Management of Primary Plasma Cell Leukemia Remains Challenging Even in the Era of Novel Agents

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ABSTRACT: Primary plasma cell leukemia (PCL) is a rare and aggressive variant of multiple myeloma (MM). PCL is characterized by peripheral blood involvement by malignant plasma cells and an aggressive clinical course leading to poor survival. There is considerable overlap between MM and PCL with respect to clinical, immunophenotypic, and cytogenetic features, but circulating plasma cell count exceeding 20% of peripheral blood leukocytes or an absolute plasma cell count of >2000/mm^3 distinguishes it from MM. After initial stabilization and diagnosis confirmation, treatment of PCL in a fit patient typically includes induction combination chemotherapy containing novel agents typically, with proteasome inhibitors (such as bortezomib) and immunomodulatory drugs (eg, lenalidomide), followed by autologous hematopoietic stem cell transplant (HSCT) and multidrug maintenance therapy using novel agents post-HSCT. Long-term outcomes have improved employing this strategy but the prognosis for non-HSCT candidates remains poor and new approaches are needed for such PCL patients not eligible for HSCT. Here, we report a case of primary PCL, and a comprehensive and up to date review of the literature for diagnosis and management of PCL. We also present the findings of Positron Emission Tomography (PET) scan. Since PCL is often associated with extra-medulary disease, including PET scan at the time of staging and restaging may be a novel approach particularly to evaluate the extra-medullary disease sites.

KEYWORDS: Plasma cell leukemia, novel agents, multiple myeloma, autologous hematopoietic stem cell transplantation

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Introduction

Primary plasma cell leukemia (PCL) is a rare and aggressive form of multiple myeloma (MM). The PCL accounts for 0.5% to 2% of MM cases with annual incidence ranging between 0.4 and 1.2 cases per million individuals per year.[1,2] Although the definition of PCL is still evolving, a circulating plasma cell count that exceeds 20% of peripheral blood leukocytes, or an absolute plasma cell count >2000/mm^3, has been the arbitrary but traditional definition of PCL.[3] Multiple myeloma (MM) patients exhibiting circulating plasma cell levels as low as 2%, counted morphologically at the time of diagnosis, demonstrated poor survival, similar to that seen in PCL patients.[4] Granell et al[5] in another analysis of 482 newly diagnosed MM patients, demonstrated that the presence of ⩾5% circulating plasma cells counted in the peripheral blood has a similar adverse prognostic impact as that of PCL. As also reported, extremely low levels (~0.26%) of circulating clonal plasma cells (CPC) in MM patients, as detected by immunophenotyping (flow cytometry) at the time of diagnosis and treated with novel agents, was also associated with inferior overall survival (OS).[6] For example, the 3-year OS for the MM patients with presence of CPC was 67% compared with 87% for those with no CPC.[6] Currently, the optimal diagnostic threshold of CPC levels necessary to define PCL is being debated by multiple myeloma experts worldwide.

Primary PCL is rare and arises de novo, but secondary PCL occurs via clonal evolution from a pre-existing MM. This is typically observed following several lines of therapy and often as a terminal event as part of aggressive relapsed of multiple myeloma. Therefore, for the purpose of this report, "PCL" will refer to *primary* PCL only.

A brief comparison of the clinical features of PCL and MM is presented in Table 1. Compared to MM, PCL is more aggressive at presentation, patients more often than not present with bone marrow insufficiency (in the form of anemia, or thrombocytopenia,) and end organ damage (in the form of hypercalcemia or renal dysfunction) and multi-organ dysfunction. The clinical course is much more aggressive and outcome is associated with poorer prognosis despite treatment in PCL when compared to MM.[5] Additionally, higher LDH and B2-microglobulin levels are often observed in PCL, indicating significantly higher disease burden and proliferation rate at the time of presentation. The higher propensity for

Table 1. Clinical features of primary plasma cell leukemia (PCL) compared to multiple myeloma.

