PLASMA CELL LEUKEMIA:

Consensus Statement on Diagnostic Requirements, Response Criteria, and Treatment Recommendations by the International Myeloma Working Group (IMWG)

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Abstract

Plasma cell leukemia (PCL) is a rare and aggressive variant of myeloma characterized by the presence of circulating plasma cells. It is classified as either primary PCL occurring at diagnosis or as secondary PCL in patients with relapsed/refractory myeloma. Primary PCL is a distinct clinic-pathologic entity with different cytogenetic and molecular findings. The clinical course is aggressive with short remissions and survival duration. The diagnosis is based upon the percentage (20%) and absolute number ($2 \times 10^{9/L}$) of plasma cells in the peripheral blood. It is proposed that the thresholds for diagnosis be reexamined and consensus recommendations are made for diagnosis, as well as, response and progression criteria. Induction therapy needs to begin promptly and have high clinical activity leading to rapid disease control in an effort to minimize the risk of early death. Intensive chemotherapy regimens and bortezomib-based regimens are recommended followed by high-dose therapy with autologous stem-cell transplantation (HDT/ASCT) if feasible. Allogeneic transplantation can be considered in younger patients. Prospective multicenter studies are required to provide revised definitions and better understanding of the pathogenesis of PCL.

Keywords

plasma cell leukemia; cytogenetics; bortezomib; transplantation; myeloma; prognosis

INTRODUCTION

More than a century ago, the first case of plasma cell leukemia (PCL) was recognized by Gluzi ski and Reichenstein[1]. This uncommon form of clonal plasma cell dyscrasia is the most aggressive variant of the human monoclonal gammopathies and it has been defined by the presence of more than 20% plasma cells in peripheral blood and an absolute plasma cell count greater than $2 \times 10^9/L$[2,3]. The incidence of PCL ranges between 2% and 4% of patients with multiple myeloma (MM)[4-7]. PCL is classified as primary when it presents "de novo" in patients with no evidence of previous MM and as secondary when it is observed as a leukemic transformation of relapsed or refractory disease in patients with previously recognized MM[8]. 60-70% of PCL are primary, and the remaining 30-40% are secondary[9].

More recent data suggest that there is an increasing incidence of secondary PCL, now accounting for about 50% of the cases[7]. The aim of this article is to provide a consensus on the diagnostic criteria for PCL, response criteria, and treatment recommendations for primary PCL based upon a critical review of: 1) presenting features, 2) biological aspects including cellular adhesion mechanisms, molecular genetics and bone marrow milieu factors, 3) response criteria, and, finally 4) current treatment approaches, including hematopoietic stem cell transplantation.

PRESENTING CLINICAL FEATURES

Because of the relative low incidence and prevalence of this entity, most clinical data come from isolated case reports and small retrospective studies[9,10]. No prospective series have been published and only seven reports including more than 20 patients have been identified[3-7,11-13]. The main clinical and laboratory features, response to therapy and survival of patients with primary PCL reported in these articles are summarized in Table 1. The median age ranged between 52 and 65 years, about 10 years younger than the median age of 65 to 70 years observed in the general myeloma population[14] and in secondary PCL[7]. However, in an epidemiology study including 291 patients diagnosed between 1973 and 2004, the median age was 67 years[6]. Although the data is limited, it appears that, as for MM, PCL is more common in African Americans than in Caucasians[15]. Primary PCL has a more aggressive clinical presentation than MM including a higher tumor burden. Patients may present with symptoms due to profound anemia, hypercalcemia or bleeding diathesis due to thrombocytopenia. On physical examination, patients may exhibit a higher prevalence of organomegaly with involvement of the liver, spleen, lymph nodes, pulmonary findings associated with pleural effusions, neurologic deficits due to central nervous system involvement, pallor, petichae and palpable extramedullary soft-tissue plasmacytomas (Figures 1 and 2). In contrast, the presence of lytic bone lesions is lower than that observed in MM[7]. Fewer IgA cases than for MM patients were found in some studies, and there was an unexpectedly low proportion of patients with IgG-type M-protein[3] in one series. In contrast, the proportion of patients with light-chain disease ranges from 26% to 44%, whereas in general myeloma series the proportion of patients with Bence Jones myeloma is only 15%[14]. Bone marrow examination will often demonstrate extensive bone marrow plasma cell infiltration, with anaplastic or plasmablastic morphology (Figure 3), resulting in a reduced bone marrow reserve, with a greater incidence of anemia and thrombocytopenia as well as fewer normal plasma cells. Also, reflecting this aggressive clinical presentation, a higher proportion of patients with primary PCL have significant leukocytosis, as well as elevated lactate dehydrogenase (LDH) and β2-microglobulin serum levels. In fact, patients with MM usually show normal or moderately increased LDH serum levels, with a significant LDH elevation only observed in patients with high tumor load (43%)[16]. Physicians must be aware of a potential tumor lysis syndrome given the high tumor burden and elevated proliferative index. Thus, serum uric acid, calcium, phosphorous and serum creatinine levels must be monitored. Importantly, similarly to acute leukemias, the progression of disease is very rapid (weeks). Rare findings, such as hemophagocytic syndrome[17], hyperammonaemia[18] or expression of solid tumor markers (CA125 and CA15.3)[19] have also been reported.

Primary PCL is a distinct clinic-pathologic entity from MM because its presenting features and its natural history including response to chemotherapy and poorer prognosis[9]. Reinforcing this fact, the PCL pattern always reappears at the time of relapse, whereas secondary PCL occurs only in 1-2% of advanced and refractory MM patients who evolve into a leukemic phase with an aggressive clinical picture. In contrast, the constellation of adverse biologic prognostic factors in patients with advanced and refractory myeloma leading to a secondary PCL is a multistep process. Thus, primary and secondary PCL are two distinct clinical and biologic entities that only share the features of plasma cells circulating in the peripheral blood and an ominous clinical course.

