit because the BCL-2 inhibitor venetoclax was not widely used during the study period, limiting its potential therapeutic impact.

Despite these limitations, this is, to the best of our knowledge, the largest multicenter study conducted in the US of this rare disease. The multicenter design also enhances the generalizability of our findings. Importantly, we incorporated the updated IMWG criteria, which define PCL by the presence of at least 5% circulating plasma cells, broadening the scope of our analysis compared to the more restrictive 20% threshold used previously.⁶ In conclusion, although significant progress has been made in the understanding and treatment of PCL, continued research is essential to further refine therapeutic strategies and address ongoing challenges. Transplantation remains a key treatment option, offering survival advantage across PCL subtypes. Future investigations should focus on novel agents to improve response rates, particularly in sPCL. Promising new therapies such as BCL-2 inhibitor venetoclax, have been shown to have potential in inducing responses in pPCL cases with t(11;14), a translocation more commonly observed in this subtype.^{3,4,46-48} Improved responses with venetoclax have also been noted in relapsed sPCL cases harboring t(11;14) FISH abnormalities.⁴⁸ Additionally, bispecific T-cell engagers targeting B-cell maturation antigen (BCMA), CD 19, and other targets represent promising avenues for future investigation.^{8,49} While the results of CAR-T therapy in PCL have been modest, continued research in this area is warranted. Integration of MRD-directed maintenance approaches may help to ascertain the minimum treatment durations necessary to achieve optimal survival. Moreover, our study lacks data on risk factors for secondary PCL, prior transplant history, and clonal evolution, as the dataset includes only patients already diagnosed with PCL or those who have progressed to sPCL. Future studies should investigate these risk factors to better understand disease progression and optimize treatment strategies. Finally, a concerted international research effort is essential for making meaningful progress in the treatment of rare diseases such as PCL.

Disclosures

No conflicts of interest to disclose.

Contributions

SS and SP wrote the manuscript. BW carried out the statistical analysis, and reviewed and edited the manuscript. AL, IC, DS, DG, ML, MO, MW, ON, LS, DD, VV, DC and KG supervised the study, and reviewed and edited the manuscript.

Data-sharing statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author. Any shared data will be provided in accordance with institutional and ethical guidelines.

