Primary Plasma Cell Leukemia: A Practical Approach to Diagnosis and Clinical Management

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Abstract

Primary plasma cell leukemia (pPCL) represents a rare but most aggressive form of multiple myeloma. Its leukemic clinical characteristics, as seen by the presence of circulating clonal plasma cells, its unique molecular and cytogenetic aberrations, and its exceedingly poor survival outcomes set it apart from traditional multiple myeloma. Recent advances in the utilization of novel agents and high-dose chemotherapy in the upfront management of patients with pPCL is finally bearing fruit in terms of improving survival outcomes, albeit modestly. Early recognition of pPCL in a newly diagnosed multiple myeloma patient is crucial for providing the optimal intensive therapy. This review highlights the current understanding of the various clinicopathologic presentations and approaches to the diagnosis and treatment of pPCL. It specifically provides a clinical approach for the optimal management of this entity. It also shines light on the future of next-generation therapies that may be incorporated in the management of pPCL. In the future, prospective multicenter studies are required to revise the diagnostic criteria of pPCL by utilizing more sensitive and specific diagnostic modalities, such as peripheral blood multiparameter flow cytometry. Such studies should also attempt to identify the optimal sequence of novel therapeutic agents to treat this disease and provide the best chance for long-term survivals.

AJHO. 2017;13(3):21-25

Introduction

Plasma cell leukemia (PCL) represents the most aggressive form of multiple myeloma (MM) in the spectrum of clinical aggressiveness of plasma cell disorders. Similar to other forms of MM, it is characterized by the expansion of malignant plasma cells within the bone marrow, activity capable of resulting in end organ damage, such as lytic bone destruction, anemia, hypercalcemia, or renal insufficiency. However, unlike other MM forms, but akin to a leukemia, it is characterized by the circulation of a large number of clonal plasma cells. Although Gluzinski and Reichenstein were the first to describe a case of PCL back in 1906, it was Kyle and Noel who went on to define it as the presence of plasma cells consisting of more than 20% of the differential white count in the peripheral blood, or an absolute plasma cell peripheral blood count of greater than 2.0 × 10^9 cells/L. If PCL is detected at diagnosis de novo without a prior history of MM, it is considered primary plasma cell leukemia (pPCL). However, if PCL arises in a patient with a known history of MM, it is considered secondary PCL (sPCL). The condition occurs as a progressive event of the disease in 1% to 4% of patients with MM. It is important to note that even lower levels of circulating clonal plasma cells below the World Health Organization's threshold for defining PCL portend a poor prognosis comparable with that of the strictly defined PCL. Similarly, the diagnosis of PCL can easily be overlooked because the identification of the circulating clonal plasma cells in the peripheral blood is difficult by light microscopy alone; it is hard to differentiate them from circulating clonal lymphocytes seen in conditions such as chronic lymphocytic leukemia, hairy cell leukemia, or marginal zone lymphoma. Therefore, immunophenotypic analysis via flow cytometry is mostly warranted.

The survival of patients with pPCL is poor compared with newly diagnosed MM. An analysis of the Surveillance, Epidemiology, and End Results database that included 445 patients with pPCL diagnosed between 1973 and 2009 demonstrated that during the time periods of 1973-1995, 1996-2000, 2001-2005, and 2006-2009, median overall survival (OS) was 5, 6, 4, and 12 months, respectively. One possible explanation for the modest improvement in outcomes in the last time period is the upfront incorporation of novel-agent therapies. Because information about therapies was not available in this analysis, no definite conclusion can be drawn. However, early mortality was still a challenge because about 15% died within the first month during the most recent period.