Consensus:

Primary PCL is observed in younger patients than MM, with a increased incidence of light-chain only (Bence Jones) type. The clinical picture is characterized by an aggressive clinical presentation with high tumor burden, high proliferative index (i.e. S-phase DNA), rapid clinical course, leukocytosis, extramedullary involvement, marked bone marrow infiltration by immature plasma cells and high LDH serum levels. Finally, the presentation of relapsed primary PCL routinely mimics the initial clinical picture.

DIAGNOSTIC CRITERIA

The original diagnostic criteria of PCL were established in 1974 by Noel and Kyle, requiring both more than 20% circulating plasma cells and an absolute count greater than 2×10^9/L plasma cells in peripheral blood. These criteria provide a framework to define this disease entity along with associated universal poor clinical outcome. These criteria have not been evaluated prospectively to determine if a need for any modification is required.

What degree of circulating plasmacytosis should be used for defining PCL?

The control mechanisms by which plasma cells initially remain predominantly confined to the bone marrow, only rarely entering the blood stream, are poorly understood. In fact, a low proportion of plasma cells can be detected in peripheral blood in patients within the entire spectrum of plasma cell dyscrasias including newly diagnosed MM, smoldering MM and, exceptionally, in monoclonal gammopathy of undetermined significance (MGUS)[20,21]. It is also important to recognize that the presence of circulating plasma cells is not always indicative of PCL, since the presence of a significant number of polyclonal peripheral blood plasma cells can be transiently observed in non-malignant conditions, such as severe sepsis, infectious mononucleosis and, particularly, serum sickness[22,23]. In this light, peripheral blood flow cytometry is important to demonstrate clonality of the plasma cells, and exclude other lymphoproliferative diseases including low grade B cell or lymphoplasmacytic lymphoma.

Do we need both an absolute value of circulating plasma cells and a percentage of WBC?

The criteria developed by Kyle[2], requiring both more than 20% circulating plasma cells and an absolute count greater than 2×10^9/L plasma cells in peripheral blood seems too restrictive and the degree of peripheral plasmacytosis merits to be reconsidered.

In many series only one of these two criteria was considered sufficient for the diagnosis of PCL[7,24-26]. Patients with significant treatment exposure and poor bone marrow reserve have baseline leukopenia and may not meet absolute criteria but may meet percentage criteria. Probably only one of these criteria should be sufficient for the diagnosis of this entity. The definition of PCL was not discussed in the recent International Myeloma Workshop Consensus[27], though it is well accepted that the presence of PCL constitutes an unfavorable prognostic factor and that it is a subset of high risk myeloma[28] with an especially poor outcome.

Should we standardize methods to detect circulating plasma cells in peripheral blood?

The correct and timely diagnosis of PCL is dependent upon the ability of the pathologist to screen and recognize plasma cells in the peripheral blood smear. Hematologists and pathologists should be aware of the clinical relevance of a careful morphological examination of peripheral blood smears in order to exclude the presence of circulating plasma cells.

With all the considerations above, the diagnostic criteria for PCL should be revisited. The current definition, even when only one of the two criteria is required, may underestimate its real frequency. In any given patient, the presence of few circulating plasma cells demonstrated by conventional morphology is still a marker for a highly proliferative and aggressive process. Patients with an "early" PCL can rapidly develop full-fledged PCL in the absence of treatment. In this regard, the current proposal for prospective studies is to investigate if lower values (such as 5% or more plasma cells in peripheral blood and/or an absolute peripheral blood plasma cell count 0.5×10^9/L) have the same prognostic impact as historical criteria. Additional criteria to detect an early PCL process, which would allow earlier intervention and therefore change the natural history of the disease, are warranted, for example incorporating flow cytometry to detect clonal plasma cells and DNA content analysis, cytogenetics and, ideally, novel molecular markers.

> Consensus: Careful examination of peripheral blood by conventional microscopy should be done in all patients with MM who present with a clinical scenario suspicious of PCL, such as leukocytosis and an elevated LDH. If there are more than 20% circulating plasma cells and/or an absolute count greater than 2×10^9/L plasma cells, the diagnosis of PCL should be established according to the present criteria. However, lower peripheral blood plasma cell counts (i.e. 5% peripheral blood plasma cells and/or an absolute number 0.5×10^9/L) should be recorded in order to revisit the diagnostic criteria of PCL and prospectively analyze the biology and the clinical course of these patients. Additional methods including flow cytometry to detect early PCL should be a high priority and warrant further studies, encouraging prospective multi-center efforts in newly diagnosed patients.

BIOLOGY OF PCL

Immunophenotype

While the main plasma cell markers (CD38 and CD138) are equally expressed in MM and PCL samples, the multiparametric flow cytometry shows a different pattern in PCL when

compared with plasma cells from MM. In this regard, a higher expression of CD20 antigen[5] and lower CD9, CD117, CD56 and HLA-DR is observed. CD28 is more frequently expressed in secondary PCL[29]. This is consistent with the fact that the acquisition of CD28 antigen on plasma cells correlates with increased plasma cell proliferation and disease progression[29]. The increased CD27 expression in PCL has been linked to activation of an antiapoptotic pathway[30,31]. Furthermore, it has recently been shown that CD27 overexpression can lead to the activation of the nuclear factor κB (NF-κB) resulting in antiapoptotic enhancement[30]. This may have therapeutic implications since NF-κB, which plays a crucial role in the survival of malignant plasma cells, is inhibited by bortezomib and other newer proteasome inhibitors. In addition, CD23 has been reported to be associated with the presence of t(11;14)[32]. When compared with the studies performed on MM, the immunophenotypic information at diagnosis as well as on the minimal residual disease follow-up in PCL is really limited.