CLINICAL FEATURES	MULTIPLE MYELOMA	PLASMA CELL LEUKEMIA
Incidence	52 to 75 cases per million individuals per year[1,2]	0.4 to 1.2 cases per million individuals per year or 0.5% to 2% of all MM cases[1,2]
Age of onset (years)	Older (median age, 65-74)[23]	Relatively younger (median age 55)[1-3]
Most common subtype	IgG (46%) followed by IgA	IgG (58%) followed by light chain only
Bone marrow failure (anemia, thrombocytopenia)	Less common	More common
Hypercalcemia	Less common	More common
B2-microglobulin	+	+++
LDH	+	+++
Renal dysfunction	+	+++
Tumor lysis syndrome	Less common	More common
Extra-medullary involvement (liver, spleen, other organs) at diagnosis	Less common	More common
Deletion 17p/TP53 mutation	Less common (~10%)	More common (~50%)[12]
t (11;14)	Less common (10%-31%)[24]	More common 30%[12] to 50%[14]
Prognosis (median overall survival)	Better (median OS = 5.2 years with median follow up 5.9 years)[25]	Worse [median OS 28% at 4 years (range 22%-35%)][10]

Abbreviations: LDH, lactate dehydrogenase; MM, multiple myeloma; OS, overall survival; PFS, progression free survival.

extra-medullary involvement at diagnosis, in addition to a larger incidence of high-risk cytogenetics (eg, 17p deletion/TP53 mutation and t[14;16]) also reflects the biologically much more aggressive nature of PCL compared to MM.[7,8]

In this review, we present a patient with primary PCL who exhibited complete response to induction therapy with lenalidomide, bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide (RVD-PACE), but relapsed quickly after autologous peripheral blood hematopoietic stem cell transplantation (HSCT). A second remission was not inducible with salvage therapy containing carfilzomib, pomalidomide, and dexamethasone, and the patient subsequently died from progression of PCL.

Case Presentation

A 62-year-old male with a history of bladder cancer status post transurethral resection of the bladder tumor 5 years prior, was seen in the emergency room for progressively worsening low back pain for 6 weeks prior to his presentation. His past medical history was complicated and included: anxiety/depression, Type II diabetes, hypertension, coronary artery disease, hypercholesterolemia, morbid obesity, obstructive sleep apnea, and cigaratte smoking(active smoker with 20-pack year history). In the emergency room, patient's vital signs were normal and laboratory studies showed WBC 10 500/mm^3, hemoglobin 13.7 gm/dL, platelets 66 000/mm^3, absolute neutrophil count 4400/mm^3, absolute lymphocyte count, 4200/mm^3, and 13% blasts. The patient's creatinine, uric acid, bilirubin, calcium, total protein, and serum albumin levels were normal. The LDH was elevated to 958 IU/L (normal range 135-225). A peripheral blood smear showed frequent (53%) atypical plasmacytoid cells (Figure 1A) and the flow cytometry of peripheral blood confirmed 50% monotypic lambda restricted clonal plasma cells consistent with PCL. The Serum protein electrophoresis with immunofixation revealed IgG lambda monoclonal gammopathy, with M spike 0.52 gm/dL, serum free kappa light chain level 4.3 mg/L (range 3.3-19.4), serum free lambda light chain level was 2695 mg/L (range 5.7-26.3), with lambda to kappa ratio of ~627. The Beta-2-microglobulin level was 4.5 mg/L (range 0.3-1.9), and levels of IgG, IgA, and IgM levels were 775, 31, and 13 mg/dL respectively. A lumbar spine magnetic resonance imaging (MRI) showed no vertebral fractures, cord compression, or cauda equina lesions but did report widespread T1 hypointensity, and heterogeneous areas of T2/inversion recovery hyperintensity, consistent with possible leukemic infiltration of the bone marrow. A bone marrow aspiration/biopsy demonstrated plasma cell neoplasm with plasmablastic features replacing the bone marrow cellularity. The MM fluorescent in situ hybridization (FISH) was positive for 17p (TP53) deletion, along with presence of additional copies of chromosomes 5, 9, and 15. Final clinical diagnosis of primary PCL, with 17P deletion, was made. The Positron Emission Tomography (PET) scan (Figure 2A) revealed numerous, intensely fluorodeoxyglucose (FDG) avid, bone marrow lesions throughout the skeleton. A core needle biopsy of right 8th rib lesion (Figure 2A arrow) confirmed the presence of plasmablastic malignancy.

