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RESEARCH ARTICLE

CLINICAL PROFILE OF PLASMA CELL LEUKEMIA AT TERTIARY CARE HOSPITAL IN KASHMIR, INDIA

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pPCL- Primary plasma cell leukemia, sPCL- Secondary plasma cell leukemia, MM- Multiple myeloma, LDH- Lactate dehydrogenase, PBF- Peripheral blood film, P.A.S- Per iodic acid Schiff, S.B- Sudan black stain.

ABSTRACT

Plasma cell dyscrasias represent 1.4-2 % of all malignancies and among hematologic malignancies; it constitutes 10 % of the tumors. Plasma cell dyscrasias are composed of multiple myeloma, primary and secondary plasma cell leukemia. Primary plasma cell leukemia (pPCL) is a rare and aggressive disease, represents 1-4 % of plasma cell dyscrasias. The prognosis of this is very poor with median survival of 8- 11 months in different reported series. We are reporting a study from our hospital over a period of ten years, in which pPCL was found in 1.8% of multiple myeloma patients, with slight male predominance and earlier age than multiple myeloma, and all had high disease burden with high LDH, β2 microglobulin, and plasmacytosis. This disease had very aggressive behavior especially with light chain lambda disease and all patients succumbed within 8 months of treatment.

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INTRODUCTION

Primary plasma cell leukemia (pPCL) is a rare and aggressive disease with a prevalence of only 1–4% of all plasma cell malignancies.[1-3] It is defined by the presence of $>2 \times 10^9$/L peripheral blood plasma cells or plasmacytosis accounting for >20% of the white cell count.[1] The prognosis of pPCL is very poor with a median overall survival (OS) of 8–11 months.[1,4] However, the outcome of pPCL has improved by the introduction of autologous stem cell transplantation as well as novel agents like Bortezomib.[1,4-7] Compared to multiple myeloma (MM), the presenting signs and symptoms of pPCL have a more rapid onset with higher tendency of hyper-metabolic symptoms (weight loss, fever, sweating, fatigue, and weakness), extra-medullary manifestations, hypercalcemia, renal involvement, bone marrow failure, and higher beta-2-

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microglobulin but rarely osteolytic bone lesions.[7] Furthermore, the presence of poor-risk cytogenetic alterations known from MM is markedly higher.[1,4,8] 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.[9] 60-70% of PCL are primary, and the remaining 30-40% are secondary.[10] More recent data suggest that there is an increasing incidence of secondary PCL, now accounting for about 50% of the cases.[4] We are submitting our experience about primary plasma cell leukemia for almost ten year period and found different biology in our patients and very poor prognosis.

Clinical Study: It is discussed under following headings.

MATERIALS AND METHODS

A study was conducted at our hospital with hemto-oncological setup for past 28 years. A cancer registry is maintained for past 15 years. Clinical survey was conducted on plasma cell leukemia for last eight years beginning from 2007 till September 2015. All patients of Multiple Myeloma and De-novo Plasma cell leukemia were enrolled in study. Patient characteristics were noted down and all patients underwent complete haemogram with peripheral blood film examination. If peripheral blood film was abnormal with presence of plasma cells with either 2000 cells/µl or 20 % of total cell count, diagnosis of PCL was established. Rests of patients of Multiple Myeloma were excluded from study with normal PBF. These patients further underwent investigations like complete liver function and kidney function tests, LDH, uric acid, acid base with electrolytes, beta 2 microglobulin, skeletal survey, serum and urinary electrophoresis with immunofixiation, light chain assay in urine and serum, bone marrow aspiration with biopsy, immunophenotyping and cytogenetic. Patients were treated with borteozomib based chemotherapy and clinical outcome and overall survival was noted down.