Mechanisms of extramedullary spread

Plasma cell dyscrasias are characterized by a proliferation of plasma cells with a strong dependence on the bone marrow microenvironment[33]. The bone marrow microenvironment plays a key role in the pathogenesis of MM by triggering signalling cascades which mediate myeloma cell proliferation, migration and survival, with all of these contributing to myeloma growth and to the homing of malignant plasma cells within the bone marrow. Disruption of these mechanisms could be crucial for the unique biology of PCL. A number of adhesion molecules have been involved in the egression of plasma cells to the peripheral blood stream. The lack of CD56 antigen[5,29], a neural cell adhesion molecule, which is important in anchoring plasma cells to the bone marrow stroma and likely impairs their circulation to peripheral blood as well as their migration to extramedullary sites, is a frequent finding as in myeloma with t(14;16). In addition, it can result in a weaker myeloma cell interaction and increased secretion of metalloproteinase-9 (MMP-9). Downregulation of CD106 and activated-CD29[34] and decreased expression of the surface molecules HLA-1 and CD40 in PCL versus MGUS cells[35] are also in this sense. A higher expression of CD54 on plasma cells as compared to adhesion molecules CD11a, CD18 and CD11b[36] has been also demonstrated. Acquisition of this last molecule also facilitates egression of plasma cells through the capillary wall and leads to tumor dissemination. The high expression of VLA-4 in PCL, a requisite for invasiveness of leukemic cells because of the contact with its ligand in capillary vessel wall, would increase extravasation of leukemic cells from the blood into extravascular space[35,37]. Low expression of chemokine receptors CCR1, CCR2, and CXCR4 has been observed in patients with active plasma cell disease as compared to those with inactive disease[38]. In this regard, recent findings indicate that thalidomide exposure induces down-regulation of CXCR4 and its ligand SDF-1alpha, which are involved in the BM homing of myeloma cells[39]. However, although the CXCR4 inhibitor AMD 3100 disrupts the interaction of myeloma cells with the BM microenvironment resulting in an increased number of circulating myeloma cells in mice[40], it seems that AMD 3100 does not induce either an increase in tumor progression or an engraftment at extramedullary sites in the AMD 3100-treated mice compared with control mice[40] or on the development of PCL. Cytokines are also involved in PCL proliferation, particularly interleukin-6 (IL-6)[41]. Primary and secondary PCL have spontaneous cell growth in culture, with increased growth

when stimulated with exogenous IL-6[41]. Autocrine IL-6 production triggered by interferon-alpha (IFN-α) has been postulated[42], based on a patient who developed PCL picture triggered by this treatment, enforcing the particular potential cytokine network in the pathogenesis of this entity. The same phenomenon has also been described with IL-3 that up-regulates IL-6 receptors[43]. Finally, association with viral infections has been hypothesized, with contradictory results[44-46].

> Consensus: Plasma cells from patients with PCL overlap in antigenic expression with those of patients with MM. However, CD20 (higher), CD56 (lower), CD117 (lower) and HLA-DR (lower) may be useful for both discrimination of PCL from MM and for follow-up studies. Further investigation of the pathogenetic role of surface cell molecules resulting in extramedullary spread in this entity is clearly warranted.

FISH and Cytogenetics

The molecular basis of PCL is poorly understood. Cytogenetic studies show that plasma cells in primary PCL have a number of genetic abnormalities. More than 80% of patients with PCL have hypodiploid or diploid cells which is associated with poor prognosis whereas about 60% of patients with MM display hyperdiploidy, a favorable finding[5]. Chromosomal abnormalities in PCL are summarized in Table 2. Results of these studies are very heterogeneous, basically based in retrospective studies and unsorted samples.

Chromosome 13 deletion and monosomy are the most frequent features[5,13]. Alterations such as monosomy 7, rarely seen in MM, has been observed in PCL[47,48]. Deletion of 17p13.1, causing allelic loss of *TP53*, has been detected in almost 50% of primary PCL and in 75% of secondary forms in one report. This deletion was complemented by coding mutations in 24% of patients with PCL[7]. The frequencies of IgH (14q32) translocations by FISH analysis are common in both types of PCL with 87% and 82% in primary and secondary forms, respectively. Thus, in a Mayo Clinic study the frequency of t(11;14) by FISH or by informative karyotype in primary PCL was 71%. Importantly, the IgH translocation in PCL involved chromosome 11 and cyclin D1 expression[7]. Conversely, no cases of t(4;14) or t(14;16) were observed in primary PCL[7]. Interestingly, p53 loss due to mutation or deletion was observed in 56% of patients with primary PCL and in 83% of patients with the secondary form[7]. Translocation t(11;14) is a favorable prognostic factor in M; however, its high prevalence in PCL suggests that this translocation when associated with high-risk cytogenetics, such as loss of p53, confers a different prognosis. Of course, PCL may simply be a completely different disease than MM, with different relevant high-risk factors. In the French and British experience[51,52], PCL also had significant differences when compared with MM: a higher incidence of t(11;14), t(14;16) and monosomy 13, with similar incidence of t(4;14).

Abnormalities in chromosome 1 are also frequent in PCL, particularly 1q21 amplification (involving *CKS1B* overexpression)[53] and del(1p21)[54]. The first finding was confirmed in all primary PCL patients in a Spanish series by comparative genomic hybridization (CGH), as well as losses on 13q, chromosome 16, 2q and 6p[55].