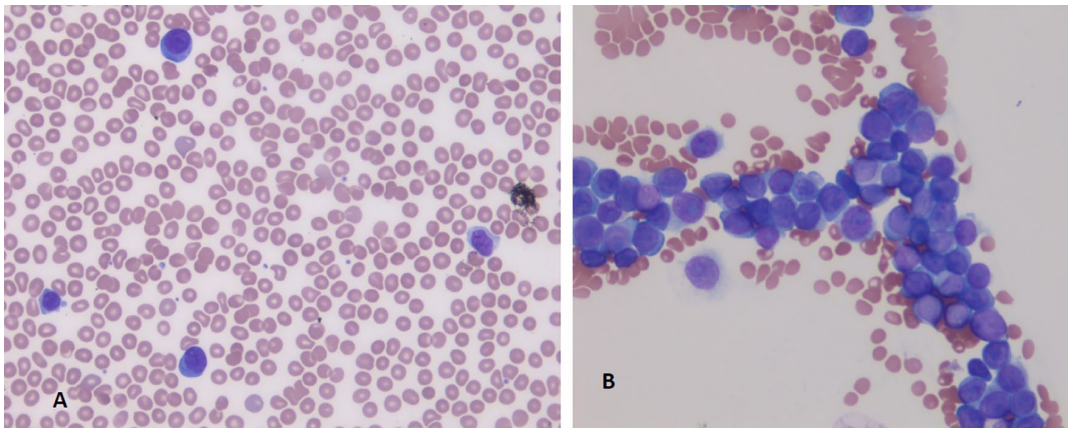

Figure 1. Peripheral blood smear at the time of diagnosis (A) and at the time of relapse (B). Peripheral blood smear, Wright-Giemsa stain, 10× shows circulating large neoplastic plasma cells and thrombocytopenia (A). Peripheral blood smear, Wright-Giemsa stain, 40× shows that the neoplastic plasma cells have blastoid features (B).

Immediate initialization of induction chemotherapy using a combination regimen with bortezomib, dexamethasone, lenalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide (RVD-PACE) achieved stringent complete response (sCR) as defined by previously published criteria[9] after 3 cycles. The patient received additional 2 cycles of bortezomib, dexamethasone, and lenalidomide (RVD) while waiting for HSCT. To prevent skeletal-related events, he also received zoledronic acid. He underwent HSCT conditioning, with melphalan (200 mg/m^2 (MEL 200)), with engraftment on day +11.

The post-HSCT course was complicated with profound physical deconditioning and prolonged hospitalization. The patient developed generalized bone pain and a repeat bone marrow biopsy was performed on day +90 post-HSCT, which reveled 40% blastoid monoclonal plasma cells with plasmablastic features consistent with relapsed PCL.

