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PLASMA CELL LEUKEMIA: REVISED DIAGNOSTIC CRITERIA, CLINICAL-BIOLOGICAL FEATURES, AND THERAPEUTIC ADVANCES

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ABSTRACT

Plasma cell leukemia (PCL) is a rare and aggressive plasma cell neoplasm, classified as primary (de novo) or secondary (transformed from multiple myeloma, MM). Revised 2013 IMWG diagnostic criteria, lowering the threshold to ≥5% circulating plasma cells (vs. ≥20%), better identify high-risk patients, with a similarly reduced median overall survival (6–13 months). Clinically, PCL presents earlier (median age 52–61 years), frequent extramedullary involvement (hepatosplenomegaly, plasmacytomas), aggressive lab features (hypercalcemia, renal failure, elevated LDH), and high-risk genomic profiles (del(17p), TP53 mutations, t(11;14)). Treatment involves quadruplet regimens combining anti-CD38 agents (e.g., daratumumab), proteasome inhibitors, immunomodulators, and dexamethasone, followed by autologous stem cell transplantation (ASCT) in eligible patients, improving survival (median PFS: 24 months). Allogeneic SCT is reserved for refractory cases. Maintenance therapy (lenalidomide, daratumumab) and minimal residual disease (MRD) monitoring optimize outcomes. Despite advances, prognosis remains poor, necessitating deeper molecular insights and clinical trials targeting genetic drivers (e.g., MYC, TP53) to personalize therapy.

KEYWORDS: Plasma cell leukemia, Primary plasma cell leukemia, Secondary plasma cell leukemia, Diagnostic criteria, Molecular biology, Cytogenetics, Treatment.

INTRODUCTION

Plasma cell leukemia (PCL) is a rare and aggressive variant of plasma cell neoplasms characterized by circulating malignant plasma cells in the peripheral blood. Unlike multiple myeloma (MM), which typically remains confined to the bone marrow, PCL exhibits a more invasive clinical phenotype with systemic dissemination. Although PCL accounts for less than 5% of all plasma cell disorders, its rapid progression and poor prognosis make it a major focus in hematology.

In 1974, Kyle established diagnostic criteria for primary plasma cell leukemia (pPCL), requiring both >20% circulating plasma cells AND an absolute plasma cell count $>2\times10^9$/L in peripheral blood.[1] These criteria were deemed overly restrictive. In 2013, the International Myeloma Working Group (IMWG) proposed that either criterion alone suffices for PCL diagnosis.[2] Recent studies suggest that even lower percentages of circulating plasma cells (≥5%) may correlate with poor prognosis in newly diagnosed MM patients, highlighting the need to redefine diagnostic thresholds.[3,4] For example, the presence of ≥5% circulating plasma cells in MM patients carries a similarly unfavorable prognostic impact as traditionally defined PCL.

PCL is classified as primary (pPCL) in the absence of prior MM or secondary (sPCL) when arising from leukemic transformation of preexisting MM.[5]

Objective of this article: To review the evolving diagnostic criteria, distinct clinical-biological features, and therapeutic strategies for PCL, with emphasis on recent advancements in risk stratification, molecular profiling, and novel treatment approaches.

REVISED DIAGNOSTIC CRITERIA BY THE IMWG

Historically, pPCL was defined by ≥20% circulating plasma cells and an absolute count $>2\times10^9$/L. However, these 1974 criteria were never prospectively validated. In 2013, the IMWG highlighted their restrictive nature, as many case series considered either criterion sufficient for diagnosis.[6] Patients with baseline leukopenia due to depleted bone marrow reserves may meet the percentage criterion but not the absolute count.[6]

The IMWG proposed revised diagnostic criteria, lowering the threshold to ≥5% circulating plasma cells based on clinical and prognostic evidence. This change aimed to evaluate whether the new threshold carries a

similar prognostic impact as the classical definition (≥20%). Two large retrospective cohorts were analyzed:

- The Catalan Myeloma Group (Spain): 482 patients, including 100 with circulating plasma cells, categorized by percentages (0%, 1–4%, 5–20%, ≥20%).
- Mayo Clinic (USA): 176 MM patients with circulating plasma cells, grouped similarly (1–4%, 5–19%, ≥20%).

Median overall survival (OS) was the primary endpoint. Analyses revealed significantly reduced OS in patients with ≥5% circulating plasma cells (6–13 months vs. 47 months for those without), comparable to classical PCL. These patients also exhibited typical PCL features, such as higher bone marrow infiltration and lower platelet counts.[6]

This redefinition, relying on accessible peripheral blood smears, increases PCL diagnosis rates from 0.7% to 2.5%, enabling earlier intervention. It underscores the importance of including these patients in high-risk MM clinical trials, integrating innovative therapies like immunotherapies and combination regimens. Further research into PCL's molecular characteristics is critical to optimize therapeutic strategies.[6]