Certain genes, such as *cMYC*[56], are overexpressed by a complex mechanisms, such as *cMYC*[56], in spite of the fact that only 15% of primary PCL have a cMYC translocation[52,57]. Mutations in *N-Ras* and *K-Ras* show a similar frequency at diagnosis in PCL and in MM[58]. Epigenetic changes, such as p16 inactivation, have also been described in primary PCL[59,60] or global DNA hypomethylation of repetitive genomic sequences[61]. Gene-specific DNA hypermethylation as either tumor suppressors, cell-cell signaling or as cell adhesion molecules in PCL versus MM cells, may allow the clone to become independent of the bone marrow microenvironment[62]. Interestingly, within the same cytogenetic group (i.e. t(4;14) or t(11;14)) PCL samples were more hypermethylated in progression-related genes than the corresponding MM cells[62]. A relative high incidence of PTEN deletion which results in Akt activation has been observed in PCL and it has been suggested that PTEN loss can be involved in the transition from MM to PCL.

Gene-expression profile and whole genome sequencing

Usmani *et al* recently described the experience in PCL with total therapy programs[63]. The clinical outcomes were similar to those achieved with less intense therapy with an OS of only 18 months. Importantly, the GEP was completed in 16/27 patients, and surprisingly only 44% of patients with pPCL had a high risk signature defined by the GEP-70 model and 31% by the GEP-80 model[63]. Importantly, in the GEP analysis there was a tight clustering within the pPCL cohort as opposed to non-pPCL suggesting distinct molecular and genomic features in these groups. CD14 (cell-membrane LPS receptor), TNF receptor associated factor 2 (TRAF2) and chemokine C-C motif ligand were among 203 genes differentially expressed in pPCL hypothesizing myeloid differentiation of plasma cells during leukemic development[63].

On the other hand, Eagan *et al* recently described whole genome sequencing (WGS) in serial samples from a single patient through different points in the natural history, including development of sPCL[64]. This methodology with WGS may provide unique insights into potential mechanisms of PCL development.

> Consensus: Cytogenetics and FISH studies on bone marrow are mandatory in all patients with suspected PCL. On cytogenetics the karyotype is frequently complex and demonstrates hypodiploidy. With FISH analysis, careful attention should be paid to the most frequent reported alterations: (t(11;14) as well as to chromosome 1 and 17 abnormalities, particularly 1q+ and del17p. Additional molecular research aimed at understanding the development of primary PCL and transformation of MM into secondary PCL is needed.

RESPONSE TO THERAPY AND SURVIVAL

The survival of patients with pPCL is short. In seven series, historically median survival, without novel therapies, has ranged from 6.8 to 12.6 months[3-7,11-13]. Furthermore, the median survival of 231 patients from a recently published epidemiology study was only 4 months[6]. Of note, the survival rate at 5 years from diagnosis is less than 10% in all series. The best survival data, incorporating hematopoietic stem-cell transplantation, reported a

median survival longer than 3 years[65]. Unfortunately, the significant improvement in survival observed in MM in the past decade has not been seen in PCL[6].

These discouraging survival results in primary PCL are due to two facts: 1) its aggressive presentation with severe complications leading to early death within the first months from diagnosis, and 2) the lack of effective therapy to achieve sustained responses. Early mortality is still of concern and reflects the aggressiveness of the disease. In the French cohort, 11 of 40 patients died within the first month after diagnosis[51]. Unfortunately, data from transplantation registries or clinical trials have a systematic bias to exclude patients not fulfilling the entry criteria and/or experiencing early death. Secondary PCL is usually a terminal event with a median OS of only one month[3].

Criteria of Response

There are no specific response criteria for PCL. Thus, the general MM response criteria have been applied without distinctive considerations. Due to the leukemic nature of the disease as well as the relative higher percentage of light-chain only (Bence Jones) and oligosecretory forms, the importance of a precise plasma cell evaluation in blood and bone marrow by morphology and flow cytometry as well as the measurement of the serum free-light chain should be considered. Thus, the evaluation of response in primary PCL should combine acute leukemia[66] and MM requirements[67,68] (Table 3). The impact of a rapid clearance in peripheral and/or bone marrow malignant plasma cells has not been evaluated. It is reasonable to suggest that in PCL, the disappearance of peripheral blood plasma cells and a bone marrow plasma cell count <5% should be required to qualify for CR after hematological recovery. Complete clearance by conventional morphology in bone marrow for complete remission is required (Table 3), and flow cytometry should be necessary to define "stringent" CR. In addition, the high frequency of extramedullary involvement justifies evaluation of the patients by imaging techniques such as magnetic resonance imaging (MRI) and, particularly, FDG positron emission tomography/computer tomography (PET/CT).

Relapse from CR is defined as the reappearance of M-protein in patients in CR, extramedullary disease, reappearance of peripheral blood plasma cells at any level or increase in bone marrow plasma cells more than 10%. In contrast to MM, immediate therapy should be initiated when any evidence of relapse is documented.

Consensus:

Improvement in PCL outcomes need to be focus on 1) reducing early mortality and 2) improving long term disease control. In the absence of specific response criteria for PCL, response to therapy has been evaluated according to MM criteria. Given the primarily leukemic nature of the disease and the frequency of oligo/non-secretory forms, the evaluation of response should combine acute leukemia and MM criteria. Measurement of immunophenotypic residual disease is needed when there is no evidence of plasma cell infiltration with routine morphologic evaluation. Finally, a careful evaluation of extramedullary disease at diagnosis and at response evaluation is required for all PCL patients.

THERAPEUTIC OPTIONS

Conventional regimens

The results of treatment with combinations of alkylating agents, mainly melphalan, and glucocorticoids, are unsatisfactory. Despite an overall response rate (ORR) ranging from 23 to 67%, the median OS has been less than one year in all the reported series[3-5,11-13]. In one study, the failure to achieve 50% clearance of blood plasma cells within 10 days after treatment initiation was a predictor of no response[4]. The addition of more agents, such as VAD (vincristine, doxorubicin and dexamethasone) or the VCMP regimen (vincristine, carmustin, melphalan and prednisone) alternating with VBAP (vincristine, carmustin, doxorubicin and prednisone) modestly improved the results in terms of response rate and OS[4,5,7].