The patient started salvage chemotherapy using carfilzomib, pomalidomide, and dexamethasone (KPD) to treat relapsed PCL with palliative intention as the patient was not felt to be a candidate for second HSCT or allogeneic HSCT. Cycle 1 of KPD therapy was complicated by acute hypoxemic respiratory failure due to bilateral pneumonia, and severe thrombocytopenia. A Flow cytometry of peripheral blood detected a small plasma cell clone and the peripheral blood smear showed blastoid neoplastic plasma cells confirming the relapsed of the PCL. Later, pomalidomide was discontinued due to intolerance (profound fatigue and cytopenia). He resumed carfilzomib at an increased dose 56 mg/m^2, weekly, with dexamethasone. Progressive PCL was noted in the next several weeks and the patient became transfusion-dependent for red blood cells and platelets. Subsequently, the patient performance status deteriorated. Anti-CD 38 monoclonal antibody immunotherapy with daratumumab was offered but the patient elected for hospice, at-home, and died peacefully 14 months after the initial diagnosis.

Discussion

Even with employing the novel agents available for treatment of clonal plasma cell neoplasms in combination regimen, the treatment of PCL remains challenging. A prompt diagnosis and early stabilization of metabolic challenges, tumor lysis syndrome (TLS), hypercalcemia, acute renal failure and immediate use of multi-agent induction therapy containing novel agents can reduce the risk of early morbidity and may help prolong survival. There is a high response rate with induction therapies containing bortezomib, lenalidomide or thalidomide. Cytotoxic chemotherapies can also be combined with novel agents, which may not be routinely available on the formulary of many USA hospitals as most myeloma care is delivered on the outpatient basis. Rapid and complete responses are often observed after multi-agent induction therapy containing novel agents, but early relapse is common in PCL. For a durable remission, the induction therapy containing proteasome inhibitor (PI) should follow immediately with consolidation therapy, often with HSCT for eligible candidates. In HSCT-ineligible patients, the optimal strategy is unknown but a several cycles of remission induction therapy, followed by long term multi-agent maintenance therapy containing PI and an immunomodulatory agent (IMiD) may provide durable remission. A recently published multicenter retrospective analysis of 348 patients with PCL by Dhakal et al[10] concluded that despite incorporation of modern induction therapy containing novel agents and despite increased utilization of both autologous and allogeneic HSCT in the last several years, the survival of PCL patients has not improved in comparison to the historical cohort of PCL patients prior to the widespread use of novel agents. The study underscored that the main reason for the lack of improvement in the survival despite utilization of modern therapies is due to the high relapse rate after HSCT (~76% relapsed at 4 years post-HSCT).[10] Allogeneic HSCT is only suitable for a minority of PCL patients as shown in a few small studies[10] demonstrating initial good response, a small PFS benefit of