Although encouraging, gains in outcomes in pPCL are far from ideal and require improvement. Several recent single-institution series, as well as prospective trials incorporating novel agents up front in the therapy, report much more impressive improvements in patients with pPCL.
Clinical and Pathologic Features
Given the relative infrequency of pPCL compared with MM, as well as the lack of prospective clinical data, information regarding the clinical presentation of pPCL is derived from retrospective single-institution series. Patients with pPCL tend to be younger (aged 50-59 years) compared with patients with MM (aged 70-79 years) and tend to have a higher predisposition to develop extramedullary disease within the liver, spleen, lymph nodes, and other soft tissues. It is also not uncommon for patients with pPCL to present with malignant pleural effusions and neurofibromatous deficits secondary to central nervous system involvement. Patients also tend to have more renal insufficiency as a result of light chain–only secreting disease, as well as to have cytopenias, such as anemia and thrombocytopenia, as a result of higher amounts of bone marrow involvement. In contrast, patients with pPCL have a lower likelihood of lytic bone disease than patients with MM. Patients with pPCL are more likely to have a higher serum lactate dehydrogenase (LDH) and increased β2 microglobulin. Patients with pPCL are believed to have a different tumor biology than patients with MM. The clonal plasma cells appear more immature, or “plasmablastic,” in morphology. From a cytogenetics standpoint, patients with pPCL are less likely to be hyperdiploid in comparison with their MM counterparts. The t(11;14) is the most common cytogenetic abnormality, but deletion 17p, t(4;14) and CKB1 duplication are also more commonly present than in MM. Whole-exome sequencing on pPCL clonal plasma cells demonstrate effects in the cadherin/Wnt signaling, extracellular matrix receptor interaction, extracellular matrix organization, and G2M cell cycle checkpoint.

Diagnostic Approach
All patients with MM suspected of having pPCL must undergo a detailed history and physical examination. A comprehensive laboratory test evaluation of their blood should be performed, including at least a complete blood count with differential, peripheral blood smear; electrolyte panel; creatinine; liver enzymes; bilirubin; alkaline phosphatase; LDH; uric acid; β2 microglobulin; albumin; serum protein electrophoresis with immunofixation; and serum free light chain analysis. If possible, multiparameter flow cytometry should be performed on the peripheral blood to confirm the presence of clonal circulating plasma cells; they typically have immunophenotypes of CD138+, CD38+, CD19–, and CD45+/–. Whole body imaging with either magnetic resonance imaging, computerized tomography (CT), or 18F-fluorodeoxyglucose positron emission tomography/CT to assess for both lytic bone lesions and extramedullary plasmacytomas is necessary. A 24-hour urine collection for electrophoresis, immunofixation, and total protein assessment should also be performed. Finally, it is essential to perform a bone marrow biopsy and aspirate to assess for morphology; proliferation rate, if possible; immunophenotyping; and cytogenetic analysis by fluorescence in situ hybridization (FISH). FISH is performed on the plasma cells from the bone marrow aspirate. The FISH probes should be directed on specific abnormalities, such as del(17p13), del(13q), del(1p21), and (1q21) amplification, and chromosome 14 abnormalities such as t(11;14), t(4;14), t(14;20) and t(14;16).

Therapy Options
The main goal of therapy is to achieve rapid cytoreduction and to reverse or prevent end-organ complications, and to do so, prevent early mortality while prolonging survival. Conventional chemotherapy has only led to an OS of 7 months. Thus, the use of novel agents and stem cell transplantation modalities are crucial parts of the therapeutic armamentarium.

Proteasome inhibitors
The incorporation of bortezomib into the induction regimens of patients with pPCL has been reported in various single-institutional studies. The largest prospective analysis was by the GIMEMA group, which enrolled 29 patients with newly diagnosed pPCL to be treated with bortezomib-based regimens. The objective response rate (ORR) was 79% and the 2-year progression-free survival (PFS) and OS were 40% and 55%, respectively. Similarly, Katodritou and colleagues from the Greek myeloma group reported on the use of bortezomib-based regimens in 25 patients with pPCL. The ORR was 80% and the OS was 18 months. Finally, Reece and colleagues reported a retrospective analysis of 10 patients with newly diagnosed pPCL treated with a combined regimen of bortezomib with cyclophosphamide and dexamethasone followed by autologous stem cell transplantation (ASCT). The ORR was 100% (very good partial response [VGPR]; 50%; complete response [CR]; 20%) after induction therapy. Consolidation with an ASCT deepened the response by increasing the CR rate to 44%. The median PFS was 18 months, and after 25 months, 70% of patients were still alive.