Investigators have also attempted to improve outcomes with standard regimens such as HyperCVAD (hyper-fractionated cyclophosphamide, vincristine, doxorrubicin, dexamethasone)[69].

Novel drugs: Thalidomide/Lenalidomide

Anecdotal reports in small series showed a potential role of thalidomide in PCL[70,71], but without confirmation thus far[72]. Severe cardiac and pulmonary toxicities have been described[73,74].

Lenalidomide, a more potent immunomodulatory drug resulted in only transient responses[75-77]. Combination of lenalidomide with melphalan and glucocorticoids has also been used[78], achieving a transient PR in one case.

Musto *et al.* have presented the results of a prospective multicenter phase II trial of lenalidomide/dexamethasone in first line in 23 patients with primary PCL[79]. Patients received lenalidomide 25 mg for days 1-21 and weekly dexamethasone 40 mg in a 28 day cycle as primary induction therapy for 4 cycles and if eligible for ASCT (autologous stem cell transplantation) could proceed to ASCT or continue long term primary therapy. The initial ORR was 60% and, with a median follow-up of 15 months, the OS and PFS were 65.2% and 52.1%, respectively.

Novel Therapies: Bortezomib

The proteosome inhibitor bortezomib has shown clinical activity in both primary and secondary PCL[80,81]. An Italian group reported the results of a retrospective analysis on twelve evaluable patients with pPCL at relapse and sPCL treated with a bortezomib based combination[82]. Response rate was 92%, including two complete responses (CR). Responses did not appear to be influenced by previous therapy, including autologous stem-cell transplantation (ASCT). The median progression-free survival (PFS) and OS after bortezomib were 8 months and 12 months, respectively. The same group described a similar high response in untreated pPCL treated at time of diagnosis with bortezomib and various combinations (VD, n=3; VTD, n =2; PAD, n =6; MPV, n=1). There was a high overall

response rate (79%) including 28% CR and 83% of patients were alive if the response was consolidated with stem-cell transplantation, but the follow-up is still very short[83].

Another single-institution experience has described a series of 25 patients (13 pPCL; 12 sPCL) with a high response rate of 16 out of 18 patients treated with a bortezomib-based regimen. Importantly, the OS of patients exposed to bortezomib was 28 months compared to 4 months in those who did not receive bortezomib at induction[84].

The efficacy of the combination of bortezomib with dexamethasone and melphalan[85] or doxorubicin[82,86] has also been reported in selected smaller case reports and series. Bortezomib and dexamethasone has been shown to be useful in three patients with primary PCL, t(4;14) and CD27 expression[87].

High dose therapy/stem cell transplantation

Considering the poor prognosis of this form of clonal plasma cell dyscrasia, intensification with high-dose therapy followed by autologous stem cell rescue should be offered, provided that age and clinical condition do not preclude this approach. In the Mayo Clinic series, patients who received ASCT had a longer median OS when compared with those who received chemotherapy alone (34 versus 11 months)[7], although at least part of this survival benefit is obviously due to a selection bias in favour of the transplant group.

The largest study in the transplantation setting is the retrospective report by the European Group for Blood and Marrow Transplantation[88], reporting data on 272 patients with primary PCL. At the time of conditioning for transplantation, a higher proportion of patients with PCL than MM were in CR (25.5% versus 11.9%). Also, patients with PCL achieved a higher CR rate at 100 days after ASCT (41.2% vs. 28.2%), but a selection bias cannot be excluded.

This response pattern is consistent with the clinical behaviour of high risk myeloma, which tends to have higher initial response rates to induction therapy and ASCT[89]; however, they also have shorter response duration with rapid relapse. The median PFS was 14.3 months in PCL and 27.4 months in MM. This is translated into significantly shorter OS in the PCL group (median of 25.7 versus 62.2 months), irrespective of the degree of response achieved, reflecting a more aggressive minimal residual disease in patients with PCL. In addition, the fact that a significant proportion of patients with PCL potentially eligible for ASCT could die or develop progression within the first few months after diagnosis[51], precluding the high-dose procedure, represents an important bias in favour of transplant results. In summary, despite the relative good response achieved in selected patients with PCL who respond to initial treatment and receive intensification with ASCT, it usually does not translate into a prolonged survival. Therefore, other therapeutic approaches should be explored, such as the use of the new drugs in induction, consolidation or maintenance or a subsequent reduced-intensity allogeneic transplant[81].

The CIBMTR reported a PFS and OS at 3 years of 34% and 62% respectively, in 97 patients with pPCL who underwent ASCT. This experience supports the role of ASCT in transplant eligible patients and offers an opportunity for relatively prolonged remission. These results for the first time demonstrated survival beyond 3 years in a proportion of selected patients[65].

Tandem ASCT could result in an improved depth and duration of remission. In this regard, in Total Therapy (TT) programs, timing of onset and eventual rate of CR were virtually identical for patients with or without PCL. However, median OS (1.8 years) and PFS (0.8 years) were inferior to those of the non-PCL group as a whole. Significant advances in clinical outcomes were observed among non-PCL patients with the transitions from TT1 to TT2, to TT3, but such advances were not observed in PCL patients[63]. Other strategies to consolidate after first ASCT, other than second ASCT, including combination regimens of VTD, RD or VRD may also play a role and need further evaluation. The addition of aggressive long-term maintenance therapy with lenalidomide or novel lenalidomide-based combinations provides yet another potential strategy to improve duration of remission. The significant PFS benefit reported by CALBG 10014 and IFM with maintenance lenalidomide suggest that maintenance lenalidomide therapy could be an attractive possibility to be investigated in PCL[90,91]. Importantly, relapses may occur very early after ASCT and therefore it is worth considering early initiation of maintenance therapy, in the first 30-60 days, as soon as a stable engraftment is documented.