STUDY AND OBSERVATION (RESULTS)

In this study a total of 441 patients of plasma cell dyscrasias were enrolled, out of which 433 patients were multiple myeloma and 8 patients were primary plasma cell leukemia (pPCL). The median age of multiple myeloma observed was 50 years, with youngest patient of 35 years and oldest of 70 years. The median age of pPCL was 53 years, with youngest patient of 45 years and oldest of 60 years. The male to female ratio in multiple myeloma was 4:1 and in pPCL was 1.7:1. So the percentage of pPCL was 1.89 % among all plasma cell dyscrasias. Further study was concentrated on pPCL patients. Fifty percent of patients were hypertensive ontreatment and 25 % were diabetic on oral hypoglycemic agents. There was no other co-morbidy observed in this series. These patients presented with multiples of symptoms and signs which is outlined in Table (1).

The most common symptom reported was fever followed by bone pain which is in contrary to multiple myeloma and most common sign observed was pallor followed by hepato-splenomegaly and lymphadenopathy, which are again rarely seen in multiple myeloma.

Table 1. Symptomatology of pPCL

Symptom	Percentage
Fever	100
Bone pain	40
Weight loss	30
Recurrent vomiting	25
Malaise	25
Cough	20
Dysuria	10
Sweating	10

Signs	Percentages
Pallor	100
Hepatomegaly	60
Splenomegaly	50
Lymphadenopathy	45
Ascites	20
Jaundice	20
Petechie	10
Consolidation	10
Fracture	10

All patients were subjected to laboratory tests in the form of complete haemogram, full chemistry, acid base and electrolytes, depicted in Table (2). On peripheral blood examination all patients were anemic with median HB of 9.2 gm/dl, had lower TLC with median of $4.15 \times 10^3/\mu l$, very low platelet count with median of $20 \times 10^3/\mu l$. On peripheral blood examination, different degree of plasmacytosis was observed in blood ranging from 22% to 38% and many were having plasmablastic appearance (image 1), with median plasma cell percentage of 28% and median peripheral plasma cell count of 1162 per µl.Skeletal survey was having multiple lytic lesions (image 2) in every patients with atypical finding in one patient having splenic hypo-echoic lesions (image 3), finding confirmed by aspiration having plasma cellinfiltration. On serum chemistry examination, they all had normal kidney and liver functions with lower serum proteins and albumin, and raised LDH and gamma globulins (Table 2).

Table 2. Laboratory investigation of pPCL patients

Parameter	Minimum value	Median value	Maximum value
HB gm/dl	8.0	09.2	10.0
TLC(103/µl)	3.5	04.15	10.0
PLT(103/µl)	17	20	40
Plasma cells in PBF/ µl	770	1162	3300
Percentage of plasma cells	22.0	28.0	33
Serum Calcium mg/dl	7.5	08.29	10.5
Serum Phosphorous mg/dl	2.4	03.40	4.5
Urea mg/dl (Normal 15-40)	28	36.0	42
Creatinine mg/dl (Normal 0.5 -1.5)	1.0	1.30	1.6
ALP (IU/dl) (Normal 140-300)	190	240	300
ALT (IU/dl) (Normal 20-40)	35	42	48
Total Bilirubin mg/dl (Normal 0.5-1)	1.0	1.5	1.9
Serum Na meq/dl	132	138	148
Serum K meq/dl	3.4	4.2	4.5
PH	7.30	7.35	7.40
HCO3 meq/dl	18	23	28
Albumin g/dl	2.0	2.98	3.5
Protein g/dl	4.0	4.80	6.0
Gamma globulin g/dl	0.66	0.78	1.6
LDHU/L(Normal 150-300)	380	760	950