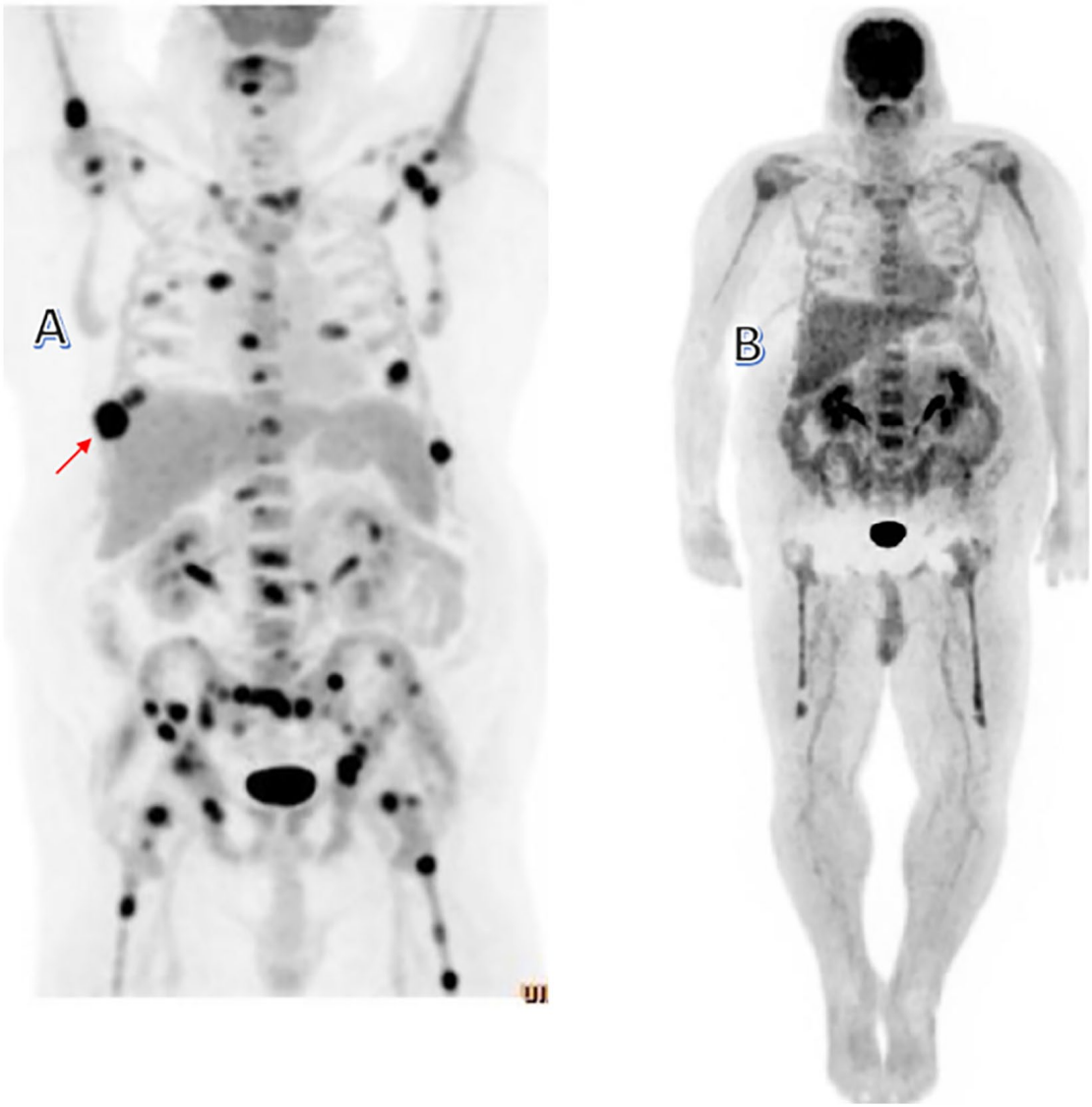

Figure 2. Attenuation corrected 3-D maximum intensity projections (MIP) positron emission tomography (PET) images of fluorine 18 FDG PET-CT scan: (A) baseline study, demonstrating numerous bone marrow tracer avid lesions involving cervical, thoracic and lumbar spine as well as bilateral ribs, scapula, humeri, pelvis, sacrum, and bilateral femurs. Maximum standard uptake value (SUVmax) in the sacrum = 27 and (B) follow up post-treatment study demonstrating resolution of previously noted tracer avid lesions. Moderate intensity heterogeneous tracer uptake throughout the bone marrow felt to be related to granulocyte colony stimulation factor therapy effect.

19% at 4 years and overall survival (OS) of only 31% at 4 years. Small studies of tandem double autologous or tandem autologous/allogeneic HSCT showed limited benefit as well.[11,12] For autologous or allogeneic HSCT, relapse was the main cause of death in approximately 80% of patients after HSCT. Allogeneic HSCT may have a role for treatment of younger and fit patients, ideally in the context of a clinical trial. For example , Currently an ongoing clinical trial in Europe (EudraCT Number: 2016-003105-33) incorporates a potent second generation irreversible PI, carfilzomib and lenalidomide during remission induction, consolidation, and maintenance phase of therapy and offers allogeneic HSCT to younger, fit, and responding patients.[13]