References

- Ramsingh G, Mehan P, Luo J, Vij R, Morgensztern D. Primary plasma cell leukemia: a Surveillance, Epidemiology, and End Results database analysis between 1973 and 2004. *Cancer*. 2009;115(24):5734-5739.
- International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757.
- Tiedemann RE, Gonzalez-Paz N, Kyle RA, et al. Genetic aberrations and survival in plasma cell leukemia. *Leukemia*. 2008;22(5):1044-1052.
- Papadimitriou SI, Terpos E, Liapis K, et al. The cytogenetic profile of primary and secondary plasma cell leukemia: etiopathogenetic perspectives, prognostic impact and clinical relevance to newly diagnosed multiple myeloma with differential circulating clonal plasma cells. *Biomedicines*. 2022;10(2):209.
- Kyle RA, Maldonado JE, Bayrd ED. Plasma cell leukemia. Report on 17 cases. *Arch Intern Med*. 1974;133(5):813-818.
- Fernández de Larrea C, Kyle R, Rosiñol L, et al. Primary plasma cell leukemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage. *Blood Cancer J*. 2021;11(12):192.
- Gonsalves WI, Rajkumar SV, Go RS, et al. Trends in survival of patients with primary plasma cell leukemia: a population-based analysis. *Blood*. 2014;124(6):907-912.
- Li C, Cao W, Que Y, et al. A phase I study of anti-BCMA CAR T cell therapy in relapsed/refractory multiple myeloma and plasma cell leukemia. *Clin Transl Med*. 2021;11(3):e346.
- Parrondo RD, Moustafa MA, Reeder C, et al. Efficacy of daratumumab-based regimens for the treatment of plasma cell leukemia. *Clin Lymphoma Myeloma Leuk*. 2021;21(5):355-360.
- Li AY, Kamangar F, Holtzman NG, et al. A clinical perspective on plasma cell leukemia: a single-center experience. *Cancers (Basel)*. 2024;16(11):2149.
- Tessier C, LeBlanc R, Roy J, et al. Poor outcome despite modern treatments: a retrospective study of 99 patients with primary and secondary plasma cell leukemia. *Cancer Med*. 2024;13(17):e70192.
- Noel P, Kyle RA. Plasma cell leukemia: an evaluation of response to therapy. *Am J Med*. 1987;83(6):1062-1068.
- Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962.
- García-Sanz R, Orfão A, González M, et al. Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. *Blood*. 1999;93(3):1032-1037.
- Jung SH, Lee JJ, Kim K, et al. The role of frontline autologous stem cell transplantation for primary plasma cell leukemia: a retrospective multicenter study (KMM160). *Oncotarget*. 2017;8(45):79517-79526.
- Jurczyszyn A, Castillo JJ, Avivi I, et al. Secondary plasma cell leukemia: a multicenter retrospective study of 101 patients. *Leuk Lymphoma*. 2019;60(1):118-123.
- Katodritou E, Terpos E, Delimpasi S, et al. Real-world data on prognosis and outcome of primary plasma cell leukemia in the era of novel agents: a multicenter national study by the Greek Myeloma Study Group. *Blood Cancer J*. 2018;8(3):31.
- Pagano L, Valentini CG, De Stefano V, et al. Primary plasma cell leukemia: a retrospective multicenter study of 73 patients. *Ann Oncol*. 2011;22(7):1628-1635.
- Gowda L, Shah M, Badar I, et al. Primary plasma cell leukemia: autologous stem cell transplant in an era of novel induction drugs. *Bone Marrow Transplant*. 2019;54(7):1089-1093.
- Royer B, Minvielle S, Diouf M, et al. Bortezomib, doxorubicin, cyclophosphamide, dexamethasone induction followed by stem cell transplantation for primary plasma cell leukemia: a prospective phase II study of the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2016;34(18):2125-2132.
- Katodritou E, Terpos E, Kelaidi C, et al. Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: analysis of the Greek myeloma study group. *Am J Hematol*. 2014;89(2):145-150.
- Lebovic D, Zhang L, Alsina M, et al. Clinical outcomes of patients with plasma cell leukemia in the era of novel therapies and hematopoietic stem cell transplantation strategies: a single-institution experience. *Clin Lymphoma Myeloma Leuk*. 2011;11(6):507-511.
- Lawless S, Iacobelli S, Knelange NS, et al. Comparison of autologous and allogeneic hematopoietic cell transplantation strategies in patients with primary plasma cell leukemia, with dynamic prediction modeling. *Haematologica*. 2023;108(4):1105-1114.
- Mahindra A, Kalaycio ME, Vela-Ojeda J, et al. Hematopoietic cell transplantation for primary plasma cell leukemia: results from the Center for International Blood and Marrow Transplant Research. *Leukemia*. 2012;26(5):1091-1097.
- Dhakal B, Patel S, Girnius S, et al. Hematopoietic cell transplantation utilization and outcomes for primary plasma cell leukemia in the current era. *Leukemia*. 2020;34(12):3338-3347.
- Atas U, Salim O, Iltar U, et al. Survival outcomes of patients with primary plasma cell leukemia in the era of proteasome inhibitors and immunomodulatory agents: a real-life multicenter analysis. *Turk J Haematol*. 2024;41(4):225-235.
- Katodritou E, Kastiris E, Dalampira D, et al. Improved survival of patients with primary plasma cell leukemia with VRd or daratumumab-based quadruplets: a multicenter study by the Greek myeloma study group. *Am J Hematol*. 2023;98(5):730-738.
- Katodritou E, Verrou E, Gastari V, Hadjiaggelidou C, Terpos E, Zervas K. Response of primary plasma cell leukemia to the combination of bortezomib and dexamethasone: do specific cytogenetic and immunophenotypic characteristics influence treatment outcome? *Leuk Res*. 2008;32(7):1153-1156.
- Martiniani R, Di Loreto V, Di Sano C, Lombardo A, Liberati AM. Biological activity of lenalidomide and its underlying therapeutic effects in multiple myeloma. *Adv Hematol*. 2012;2012:842945.
- Shalaby K, Azad F, Parker S, et al. Clinical characteristics and survival outcomes of patients with primary and secondary plasma cell leukemia according to the 2021 definition: a single center retrospective study. *Clin Lymphoma Myeloma Leuk*. 2025;25(1):67-75.
- Wang H, Zhou H, Zhang Z, Geng C, Chen W. Bortezomib-based regimens improve the outcome of patients with primary or secondary plasma cell leukemia: a retrospective cohort study. *Turk J Haematol*. 2020;37(2):91-97.
- Skerget S, Penaherrera D, Mikhael J, Keats JJ. High-risk gene