Then patients were subjected to Multiple myeloma profile, which is tabulated as Table (3). All patients had very high β2 microglobulin with median value of 5.8 $_{mg/l}$ and positive serum M spike with undetectable M spike in urine on protein electrophoresis. But urine immunofixiation was positive for M spike in λ region. On Immunoglobulin assay, all immunoglobulin's like Ig G, Ig A, Ig M were markedly suppressed with very high levels of lambda (λ) free light chains in serum. The median value of lambda (λ) free light chains in serum was 3250 $_{mg/l}$. Our all patients had significant light chain disease and that too lambda chain. Serum Immune flow-cytometery of peripheral blood revealed the plasma cell leukemia phenotype which is also depicted in flow diagrams (image 4). It showed high expression and positivity of CD 38, CD138 and its co-expression but it was having very low expression and negativity of CD 27, CD56 and CD20. Different CD marker positivity intensity is tabulated as under (Table 4). Bone marrow aspiration and biopsy revealed plasmacytosis between 40 to 90 %, with median plasmacytosis of 70%. These bone marrow aspiration slides revealed high degree of plasmacytosis with all having plasmablastic appearance, rest of cell lines were markedly suppressed (Image 5). Under immunohistochemistry, cells were P.A.S, S.B. and Myeloperoxidase negative. On conventional cytogenetic karyotype, no abnormality was noted down. FISH was not carried out due to financial constraints.

Finally based on all these parameters patients were diagnosed as primary plasma cell leukemia expressing lambda light chains exclusively with suppressed rest of immunoglobulin's and patients were put on weekly intravenous borteozomib 2mg and dexamethasone 40 mg based treatment along with other supportive treatment in the form of tumor lysis prophylaxis, antivirals, antimicrobials and blood products. On average 15 weeks of treatment was received with longest treatment received was 24 weeks. Our patients were not transplant candidates on the basis of general performance. Interim assessment of disease was carried out after 8 weeks of treatment with complete haemogram, PBF and myeloma profile. There was no plasma cell seen on PBF examination and serum light chains were reduced by 80 %. Most of our patients dropped general performance from ECOG PS II to PS IV. They developed renal failure and respiratory tract infection which were treated with broad spectrum antibiotics, dialysis support and other intensive care support. Our all patients succumbed to different kinds of infection. The median survival seen was 5 months and longest survival was 8 months. There was no patient available after 8 months for disease assessment. So, we conclude that pPCL is a very rare disease in plasma cell dyscrasias contributing 1.89% of all plasma cell dyscrasias, with slight male predominance and earlier age than multiple myeloma, and all had high disease burden with high LDH, β2 microglobulin, and plasmacytosis. This disease had very aggressive behavior especially with light chain lambda disease and all patients succumbed within 8 months of treatment.

Table 3. Multiple myeloma profile

Parameter	Minimum value	Median value	Maximum value
β2 microglobulin mg/l(Normal 0.7-1.8)	3.5	5.8	7.0
Serum M spike	0.20	0.26	0.75
Urine M spike	Not detected	Not detected	Not detected
Serum IgA mg/dl(Normal 70-400)	55	70	220
Serum IgMmg/dl(Normal 40-230)	28	33	100
Serum IgGmg/dl (Normal 700-1600)	550	639	1000
Serum free λ mg/l (Normal 5.71-26.30)	2600	3250	5500
Serum free Ќ mg/dl (Normal 3.3-19.40)	6.5	8.5	16.5
Urine Immunofixiation	Faint M spike in λ region	Faint M spike in λ region	Faint M spike in λ region

Table 4. Immunoflow cytometery in pPCL

Parameter	Minimum expression	Median expression	Maximum expression
CD 38	85.3 %	90.2 %	95.0 %
CD 138	82.5 %	86.2 %	89.9 %
Co expression CD38/138	80.0 %	83.3 %	86.0 %
CD 45	0.00 %	0.00 %	0.00 %
CD 27	02.0 %	04.0 %	5.80 %
CD 56	0.03 %	0.70 %	0.90%
CD 20	5.00 %	6.80 %	10.0 %