The median overall survival of PCL patients, before the use of novel agents, was historically measured in only a few months.[14] However, with the incorporation of novel agents (bortezomib, lenalidomide or thalidomide) and autologous HSCT, survival has been reported to improve to 12 months.[15] While this represents favorable progress for this patient group, more improvement is necessary to improve outcomes in the treatment of PCL. There is signal showing that further improvement can be achieved with post-HSCT maintenance therapy with novel agents. This was demonstrated by Mina et al[16] in their retrospective analysis of 38 patients with PCL treated with bortezomib plus either thalidomide or lenalidomide as induction therapy followed by HSCT and maintenance therapy with bortezomib and lenalidomide for 3 years in majority of the cohort. The median PFS was 20 months, and the median OS was 33 months with PFS better for those who received HSCT (25 vs 6 months). Most important finding was that the patients who received maintenance therapy after HSCT had prolonged median PFS (27 vs 11 months) and a trend toward prolonged OS (median, 38 vs 22 months) compared with those who did not receive maintenance therapy.[16]

Over half of patients with PCL harbor highly adverse prognostic factor of 17p deletion.[17] Bortezomib and other proteasome inhibitors (carfilzomib, ixazomib) are postulated to help overcome the adverse prognostic impact of poor cytogenetics in MM, especially in 17p deletion/TP53 mutation and cytogenetic aberrations involving chromosome 14 in high risk MM.[18] Due to this observation and the retrospective data in high risk MM, PI appears to be an important therapeutic tool to be used in the treatment of PCL. To conduct a well-funded randomized phase III study is challenging due to multiple logistic factors and relatively rare nature of PCL. Therefore, randomized phase III studies in PCL are lacking. A phase II study evaluated the effectiveness of bortezomib and chemotherapy (doxorubicin or cyclosphosphamide), followed by HSCT, and 1 year of maintenance therapy with RVD. The results thereof indicated a good response rate (the overall response rate to induction therapy was 69%) and improved median survival to 3 years.[19] In another report Nooka et al[20] reported encouraging results of RVD maintenance with 51% of patients achieving stringent complete response (sCR) and 96% achieving VGPR or better and median PFS of 32 months and a 3-year OS of 93%. These studies support induction therapy with regimen containing novel agents followed by early HSCT for consolidation and post-HSCT maintenance therapy with RVD for the best results. Only 27% of post-autologous HSCT and only 12% of post allo-HCT PCL patients had received maintenance therapy in the study by Dhakal et al[10] which may have contributed to the high relapse rate in the HSCT survivors in their cohort.

In summary, patients who are fit enough to undergo HSCT, and who receive PI containing multi-agent maintenance therapy after HSCT, tend to exhibit improved survival compared to patients who did not undergo HSCT and did not receive maintenance therapy. The standard low dose lenalidomide maintenance monotherapy (10-15 mg daily), prescribed after HSCT in MM, appears to be inadequate in PCL due to reported 50% relapse rate within first year.[21] The maintenance strategy with combination therapy of RVD appears to be more effective and is tolerated by majority of patients after HSCT in PCL.[21,22] Three factors affecting survival outcomes in PCL appear to be (1) incorporating novel agents with PI and IMiD in the induction therapy, (2) consolidation with HSCT in fit stronger and younger patients, and (3) maintenance therapy containing multiple novel agents (bortezomib and lenalidomide). Patients who are able to tolerate these therapies tend to have the best possible outcomes but relapses still do occur including at unusual sites for example, meningeal relapses after both allogeneic and autologous HSCT.[19]