- expression subtype provides molecular basis for different clinical presentation of primary and secondary plasma cell leukemia. *Blood*. 2021;138(Suppl 1):726.
33. Sica S, Chiusolo P, Salutari P, et al. Long-lasting complete remission in plasma cell leukemia after aggressive chemotherapy and CD34-selected autologous peripheral blood progenitor cell transplant: molecular follow-up of minimal residual disease. *Bone Marrow Transplant*. 1998;22(8):823-825.
 34. Yeh KH, Lin MT, Tang JL, Yang CH, Tsay W, Chen YC. Long-term disease-free survival after autologous bone marrow transplantation in a primary plasma cell leukaemia: detection of minimal residual disease in the transplant marrow by third-complementarity-determining region-specific probes. *Br J Haematol*. 1995;89(4):914-916.
 35. Kaiser MF, Hall A, Walker K, et al. Depth of response and minimal residual disease status in ultra high-risk multiple myeloma and plasma cell leukemia treated with daratumumab, bortezomib, lenalidomide, cyclophosphamide and dexamethasone (Dara-CVRd): results of the UK optimum/MUKnine trial. *J Clin Oncol*. 2021;39(15_suppl):8001.
 36. Blum A, Haussmann K, Streitz M, et al. Standardized assay for assessment of minimal residual disease in blood, bone marrow and apheresis from patients with plasma cell myeloma. *Sci Rep*. 2019;9(1):2922.
 37. Avet-Loiseau H, Daviet A, Brigaudeau C, et al. Cytogenetic, interphase, and multicolor fluorescence in situ hybridization analyses in primary plasma cell leukemia: a study of 40 patients at diagnosis, on behalf of the Intergroupe Francophone du Myélome and the Groupe Français de Cytogénétique Hématologique. *Blood*. 2001;97(3):822-825.
 38. Chang H, Qi X, Yeung J, Reece D, Xu W, Patterson B. Genetic aberrations including chromosome 1 abnormalities and clinical features of plasma cell leukemia. *Leuk Res*. 2009;33(2):259-262.
 39. Cazaubiel T, Leleu X, Perrot A, et al. Primary plasma cell leukemias displaying t(11;14) have specific genomic, transcriptional, and clinical features. *Blood*. 2022;139(17):2666-2672.
 40. Deng J, Qin X, Ma G, et al. Development of a clinical prognostic model for primary plasma cell leukemia patients treated with novel agents: a multicenter retrospective cohort study. *Ann Hematol*. 2024;103(9):3691-3699.
 41. Schinke C, Boyle EM, Ashby C, et al. Genomic analysis of primary plasma cell leukemia reveals complex structural alterations and high-risk mutational patterns. *Blood Cancer J*. 2020;10(6):70.
 42. Usmani SZ, Nair B, Qu P, et al. Primary plasma cell leukemia: clinical and laboratory presentation, gene-expression profiling and clinical outcome with Total Therapy protocols. *Leukemia*. 2012;26(11):2398-2405.
 43. Kraj M, Kopeć-Szłęzak J, Pogłód R, Kruk B. Flow cytometric immunophenotypic characteristics of 36 cases of plasma cell leukemia. *Leuk Res*. 2011;35(2):169-176.
 44. Jimenez-Zepeda VH, Neme-Yunes Y, Braggio E. Chromosome abnormalities defined by conventional cytogenetics in plasma cell leukemia: what have we learned about its biology? *Eur J Haematol*. 2011;87(1):20-27.
 45. DeGraaff D, Coffey DG. Spinal disease predicts CNS involvement in patients with plasma cell leukemia. *Blood*. 2021;138(Suppl 1):4746.
 46. Charalampous C, Doucette K, Chappell A, Vesole DH. Venetoclax-based induction therapy for primary plasma cell leukemia with high BCL-2 expression. *Leuk Lymphoma*. 2024;65(12):1901-1904.
 47. Roy T, An JB, Doucette K, Chappell AM, Vesole DH. Venetoclax in upfront induction therapy for primary plasma cell leukemia with t(11;14) or BCL2 expression. *Leuk Lymphoma*. 2022;63(3):759-761.
 48. Elsabah H, Ghasoub R, El Omri H, Benkhadra M, Cherif H, Taha RY. Venetoclax in the treatment of secondary plasma cell leukemia with translocation t(11;14): a case report and literature review. *Front Oncol*. 2024;14:1390747.
 49. Garfall AL, Stadtmauer EA, Hwang WT, et al. Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. *JCI Insight*. 2018;3(8):120505.