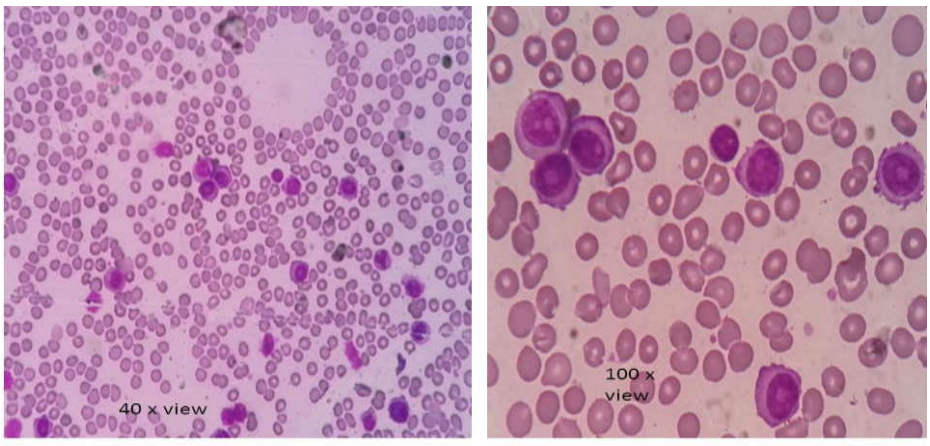
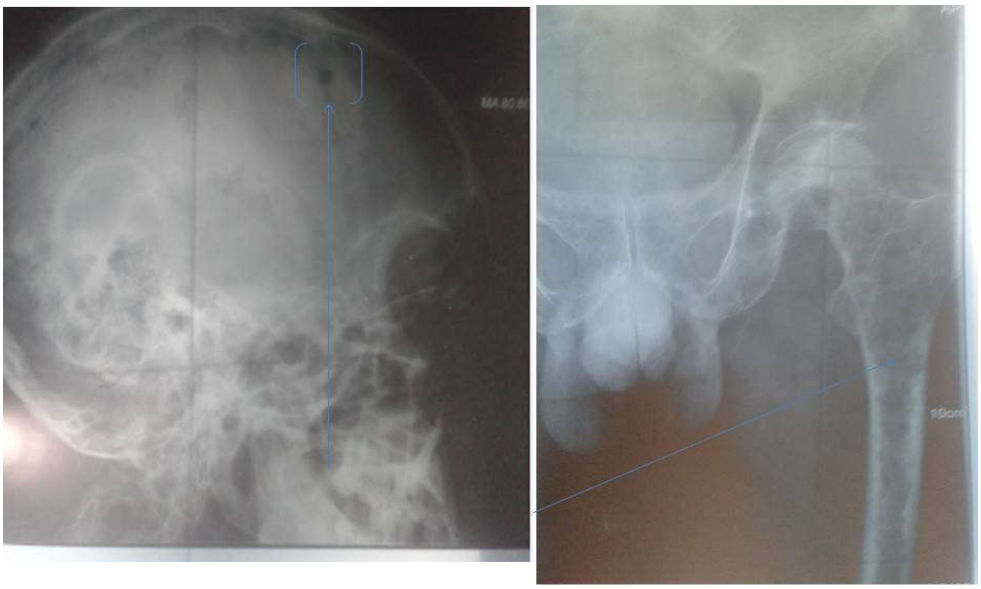