The timing and sequencing of newer generation proteasome inhibitors, carfilzomib and ixazomib, is still evolving in PCL and there are no published studies as of the writing of this review. Ixazomib, as an oral agent, may be suitable as a combination therapy with an IMiD, such as lenalidomide or pomalidomide, particularly for maintenance therapy. Both ixazomib and pomalidomide are effective agents against relapsed myeloma, but no study has been conducted to prospectively examine the efficacy of either in PCL. However, a phase II study of pomalidomide, ixazomib, and dexamethasone, in treating patients with previously treated MM or secondary PCL, is currently ongoing and will help answer questions surrounding the effectiveness of these biologic agents for patients with relapsed myeloma and secondary PCL (ClinicalTrials.gov Identifier: NCT02547662). Additionally, a phase I study of filanesib and carfilzomib in treating patients with relapsed or refractory MM, or secondary PCL, was completed and the final results of which are pending (ClinicalTrials.gov Identifier: NCT01372540). The results of a clinical study of carfilzomib, pomalidomide, and dexamethasone (KPD) for relapsed or refractory myeloma indicate that the regimen is a well-tolerated and highly active combination for patients with relapsed/refractory multiple myeloma[22] and there is evolving preliminary safety and efficacy data from an ongoing phase II non-randomized clinical trial that examined carfilzomib, lenalidomide and dexamethasone (KRD) for first line treatment of PCL.[23] In this study patients eligible for HSCT underwent 4 cycles of KRd induction followed by HSCT, KRd consolidation, and then maintenance with KD until progression. Patients not eligible for HSCT received KRd followed by KD maintenance. The final results are not published yet but preliminary results are encouraging with high response rate and acceptable safety (⩾VGPR in 80% and ⩾CR in 33%).[23] The patient in this report received KPD therapy at the time of relapse, with less than partial response (Figure 3) attesting to the much more aggressive biology of relapsed PCL.

Daratumumab and isatuximab are highly effective anti-CD38 monoclonal antibodies approved for MM in combination with novel agents.[24-27] Studies are needed to understand how and when to incorporate this highly active novel immunotherapy for treatment of PCL. Unfortunately, a phase I study of daratumumab, in combination with bortezomib, dexamethasone, pegylated liposomal doxorubicin hydrochloride, and lenalidomide in treating patients with PCL has been withdrawn citing budgetary constraints (ClinicalTrials.gov Identifier: NCT03591744). Similarly, antibody drug conjugates, bi-specific antibodies and CAR-T therapy may have a future for the treatment of PCL, but initial trials usually exclude PCL from the inclusion criteria (ClinicalTrials.gov Identifier: NCT03815383).

Venetoclax is an attractive molecule for patients with PCL given its good tolerability as an oral inhibitor of BCL-2 and the high prevalence (30-50%) of the t(11;14) in PCL population.[17,18] When venetoclax was evaluated in a phase 1 study in relapsed/refractory MM, 86% of responders had the t(11;14) with overall response rate of 40%, with 27% of patients

