Update on primary plasma cell leukemia

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Abstract

Plasma cell leukemia (PCL) is a rare and highly aggressive plasma cell neoplasm developing in 0.5–4% of patients with multiple myeloma (MM). The diagnostic criteria were recently revised from 20% to ≥5% of circulating plasma cells in peripheral blood smears. PCL is classified as primary or secondary; primary PCL is when it presents in patients with no MM. Primary PCL shows clinical and laboratory features at presentation that differ from MM and exhibits a dismal prognosis even with the use of effective agents against MM. Therefore, intensive chemotherapy should be initiated immediately after diagnosis, and autologous stem cell transplantation is recommended for transplant-eligible patients. Maintenance therapy after transplantation may reduce the rate of early relapses. We reviewed the definitions of PCL, revised diagnostic criteria, clinical features, and appropriate initial treatments for primary PCL.

Key Words   Plasma cell leukemia, Diagnosis, Treatment

INTRODUCTION

Plasma cell leukemia (PCL) is a rare plasma cell dyscrasia with a dismal prognosis. In 1974, Kyle developed diagnostic criteria for PCL, which required more than 20% circulating plasma cells and an absolute count greater than 2×10^9/L plasma cells in peripheral blood [1]. These diagnostic criteria were too strict; the International Myeloma Working Group (IMWG) suggested (in 2013) that either criterion was sufficient for PCL diagnosis [2]. Based on these diagnostic criteria, PCL is diagnosed in 0.5–4% of all patients with multiple myeloma (MM) [3]. PCL is considered primary when it presents at initial diagnosis and secondary when it occurs in patients with pre-existing MM. Primary PCL accounts for 60–70% of all PCL; the secondary PCL rate is 30–40% [4].

In general, PCL diagnostic evaluation and treatment are similar to those for MM, but PCL survival remains inferior to that of MM despite the use of novel agents and autologous stem cell transplantation (ASCT). The Surveillance, Epidemiology, and End Results (SEER) epidemiological study of PCL patients showed that novel agents afforded modest improvement (from 5 mo in 2006 and 2009 to 12 mo in 2006 and 2009) [5]. PCL patients who underwent ASCT survived for 2–3 years, similar to those with ultra-high-risk MM.

Here, we review primary PCL focusing on its clinical characteristics, revised diagnostic criteria, biological characteristics, and treatments.

REVISED DIAGNOSTIC CRITERIA AND DIAGNOSTIC EVALUATION

The diagnostic criteria for PCL proposed by Kyle were not based on the results of prospective studies, and the cutoff peripheral plasma cell level was thus artificial. Two recent retrospective studies explored the optimal cutoff number of peripheral plasma cells. A study of 482 Spanish patients evaluated survival outcomes based on the percentages of circulating plasma cells: 0, 1–4, 5–20, and >20% [6]. A Mayo Clinic study reviewed the survival outcomes of 176 patients with circulating plasma cell proportions of 1–4, 5–19, and ≥20% [7]. The survival outcomes of patients with ≥5 and ≥20% circulating cells were similar in both studies, and patients with ≥5% circulating cells had inferior survival compared to those with less than 5% circulating cells. Thus, the IMWG recently revised the diagnostic criterion of primary PCL to ≥5% circulating plasma cells in peripheral blood smears [8].

The diagnostic workup for PCL was not different from that for MM. The laboratory tests included measurements of lactate dehydrogenase (LDH), B2-microglobulin, serum

immunoglobulins, and serum free light chains; a peripheral blood smear; serum and 24 h protein electrophoresis/immunofixation; and bone marrow examination, including fluorescence in situ hybridization. Careful examination of peripheral smears is important. At least 100–200 nucleated cells/smear should be analyzed by a specialized pathologist or hematologist [8]. After the initial diagnosis, positron emission tomography (PET)/computed tomography (CT) is required to evaluate the extramedullary plasmacytoma status. If cerebrospinal involvement is suspected, lumbar puncture should be performed.