CLINICAL AND BIOLOGICAL FEATURES

Compared to MM, pPCL displays distinct clinical-biological features.[7] The median age at diagnosis is 52–61 years, approximately a decade earlier than MM.[5,8,9] pPCL presents aggressively, with higher tumor burden, symptoms of profound anemia, hypercalcemia, or bleeding diathesis due to thrombocytopenia. Clinical findings may include hepatosplenomegaly, lymphadenopathy, pleural effusions, neurological deficits, and extramedullary soft-tissue plasmacytomas.[2]

pPCL is associated with higher rates of renal failure (serum creatinine >2 mg/dL: 44% vs. 21% in MM), elevated β2-microglobulin (>6 mg/L: 65% vs. 27%), and elevated lactate dehydrogenase (LDH >460 U/L: 48% vs. 9%).[10] Conversely, osteolytic lesions are less frequent in pPCL (35%) compared to MM (81%) and sPCL (53%).[11]

Immunoglobulin heavy chain subtypes in pPCL include IgG (46%), IgA (13%), light-chain-only (30%), and non-secretory (10%).[12]

Genetic and Molecular Profile

pPCL is characterized by cytogenetic abnormalities typically seen in advanced MM. Flow cytometry reveals frequent expression of CD20, CD44, CD45, CD19, and CD23, with reduced CD27, CD56, CD71, CD117, and HLA-DR. CD38, a target for immunotherapy, is universally expressed.[13,14]

pPCL often exhibits complex hypodiploid karyotypes, whereas hyperdiploidy—linked to better prognosis—is rare. Hyperdiploidy is more common in sPCL, likely reflecting evolution from hyperdiploid MM clones.[15,16] Recurrent abnormalities include del(17p), t(11;14), and t(14;16).[17,18] Chromosome 1 abnormalities are more frequent in PCL than MM, particularly in sPCL.[19]

TP53 mutations occur in 21% of pPCL cases, with biallelic inactivation in 17%. The t(11;14) translocation is present in 51% of pPCL patients.[20] Transcriptomic studies identify 203 differentially expressed genes in pPCL versus MM, including CYB5D2, EDEM3, and YIPF6, which correlate with lenalidomide-dexamethasone response.[21] MYC dysregulation is common, though FISH often underdetects these anomalies.[16]

Distinct genomic clusters exist in pPCL: t(11;14)-positive cases often harbor TP53 mutations, while t(11;14)-negative cases show trisomy 21, 1q gain, and 1p32 deletion.[22] Despite shared molecular features, PCL remains genetically heterogeneous, complicating unified classification.[23]

TREATMENT

Plasmacytic leukemia (PL) represents a therapeutic challenge due to its resistance to conventional treatments and its poor prognosis (median survival < 12 months without treatment).[24] Recent advances, inspired by multiple myeloma (MM) protocols, now incorporate targeted therapies and personalized approaches, modestly improving outcomes.

- **Induction**

The initial goal is a rapid reduction in tumor burden. A quadruple regimen combining an anti-CD38 (daratumumab or isatuximab), a proteasome inhibitor (bortezomib/carfilzomib), an immunomodulator (lenalidomide/pomalidomide), and dexamethasone is recommended as first-line therapy.[25] The Phase II CASSIOPEIA trial (NCT02541383) demonstrated the efficacy of daratumumab combined with bortezomib, cyclophosphamide, and dexamethasone (D-VCD), with an overall response rate (ORR) of 89% in PL patients.[26] In case of contraindications to immunomodulators, VCD-based regimens (bortezomib, cyclophosphamide, dexamethasone) remain a validated alternative according to the International Myeloma Working Group.[27]

- **Hematopoietic Stem Cell Transplantation (HSCT):** HSCT plays a central role in the therapeutic strategy for PL, especially in young patients with no major comorbidities. Two modalities are considered: autologous stem cell transplantation (ASCT) and allogeneic stem cell transplantation (allo-SCT), each with distinct indications, benefits, and risks.

ASCT: In eligible patients (< 70 years, without severe comorbidities), autologous stem cell transplantation (ASCT) after induction is associated with prolonged

survival. A 2023 retrospective study involving 112 patients reported a median progression-free survival (PFS) of 24 months post-ASCT, compared to 8 months without transplantationn.[28]

Allo-SCT: Allogeneic stem cell transplantation, unlike autografting, utilizes the graft-versus-leukemia effect and is used to achieve a cure in certain hematological diseases. In a retrospective study from the Center for International Blood and Marrow Transplant Research, it was reported that both ASCT and allo-SCT seem to improve survival; however, autografting showed better overall survival rates.[29] Allo-SCT, although risky, is considered in primary refractory PL, with durable response rates reaching 40% in selected cohorts.[30]

- **Maintenance Therapy:** Maintenance therapy with lenalidomide or proteasome inhibitors (e.g., bortezomib) is recommended to prevent relapse. The GRIFFIN trial (NCT02874742) extended its analysis to PL, showing a benefit of daratumumab in maintenance with a 60% reduction in progression risk.[31] The detection of minimal residual disease (MRD) by flow cytometry or next-generation sequencing (NGS) now guides therapeutic intensification.[32]

CONCLUSION

PCL remains a high-risk malignancy requiring tailored approaches. Revised diagnostic criteria, molecular insights, and novel therapies like anti-CD38 agents and SCT have modestly improved outcomes. Ongoing research into its genetic landscape and immunotherapy combinations is essential to advance care.

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