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.

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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,[1] 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 x 10^9 cells/L.[2] 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.[3] With the improvement in survival experienced by patients with MM,[4] many are living long enough to have their MM transform into sPCL.

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.[5,6] 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.[7] 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.[7]

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.[8-10]

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.[2,11-17] Patients with pPCL tend to be younger (aged 50-59 years) compared with patients with MM (aged 70-79 years)[13] 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 neurological deficits secondary to central nervous system involvement.[17] 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.[12,18] In contrast, patients with pPCL have lower likelihood of lytic bone disease than patients with MM.[13] Patients with pPCL are more likely to have elevated serum lactic dehydrogenase (LDH) and increased β2 microglobulin.[16,19]

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.[12] The t(11;14) is the most common cytogenetic abnormality, but deletion 17p, t(4;14) and CKSB1 duplication are also more commonly present than in MM.[13] 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.[20]

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 18[F]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 in so doing, 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-institution 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.[21] The ORR was 80% and the OS was 18 months.[21] 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.[22] 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.9 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.[9,23,24] 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,[25] 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.[13] 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.[26] The median PFS and OS were 14.3 months and 25.7 months, respectively.[26] 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.[27] 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.[27]

Allogeneic stem cell transplant

The CIBMTR also reported on 50 patients who received an allogeneic stem cell transplant between 1995 and 2006.[27] 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%).[27] As a result, the 3-year OS rates were 64% and 39% for the ASCT and allogeneic stem cell transplant groups, respectively.[27]

Treatment Approach

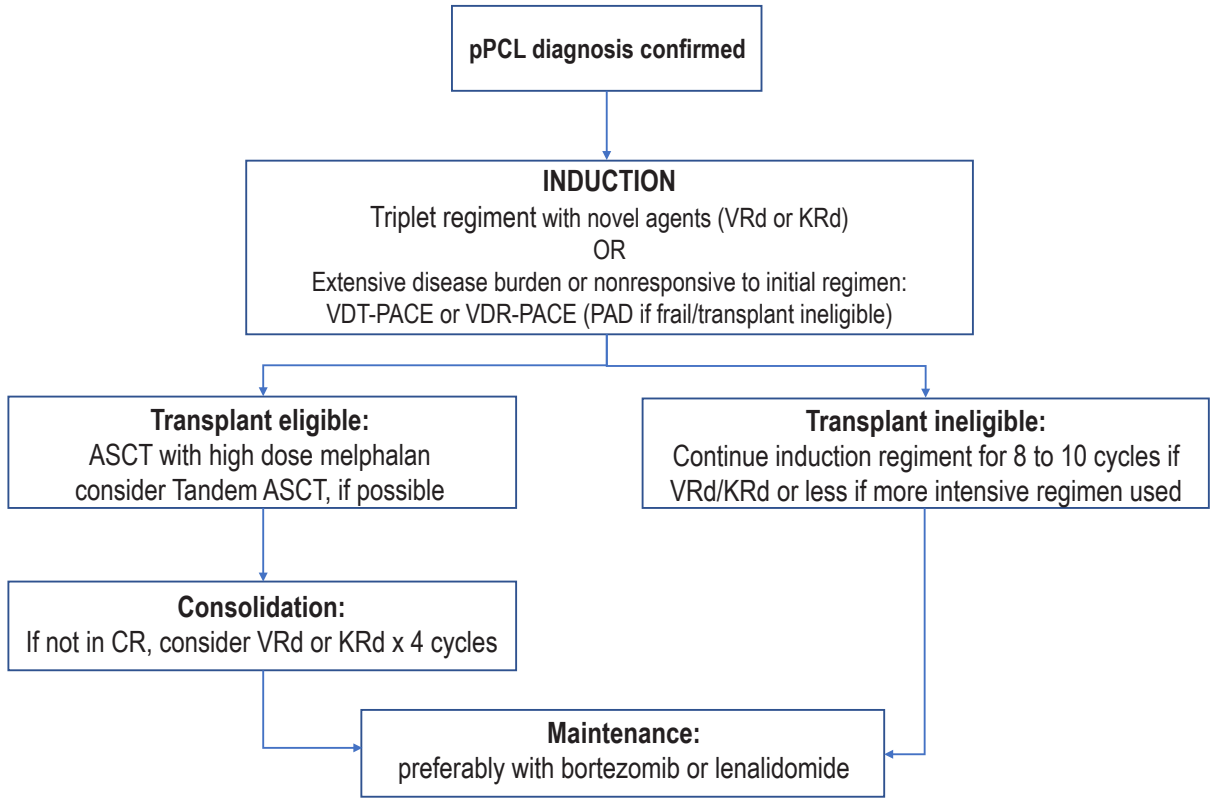
Until recently, there were very few prospective studies available to evaluate the best course of therapy for patients with newly diagnosed pPCL. However, the Intergroupe Francophone du Myélome reported on a prospective study in pPCL that investigated 40 patients who received a bortezomib and dexamethasone induction regimen with alternating doses of either doxorubicin or cyclophosphamide for a total of 4 cycles.[8] This was followed by an upfront ASCT, which was then followed by allogeneic transplant for younger patients or a second ASCT for the remainder of the patients.[8] Those included in the tandem ASCT arm underwent another year of consolidation therapy with bortezomib, lenalidomide, and dexamethasone alternating with maintenance therapy with lenalidomide.[8] In the group of 40 patients, the median OS and PFS were 36.3 months and 15.1 months, respectively.[8] The ORR to induction was 69%, with a VGPR or better in 36%.[8] This response was deepened at the end of the treatment program, with 59% achieving a VGPR or better.[8] The median OS and PFS was 36.3 and 17.9 months, respectively, for patients undergoing an allogeneic stem cell transplant versus not reached for both in the group who underwent a tandem ASCT. Unlike the CIBMTR registry data,[27] relapse mortality, was largely driving decreased PFS and OS in patients receiving ASCT followed by allogeneic stem cell transplant. Moreover, patients receiving an allogeneic stem cell transplant did not receive posttransplant consolidation/maintenance therapy, unlike patients in the tandem ASCT cohort, who did.