Allogeneic Stem Cell Transplantation

A retrospective report of 147 patients with primary PCL from the CIBMTR experience showed that 19 of the 50 patients (39%) who underwent allogeneic transplantation were alive at 3 years[65]. Few of these patients had received novel agents (thalidomide, lenalidomide or bortezomib) as part of their induction regimen. Progressive disease accounted for 22% of the deaths in the allogeneic transplant group, compared to 85% of the deaths in the ASCT group.

The EBMT recently described their experience with 85 patients who underwent allogeneic transplantation in comparison to 411 patients who underwent autologous SCT for PCL. PFS curves with the myeloablative and RIC allo-SCT possibly crossed the ASCT curve between 2 and 4 years, but with similar OS at 5 years. As seen in previous experiences with allo-SCT described by the CIBMTR, there was a high early mortality; however, there was also a clear plateau in survival at 20%[92].

Careful selection of patients undergoing either myeloablative or reduced-intensity conditioning (mainly by age), and incorporating new drugs in induction and consolidation/maintenance could potentially further exploit the alloreactive immunotherapeutic effect.

> Consensus: The diagnosis of PCL needs to be made in a timely manner and immediate therapy initiated. The goal of induction therapy is to achieve rapid cytoreduction to minimize the risks contributing to early death. Intensive chemotherapy with alkylating agents or anthracyclines such as HyperCVAD or PACE regimens and bortezomib-based combinations (VTD-PACE [cisplatin, doxorubicin, cyclophosphamide, and etoposide], HyperCVAD-VD or PAD) can meet these goals. Although the data are still limited, the use of bortezomib likely improves disease outcome and this drug will likely become the backbone in the treatment of PCL. Strategies to improve long term survival include the incorporation of high-dose therapy with autologous SCT. Much of the improvement in outcomes with novel therapies and ASCT have been observed in

primary PCL, but without significant improvement in secondary PCL. The role of consolidation and maintenance therapy needs to be evaluated. The impact of tandem autologous cell transplant and allogeneic transplantation also remains to be defined.

In patients younger than 50 years of age with a suitable donor, a myeloablative allogeneic transplantation can be considered. Otherwise, a tandem transplant with an ASCT followed by a reduced-intensity conditioning allogeneic transplantation if a related or and unrelated donor is available (Figure 3) can be considered.

In patients not candidates for HDT/SCT, a bortezomib-based induction regimen (MPV, VRD or VTD) in order to achieve a rapid response appears to be the best choice (Figure 4). However, these recommendations are supported by limited data and are mainly based on expert opinion.

Treatment in secondary PCL or relapsed primary PCL depends on the type of and response to previous therapy. Fit patients may be candidates for bortezomib-based regimens or intensive chemotherapy (i.e. HyperCVAD or Dexamethasone-PACE) or early phase clinical trials in eligible patients, followed by stem-cell transplantation if suitable (Figure 5)