CLINICAL CHARACTERISTICS AND BIOLOGY

Patients with primary PCL generally show unfavorable clinical characteristics at initial diagnosis. In studies on primary PCL diagnosed using earlier criteria, primary PCL was more common in younger patients of a more advanced International Staging System (ISS) stage, and was frequently accompanied by hepatomegaly, splenomegaly, extramedullary disease, renal failure, hypercalcemia, thrombocytopenia, increased LDH levels, and an elevated plasma cell labeling index [2, 9]. In a Spanish study, the differences in age, sex, myeloma isotype, LDH level, and ISS stage by circulating plasma cell numbers were not significant; however, patients with 5–20% circulating plasma cells showed lower platelet counts and more plasma cells in the bone marrow [6].

Primary PCL exhibits cytogenetic abnormalities that differ from those of secondary PCL and MM. Patients with primary PCL frequently have complex and hypodiploid karyotypes; hyperdiploidy associated with a favorable prognosis is rare in such patients. The del(17p), t(11;14), and t(14;16) are common in primary PCL patients [10-12]. Chromosome 1 abnormalities are more common in PCL than in MM and are more frequent in secondary PCL than in primary PCL [13]. A recent large study evaluating genetic abnormalities in primary PCL found that TP53 mutations were significantly more common in primary PCL than in MM patients. In addition, the former patients exhibited more double-hit profiles and TP53 bi-allelic inactivation. TP53 mutations were associated with significantly inferior progression-free survival (PFS) and overall survival (OS) in primary PCL patients [14].

Recent high-throughput genomic analyses have revealed distinct biological features of primary PCL. A transcriptome study described significant differences in the RNA splicing machineries of primary PCL and MM with 17p deletion [15]. The molecular abnormalities of primary PCL differed from those of MM, although cytogenetic abnormalities were similar. Gene-expression profiling (GEP) of primary PCL revealed the expression of 203 genes involved in LXR/RXR activation, inositol metabolism, hepatic fibrosis/hepatic stellate cell activation, and lipopolysaccharide/interleukin-1-mediated inhibition of RXR functional pathways, were affected [16]. GEP performed by Todoerti et al. [17] revealed a 27-gene signature associated with the overall survival of primary PCL; the expression levels of CYB5D2, EDEM3,

and YIPF6 correlated with the response to lenalidomide and dexamethasone. Lionetti et al. [18] explored microRNA (miRNA) expression in primary PCL and MM patients; miR-92a, miR-330-3p, miR-22, and miR-146 affected treatment responses and clinical outcomes. Cifola et al. [19] evaluated the mutational profile of primary PCL via whole-exome sequencing; 14 repeatedly mutated genes were involved in cell-matrix adhesion, cell cycle, genome stability, RNA metabolism, and protein folding. Cadherin/Wnt signaling, the extracellular matrix, and the cell cycle G2/M checkpoint are particularly affected. Genome-wide methylation analysis of 14 primary PCL patients using a high-density array revealed that the primary PCL was characterized by global hypomethylation of genes involved in cell adhesion/migration [20].

TREATMENT

As primary PCL is rare, few studies have explored appropriate treatments, and most were small and retrospective. The therapeutic recommendations were similar to those for MM. In general, primary PCL requires prompt intensive therapy with novel agents to decrease early mortality and disease-related complications. For transplant-eligible patients, ASCT followed by maintenance therapy is recommended.

Induction therapy

Although no optimal induction therapy for primary PCL has been defined yet, proteasome inhibitors, immunomodulatory drugs, or both should be prescribed. A few retrospective studies have evaluated the efficacy of bortezomib-based regimens in patients with primary PCL because proteasome inhibitors have been useful in MM patients with high-risk cytogenetic abnormalities. A bortezomib-based regimen for primary PCL was effective; the overall response rate (ORR) was 76–80%, including at least a very good partial response (VGPR) in 28–38% of patients [12, 21, 22]. A prospective study by the Intergroupe Francophone du Myélome (IFM) demonstrated the efficacy of induction therapies featuring bortezomib, dexamethasone plus doxorubicin, or cyclophosphamide. In 40 patients with primary PCL, the ORR was 69%, including a complete response (CR) of 10% and VGPR of 26% [23]. Lenalidomide was efficacious in a prospective study of 23 patients with primary PCL who received four cycles of lenalidomide and dexamethasone (Rd) as induction therapy, with an ORR of 73.9%, including a CR of 13%, a VGPR of 26.1%, and a partial response of 34.7% [24]. In addition, one study reported that combination treatment with proteasome inhibitors and immunomodulatory drugs had higher response rates than the proteasome inhibitor or immunomodulatory drug alone regimens [25]. Thus, bortezomib, lenalidomide, and dexamethasone (VRd) may be the optimal induction regimens for patients with primary PCL. In the high-risk subset of the SWOG S0777 trial that compared VRd and Rd for newly diagnosed MM patients, VRd afforded better PFS than Rd (38 vs. 16 mo) [26].