An intensive risk-adapted approach is encouraged when managing patients with PCL (**Figure**). Induction therapy with a triplet, novel agent–containing regimen that includes proteasome inhibitors and IMiDs, such as VRd (bortezomib, lenalidomide, and dexamethasone) or KRd (carfilzomib, lenalidomide, and dexamethasone), is a reasonable choice. In some patients with pPCL with an extensive burden of disease, more aggressive combination regimens such as VDT-PACE (bortezomib, dexamethasone, thalidomide or lenalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) could be utilized. This is because VDT-PACE incorporates drugs, such as cyclophosphamide and doxorubicin, which are particularly active in proliferative diseases. For elderly or frail patients who may not be able to tolerate such an intensive regimen, CyBorD (cyclophosphamide, bortezomib, and dexamethasone) or PAD (bortezomib, doxorubicin, and dexamethasone) can be used as a milder alternative.

After induction therapy, in transplant-eligible patients with pPCL, an upfront ASCT is recommended to achieve a deeper response and likely longer disease control. If possible, a tandem ASCT should be considered. Given the inferior results of allogeneic stem cell transplant compared with tandem ASCT as a result of higher relapse mortality, an allogeneic stem cell transplant should be considered and performed preferably only in the setting of a clinical trial. Although the data are scarce, post–ASCT maintenance is highly recommended given the high propensity for early relapse. These maintenance regimens can include either bortezomib or lenalidomide, or both, in combination-based regimens because of the significant disease control experienced by patients with MM who have high-risk cytogenetics.[28]

Patients with pPCL not eligible for ASCT-based options should still be treated with combinations of novel agents as induction therapy, with plans for indefinite maintenance therapy to keep the disease controlled. Infectious disease prophylaxis is crucial in these individuals because of their significantly impaired immunity. Standard antiviral prophylaxis, as well as bacterial prophylaxis, is warranted, especially with proteasome inhibitor and steroid therapy, respectively. Although rare, the high tumor burden and proliferation does predispose these patients to tumor lysis, and appropriate prophylaxis with allopurinol (and in some severe cases, rasburicase) may be indicated. Adequate antithrombotic prophylaxis is also crucial, especially in the setting of IMiDs. Finally, whereas osteolytic bone lesions are less common in pPCL than in MM, all patients with pPCL should be started on bisphosphonate therapy at diagnosis to decrease the risk of future skeletal-related events, as is traditionally done in MM.

FIGURE. Primary Plasma Cell Leukemia



ASCT indincates autologous stem cell transplatation; CR, complete response; KRd, carfilzomib, lenalidomide and dexamethasone; PAD, bortezomib, doxorubicin, dexamethasone; pPCL, primary plasma cell leukemia; VDR-PACE, bortezomib, dexamerthasone, lenalidomide, cisplatin, doxorubicin, cyclosphamide, etoposide; VDT-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; VRd, bortezomib, lenalidomide, dexamethasone.

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.[29]

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