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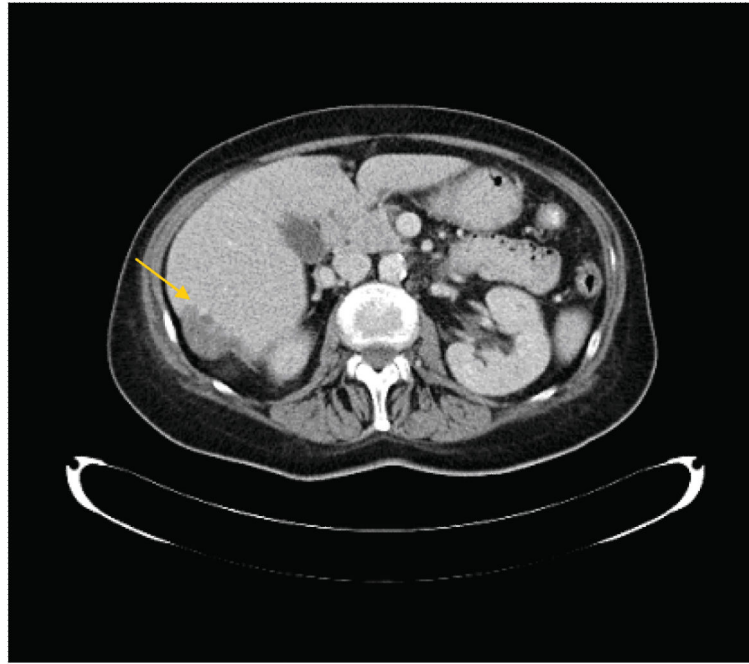
Figure 1.
Abdominal tomography showing a focal lesion (40 mm), highlighted by the arrow, suggestive of metastasic infiltration of the liver in a patients with plasma cell leukemia.
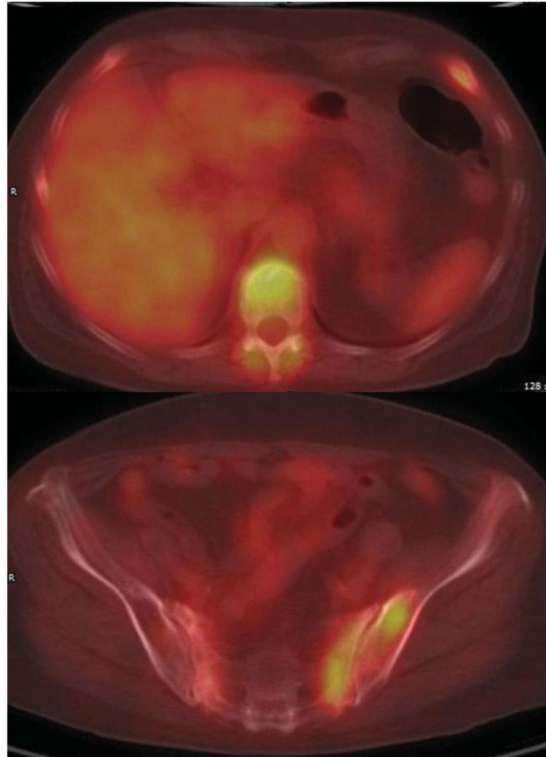
Figure 2.
PET/CT-scan of a patient with primary PCL showing focal bone lesion with increased
uptake of FDG in vertebrae, ribs and pelvis.
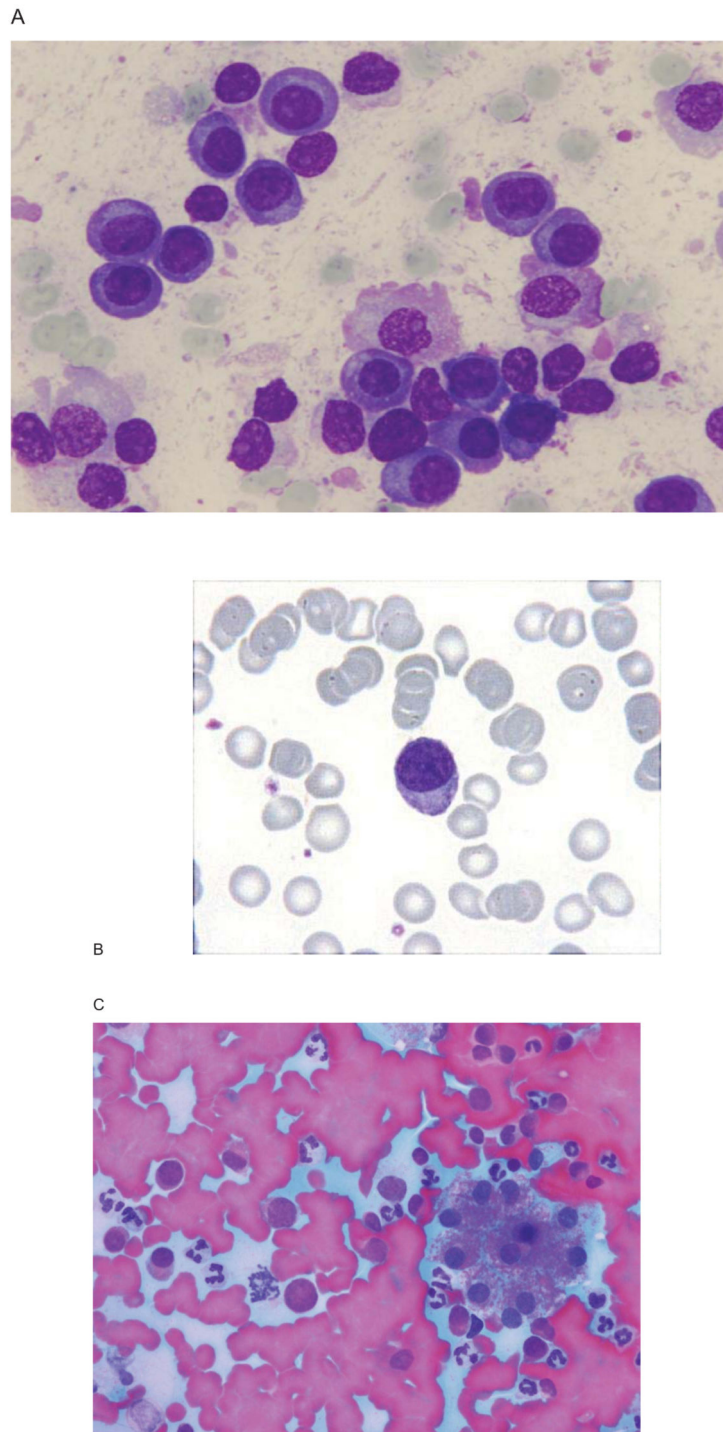
Figure 3.
Conventional morphology in plasma cell leukemia cases shows bone marrow infiltration (Panel A), with circulating plasma cells (Panel B) and frequent extramedullary involvement, as hepatic infiltration (Panel C).

A

Transplant candidate

↓

**Bortezomib-based induction plus
chemotherapy +/- IMID
(i.e. VTD-PACE, HyperCVAD-VTD, PAD, VCD)**

Age ≤ 50 yrs and suitable donor

Yes   >50 yrs

Consider   **ASCT**
**Myeloablative**   (Melphalan 200)
Allo-SCT

Suitable donor

Yes   No

Consider   **Consolidation/maintenance**
Allo-RIC   Bortezomib +/- Lenalidomide-
based (indefinite)

B   **Non-transplant candidate**

↓

**Bortezomib-based induction
(MPV, CyborD, VTD)**

Response ≥PR

Yes   No

Maintenance   **Clinical trials
Palliation**

Figure 4.
Treatment algorithm for primary plasma cell leukemia

Fit patients   **Unfit patients**

**Bortezomib-based treatment (VTD, PAD) and/or
Intensive Chemotherapy (HyperCVAD, D-PACE)**   **Palliation**

Response ≥PR   No

Yes

Transplant candidate

Yes   No

SCT   **Maintenance**
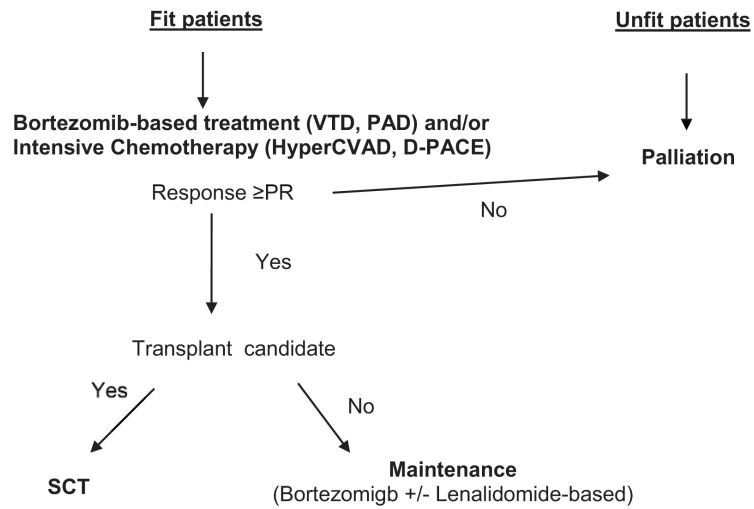(Bortezomigb +/- Lenalidomide-based)