Immunomodulators (IMiDs)
There have been conflicting reports on the efficacy of thalidomide in the treatment of pPCL, especially because it is not believed to be active in extramedullary MM. Petrucci and colleagues reported on 5 cases of pPCL and sPCL treated with single-agent thalidomide; no response was shown and all patients died within 120 days of treatment. Nevertheless, the use of thalidomide can be effective from a synergistic standpoint when used in combination with other novel agents and alkylator therapies. On the other hand, lenalidomide has the most data available from an IMiD in newly diagnosed patients with pPCL; the combination of lenalidomide and dexamethasone was evaluated in a prospective phase II study of 23 patients with newly diagnosed pPCL. Of these, 61% and 35% achieved a partial response and VGPR, respectively. After a median follow-up of 15 months, the OS and PFS were 63% and 52%, respectively, suggesting the efficacy of this combination in comparison with historical outcomes of patients with pPCL. Finally, a single case report has demonstrated the use of pomalidomide plus low-dose dexamethasone in a case of sPCL. Furthermore, given that it has resulted in 2 complete and 2 partial responses among 13
patients with extramedullary disease, it should be considered for use due to the extramedullary features present in pPCL.

**Autologous stem cell transplantation**

Given the generally poor prognosis of patients with pPCL, ASCT has been widely adopted as an integral part of therapy for these patients. The retrospective series from the Mayo Clinic supported this approach by demonstrating an improved median OS of 34 versus 11 months when comparing patients who received and did not receive an ASCT. The European Group for Blood and Marrow Transplantation registry reported the outcomes of 272 patients with pPCL who underwent an ASCT between 1980 and 2006. The median PFS and OS were 14.3 months and 25.7 months, respectively. Similarly, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported the outcomes of 97 patients with pPCL who received an upfront ASCT between 1995 and 2006. The 3-year PFS and OS were 34% and 64%, respectively. There appeared to be a trend toward a superior OS in patients who received a tandem ASCT compared with those receiving a single ASCT.

**Allogeneic stem cell transplant**

The CIBMTR also reported on 50 patients who received an allogeneic stem cell transplant between 1995 and 2006. Most (68%) received a myeloablative conditioning regimen, whereas the others received a nonmyeloablative, or reduced intensity, conditioning regimen. At 3 years, the cumulative incidence of relapse was significantly lower in the allogeneic group (38% vs 61%) compared with the ASCT group, but treatment-related mortality (TRM) was higher in the allogeneic transplant group (41% vs 5%). As a result, the 3-year OS rates were 64% and 39% for the ASCT and allogeneic stem cell transplant groups, respectively.

**Treatment Approach**

Until recently, there were very few prospective studies available to evaluate the best course of therapy for patients with newly diagnosed pPCL. However, the Intergroupe Francophone du Myélome reported on a prospective study in patients with a median OS of 34 versus 11 months when comparing patients who received and did not receive an ASCT. The European Group for Blood and Marrow Transplantation registry reported the outcomes of 272 patients with pPCL who underwent an ASCT between 1980 and 2006. The median PFS and OS were 14.3 months and 25.7 months, respectively. Similarly, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported the outcomes of 97 patients with pPCL who received an upfront ASCT between 1995 and 2006. The 3-year PFS and OS were 34% and 64%, respectively. There appeared to be a trend toward a superior OS in patients who received a tandem ASCT compared with those receiving a single ASCT.

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Future Perspectives
The correct and timely diagnosis of pPCL is highly dependent upon the ability of the hematologist or pathologist to identify circulating plasma cells on a peripheral blood smear. This expertise varies among individuals and institutions, making the likelihood of diagnosis not uniform. In the future, routine quantification of circulating clonal plasma cells by flow cytometry could identify a new cutoff to define PCL that would be more amenable to identification. Finally, given that patients with pPCL do not benefit as much from the currently available treatment strategies compared with other patients with MM, these patients should be considered for enrollment in therapeutic clinical trials. It remains unknown as to where the incorporation of novel antibodies, such as elotuzumab and daratumumab, will fit in the treatment schema of patients with pPCL. Similarly, the emergence of adoptive immunotherapy modalities, such as chimeric antigen receptor T-cell therapy targeting either B-cell maturation antigen or CD19 plasma cell antigens, appears to hold promise as therapies for pPCL in the future. One particular agent of considerable interest will be venetoclax, a selective BCL-2 inhibitor, which has shown encouraging efficacy in MM, especially in clonal plasma cells harboring a t(11,14) cytogenetic abnormality that coincidentally is the most common abnormality in pPCL.

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Disclosures: This work is supported in part by the CTSA Grant UL1 TR000135 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health, and the Marion Schwartz Foundation for Multiple Myeloma.

References