Unfortunately, the efficacy of VRd alone against primary PCL has not been reported; however, carfilzomib (a second-generation proteasome inhibitor) combined with lenalidomide, and dexamethasone (KRd) has been evaluated as an induction therapy for patients with newly diagnosed primary PCL (in the EMN12/HOVON129 study). In an interim analysis of 14 patients who received four treatment cycles, KRd showed remarkable efficacy, with an ORR of 93%, including a CR of 33%, and a VGPR of 55%. No early mortality was reported [27]. Therefore, combination treatment with a proteasome inhibitor and an immunomodulatory drug should be considered as induction therapy. Table 1 summarizes the results of major retrospective and prospective studies evaluating the efficacy of induction therapy for primary PCL.

Hematopoietic stem cell transplantation

In transplant-eligible patients with primary PCL, high-dose chemotherapy followed by ASCT after induction therapy is recommended to induce a deep response and improve survival. Several registry studies have demonstrated the efficacy of ASCT as a treatment for primary PCL. The European Group for Blood and Marrow Transplantation retrospectively evaluated the outcomes of 272 patients who underwent ASCT [28]. The CR rate post-transplantation was significantly higher in primary PCL than in MM patients (41.2% vs. 28.2%, $P < 0.001$), but the median PFS and OS were significantly inferior (PFS: 14.3 vs. 27.4 mo, OS: 25.7 vs. 62.2 mo). In a study by the Center for International Blood and Marrow Transplant Research (CIBMTR), the PFS and OS at three years were 34 and 61%, respectively [29]. Most patients in these studies did not receive induction therapies, including proteasome inhibitors or immunomodulatory drugs. Dhakal et al. [30] evaluated the survival of 277 patients with primary PCL who underwent ASCT after induction therapy with novel agents; survival was not better than that of the historical cohort. Thus, ASCT may result in a deep response; however, early relapse limits the duration of remission. In a prospective study of 40 patients with primary PCL, 35% relapsed after allogeneic SCT, but only 1 of 7 who received maintenance therapy with lenalidomide relapsed [22]. In addition, two retrospective studies showed that maintenance therapy after ASCT significantly improved median PFS or OS [31, 32]. These results suggest that main-

tenance therapy can reduce early relapse rates and improve survival. An ongoing clinical trial on patients with primary PCL (EMN12/HOVON129, NCT02440464) includes maintenance therapy with carfilzomib or ixazomib and will yield valuable information about the role of maintenance therapy in primary PCL.

However, the utility of tandem transplantation in patients with PCL remains unclear. The CIBMTR study reported the survival outcomes of 25 patients who underwent tandem transplantation [29]. Compared to patients who received single ASCT, the PFS at three years did not differ (36% vs. 37%), but the 3-year OS was better in patients who underwent tandem transplantation (56% vs. 84%).

Allogeneic SCT can be considered for some patients with primary PCL. The CIBMTR study reported the outcomes of 50 patients who received allogeneic SCT [29]. The relapse rate at three years was significantly lower in patients who received allogeneic SCT than in those who received ASCT (38% vs. 61%), but the 3-year OS was inferior (39% vs. 64%) because of higher non-relapse mortality (NRM). The recent CIBMTR trial reported the outcomes of 71 patients who underwent allogeneic SCT. None of the relapse rates, PFS, or OS differed from the ASCT patients. Compared to patients who received allogeneic SCT in a previous CIBMTR study, the NRM at one year was decreased (9% vs. 26%), but more patients experienced relapse. Therefore, reduced NRM did not translate to improvements in PFS and OS [30]. The different outcomes of allogeneic SCT may reflect differences in conditioning regimens, patient biology, therapies, or supportive care offered after transplantation. Although the outcomes of allogeneic SCT are disappointing, some patients show long-term remission; allogeneic SCT might cure primary PCL. Further studies (especially on the conditioning regimens for patients with primary PCL) are needed.