Image 1: PBF showing plasma cells with plasma blasts and prominent nucleolus



1mage 2: showing lytic lesions in skull x ray and femur

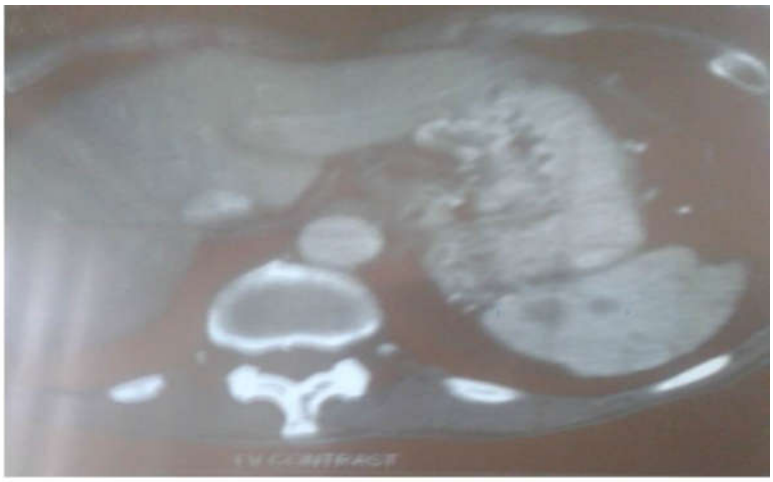


Image 3: CECT showing Hypoechoic Lesions in spleen

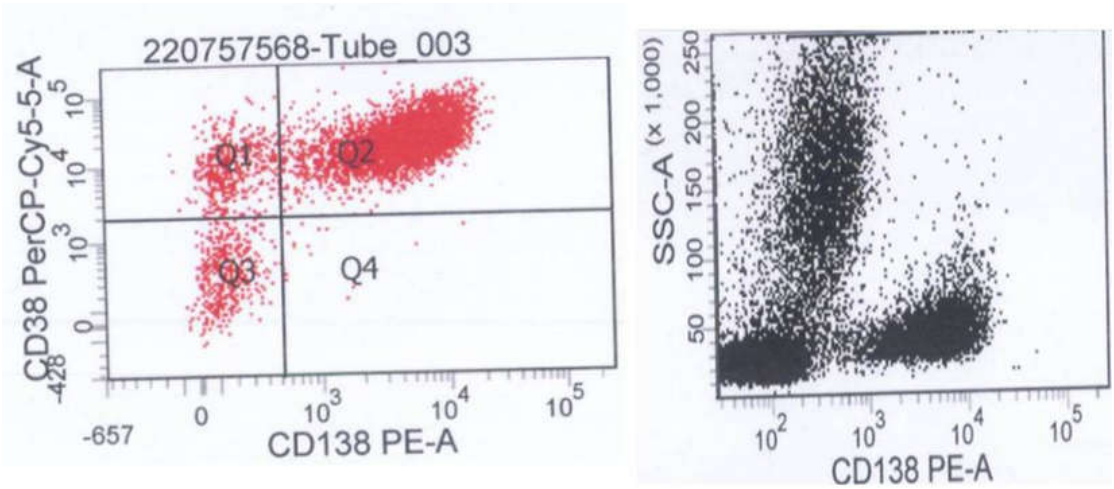


Image 4. Flow-cytometery of peripheral blood revealing the plasma cell leukemia phenotype depicted in flow diagrams, high positivity of CD38/138