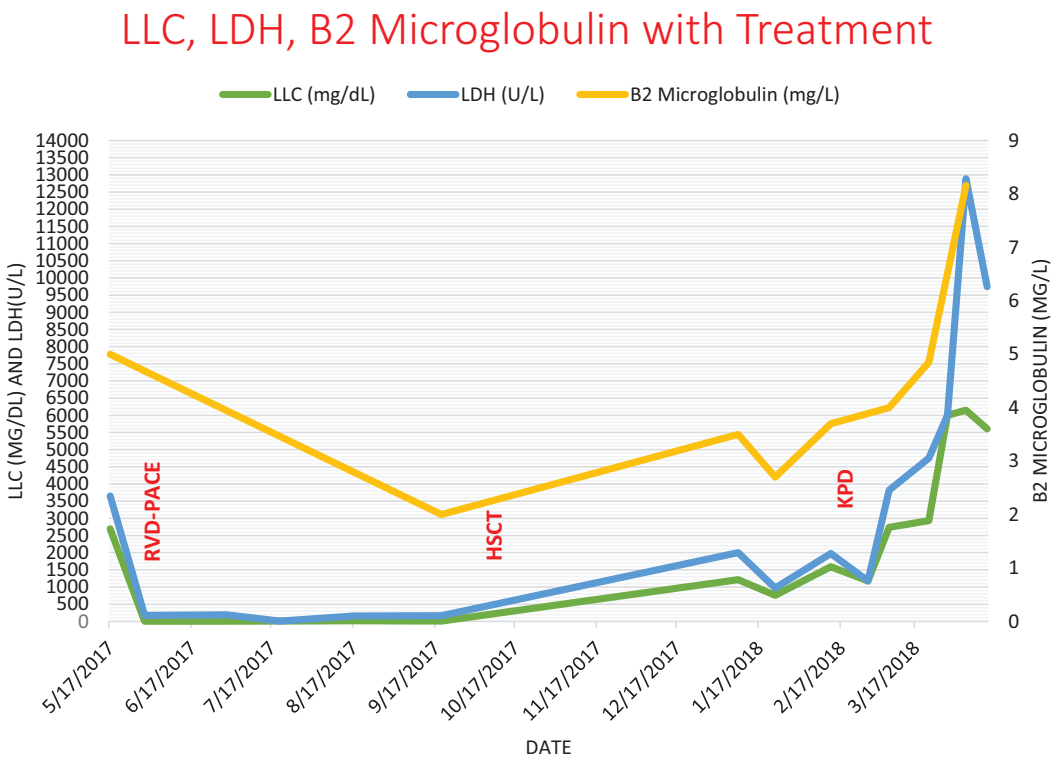

Figure 3. The levels of serum free lambda light chain (LLC), lactate dehydrogenase (LDH) and beta 2 microglobulin at the time of diagnosis, relapse, and disease progression.
RVD-PACE = lenalidomide, bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide; HSCT = hematopoietic stem cell transplantation; KPD = carfilzomib, pomalidomide, and dexamethasone; LDH = lactate dehydrogenase.

achieving very good partial response (VGPR) or better in this heavily pretreated population.[28] Future studies of PCL should examine venetocalx either as single agent or in combination with novel agents, cellular therapies or immunotherapies.

Finally, due to the high frequency of extra-medullary involvement, international myeloma working group (IMWG) has recommended that PET scan be included in the diagnosis and monitoring of PCL.[29]

Conclusion

Primary plasma cell leukemia (PCL) is a rare and aggressive hematologic malignancy. Response to induction therapy, with a combination of novel agents (PI and IMiD) with or without cytotoxic chemotherapy, is common but durability of such response is brief unless consolidated with HSCT followed by maintenance therapy. A single agent lenalidomide, as maintenance therapy after HSCT, is inadequate due to high relapse rate. Therefore, it is recommended to incorporate both lenalidomide and bortezomib, in combination with dexamethasone (RVD), for maintenance in PCL when tolerated. For HSCT-ineligible patients, efficacious treatment remains a challenge and we recommend treating with multiple cycles of therapies containing lenalidomide and bortezomib or participation in a clinical trial when available. Employing immunotherapy with monoclonal antibodies, antibody drug conjugates, bi-specific antibodies and engineered cellular therapy such as CAR-T cell therapy, are all attractive concepts that require investigations in future in treatment of PCL. Incorporating newer generation proteasome inhibitors (carfilzomib, ixazomib) and immunomodulatory agent such as pomalidomide may further improve the outcomes. Venetoclax may also play an important role in future for the treatment of PCL harboring t(11;14) mutation. Prospective multicenter studies are required to further understand the definitions, pathogenesis, treatment and prognosis of PCL. Employing novel imaging technique such as PET scan when done at diagnosis and follow up may provide valuable insight in to the status of the disease outside of the bone marrow.

Informed Consent

Informed patient consent was not possible due to the death of the patient. Patient's surviving spouse provided the verbal informed consent to publish the case report on 7/15/2020. This was documented in patient's chart in the electronic medical record system of Cleveland Clinic per Cleveland Clinic IRB guidance.

Ethics Approval

Ethics approval is not required for case report because such report does not constitute a research per Cleveland Clinic Institutional Review Board (IRB).

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