Emerging treatments

Although efficacy data are lacking, ixazomib and daratumumab show promise as treatments for primary PCL. Ixazomib, an oral proteasome inhibitor, is efficacious in patients with high-risk relapsed/refractory MM. In the phase 3 TOURMALINE-MM1 study, adding ixazomib to Rd significantly improved the PFS of relapsed refractory MM pa-

Table 1. Summary of prospective and retrospective studies of treatment with novel agents for primary plasma cells leukemia.

References	Study design	Patients, N	Median age, yr (range)	ORR/CR (%)	ASCT, N	Median PFS (mo)	Median OS (mo)
Musto et al. [24]	Prospective	23	60 (44–80)	73.9/13	9	14	28
Royer et al. [23]	Prospective	39	57 (27–71)	69/10	25	15.1	36.3
Nandakumar et al. [25]	Retrospective	68	62 (34–91)	90/47	20	13	23
Dhakal et al. [30]	Retrospective	277	60 (25–77)	87/19	277	17% at 4 yr	28% at 4 yr
Mina et al. [31]	Retrospective	38	58 (34–80)	82/18	28	20	33
Gowda et al. [32]	Retrospective	23	56 (42–71)	65/13	23	5.5	18.1
D'Arena et al. [22]	Retrospective	29	62 (42–82)	79/28	12	40% at 2 yr	55% at 2 yr

tients with high-risk cytogenetic features [33]. In addition, daratumumab, a monoclonal antibody targeting CD38, showed remarkable efficacy when combined with VRd in treating newly diagnosed MM patients in the GRIFFIN trial [34]. Clinical trials using novel combinations of pomalidomide, ixazomib, and dexamethasone (NCT02547662); and daratumumab, bortezomib, dexamethasone, pegylated liposomal doxorubicin, and lenalidomide (NCT03591744) have been conducted in patients with PCL.

Venetoclax, an oral BCL-2 inhibitor, is another emerging agent used to treat primary PCL. The drug was efficacious in relapsed refractory MM patients with t(11;14). A high prevalence of t(11;14) (up to 50%) has been reported in primary PCL. In one case of refractory primary PCL with t(11;14), venetoclax, daratumumab, and dexamethasone resulted in stringent CR [35]. Thus, venetoclax may be useful for treating primary PCL patients with t(11;14).

B-cell maturation antigen (BCMA)-targeting agents, including chimeric antigen receptor (CAR) T-cells, bispecific T-cell engagers, and antibody-drug conjugates, may change the treatment landscape of patients with primary PCL. BCMA-targeted CAR-T cells resulted in a deep response in heavily treated patients with MM or extramedullary plasmacytoma [36, 37]. A phase I study of anti-BCMA CAR-T cell therapy enrolled two patients with relapsed refractory primary PCL who benefited from therapy, but the duration of response was brief [38]. Further studies on BCMA-targeted immunotherapies in patients with primary PCL are required.

CONCLUSION

Primary PCL features more aggressive clinical characteristics and unfavorable molecular abnormalities at initial diagnosis than MM. Although improved survival has been reported after introducing novel agents to treat primary PCL, survival remains poorer than that of patients with MM. Therefore, initial rapid control of PCL via intensive chemotherapy followed by ASCT is recommended. Maintenance with lenalidomide may reduce early relapse rates after ASCT. Immunotherapies using monoclonal antibodies, CAR-T cells, bispecific T-cell engagers, or antibody-drug conjugates may further improve the prognosis of patients with primary PCL. Given the recent changes in diagnostic criteria, more clinical studies are needed to determine the clinical and molecular features of primary PCL and to determine optimal treatments using emerging agents.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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