Figure 5.
Treatment algorithm for secondary plasma cell leukemia or relapsed primary plasma cell leukemia

Table 1

Main clinical and laboratory features of seven retrospective series of patients with primary plasma cell leukemia.

	Noel and Kyle (1987)	Dimopoulos *et al* (1994)	Garcia-Sanz *et al* (1999)	Tiedemann *et al* (2008)	Colovic *et al* (2008)	Peijing *et al* (2009)	Pagano *et al* (2011)
Number of patients	25	27	26	41	30	22	73
Median age (years)	53	57	65	54.5	60	49.5	NA
Sex, M/F	15/10	NA	12/14	24/17	22/8	14/8	43/30
Lytic bone lesions (%)	44	NA	48	35	60	44.4	64
Extramedullary involvement (%)							
Liver	52	32	0	32	56	44.4	23
Spleen	44	18	0	18	53	33.3	18
Lymph nodes	12	6	11	6	3	NA	4
Other	NA	NA	NA	NA	NA	NA	14
M-protein type (%)							
IgG	12.5	52	54	28	53	54.5	30
IgA	25	15	4	13	23	9.1	8
IgD	6	0	8	2	3	0	3
Light chain	44	28	31	41	20	27.3	30
Nonsecretory	12.5	7	4	8	0	9.1	18
Hemoglobin <10 g/dL (%)	>50	82	54	>50	100	>50	48
Platetelet count < 100 × 109/L (%)	>50	67	48	>50	100	>50	NA
High β2-microglobulin (%)	NA	91	65	50	64	50	100
High LDH (%)	NA	63	48	50	37	NA	52
Response to treatment (%)	47	37	38	NA	NA	45.5	55

Table 2

Cytogenetics data available in plasma cell leukemia series

Cytogenetics abnormalities (%)	Garcia-Sanz et al (1999)	Dimopoulos et al (1994)	Tiedemann et al (2008)	Pagano et al (2011)	Avet-Loiseau et al (2001)	Chiecchio et al (2009)
Hypodiploidy		41	60	12.2	47	41.6
Hyperdiplody			0	4.9	8.8	33.3
Complex karyotype		92	54.5	34.2	58.8	66.7
del(13q14) or monosomy	84	50	85	19	68	58
del(17p13)			50	7.3	11.8	25
t(11;14)			71	19.5	33	42
t(4;14)			0	0	12	8.3
t(14;16)			0	0	16	25

Table 3

Response criteria for plasma cell leukemia

Category	Bone marrow criteria[1]	Peripheral blood criteria[1]	Serologic criteria[2]	Other criteria
Stringent Complete Remission (sCR)	-Bone marrow plasma cells <5% and -No malignant plasma cell by flow cytometry	-No plasma cells in peripheral blood by flow cytometry	-Negative serum and urine immunofixation -Normal serum FLC ratio	-Absence of extramedullary disease
Complete remission (CR)	-Bone marrow plasma cells <5%	- No plasma cells in peripheral blood	-Negative serum and urine immunofixation[3]	-Absence of extramedullary disease.
Very Good Partial response (VGPR)	-Bone marrow plasma cells <5%	-No plasma cells in peripheral blood	- 90% reduction of serum M-protein, and -24-h urinary M-protein <100 mg per 24 h[4]	-Absence of extramedullary disease.
Partial response (PR)	-Bone marrow plasma cells to 5% to 25%	-Peripheral plasma cell from 1% to 5%	- 50% reduction of serum M-protein and -Reduction in 24-h urinary M-protein by 90% and <200 mg per 24 h[5]	- 50% reduction in the size of extramedullary disease
Stable disease (SD)	Not meeting the criteria of either partial response or progressive disease			
Progressive disease (PD)	>25% increase in plasma cells in a bone marrow aspirate or absolute increase 10%	-Plasma cells >5% absolute increase in peripheral blood	->25% increase in the level of the serum monoclonal paraprotein with an absolute increase 5 g/L ->25% increase in the 24h urinary light chain excretion with and absolute increase 200 mg/24 hours	-Hypercalcemia -Definite increase in lytic bone lesions -Definite increase in the size or number of extramedullary disease
Relapse from CR	-More than 10% increase in bone marrow plasma cells	Reappearance of peripheral blood plasma cells at any level	-Reappearance of original M-protein in serum and/or urine immunofixation	-Any extramedullary disease

[1] It is recommended that at least 200 leukocytes on blood smears and 500 nucleated cells on marrow smears be counted.

[2] It should be maintained for a minimum of 6 weeks. In case of discrepancy or undetectable serological parameter, the patient must be classified according to bone marrow criteria.

[3] If the serum and urine M-protein are unmeasurable, a normal serum kappa/lambda FLC ratio is also required.

[4] If the serum and urine M-protein are unmeasurable, a 90% decrease in the difference between involved and uninvolved FLC levels is required instead of the M-protein.

[5] If the serum and urine M-protein are unmeasurable, a 50% decrease in the difference between involved and uninvolved FLC levels is required instead of the M-protein.