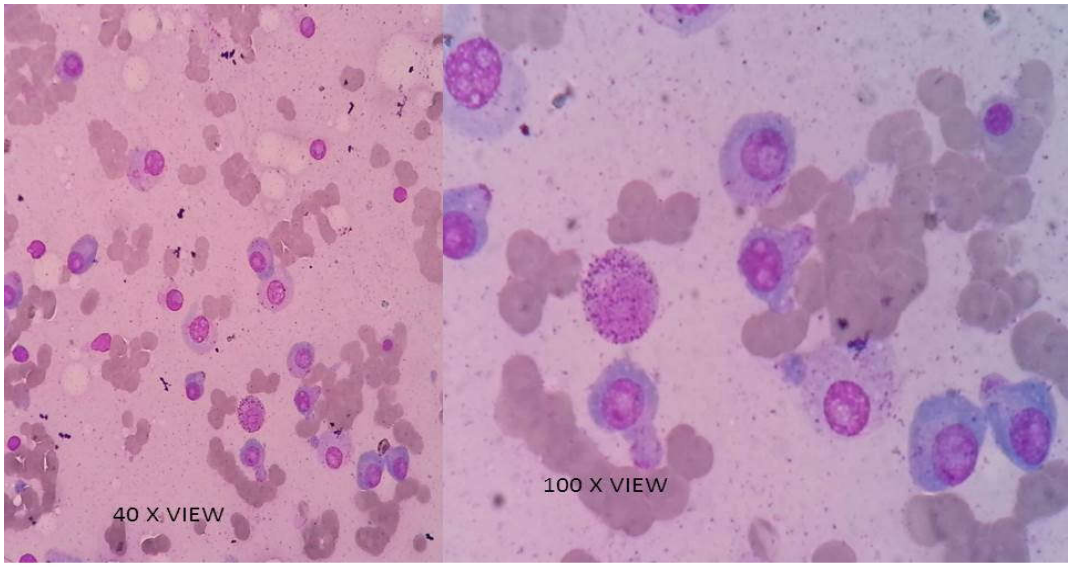


Image 5: Bone marrow showing immature plasma cells with plasma blasts

DISCUSSION

Primary plasma cell leukemia (pPCL) is the most aggressive form of the plasma cell dyscrasias. It is defined by the presence of > 2 × 10^9/L peripheral blood plasma cells or plasmacytosis accounting for > 20% of the differential white cell count, and does not arise from preexisting multiple myeloma (MM).[3,9] We also used same criteria for diagnosis and our all patients had low median TLC, with median plasma cell of 1160/µl (28 %). pPCL is rare, with only 1%-4% of MM patients presenting as pPCL.[1-2,4,11-14]In addition, < 1% of patients presenting with extreme leukocytosis (> 50 × 10^9/L) are diagnosed with PCL.[15]In our study as well, the total pPCL patients were 1.89 % among 441plasma cell dyscrasias which corresponds to other international studies. None of our patient has TLC more than 10 × 10^3/dl. In PCL, tumor cells accumulate in the BM but also have an increased capacity to recirculate in blood, with subsequent egression, and formation of extra--medullary disease. The dissemination of tumor cells out of the BM is not only related to changes in expression of adhesion molecules and chemokine receptors but also to the presence of several molecular aberrations, which contribute to BM microenvironment-independent tumor growth, inhibition of apoptosis, and escape from immune surveillance. Interestingly, gene expression profiling identifies pPCL as a distinct molecular entity among myeloma samples.[14] Compared with MM, tumor cells from pPCL and sPCL patients have reduced expression of the adhesion molecules NCAM (neural cell adhesion molecule/CD56) and LFA-1 (leukocyte function-associated antigen-1), which may contribute to the extra-medullary accumulation of tumor cells in PCL.[1,16-18] The absence of CD56 or LFA-1 is associated with reduced binding of tumor cells to BM stromal cells.[19-20] Furthermore, loss of CD56 results in increased production of matrix metalloproteinase-9, which leads to destruction of the basal membrane and extracellular matrix.[21] In our study all patients werenegative for CD56 and CD27. pPCL patients have a younger age at presentation compared with MM or sPCL patients.[4,11-12,22-23] However, their performance status at diagnosis is usually worse,[1] which may be related to the more advanced stage of disease (Durie-Salmon stage III: ~ 80%-96%; International Staging System stage III: ~ 63%-80%).[1,6-7,1124-26] Extra-medullary involvement, such as hepatomegaly, splenomegaly, lymphadenopathy, leptomeningeal infiltration, or extra-medullary plasmacytomas, is more frequent in pPCL,[1-2,4,7,12-14,23,25-27] with extensive bone disease being more common in patients with MM.[1,4,25] Our all patients were younger than MM, with median age of 53 years. Performance of all our patients was also worse at presentation.However the stage as perDurie-Salmon staging system was II, but as per ISS it was III. Extra-medullary involvement was very high, with hepatomegaly in 60%, splenomegaly in 50%, lymphadenopathy in 45% and none had CNS involvement. Bone involvement was seen less than half of the patients. There are various parameters which detect tumor burden in PCL, for example plasma cell percentage, LDH and β2 microglobulin. The median percentage of BM plasma cells is significantly higher in pPCL than in MM[1,4,26,54] as was seen in our patients as well. We documented bonemarrow plasmacytosis between 40 to 90 %, with median plasmacytosis of 70% and mostly plasmablastic appearance. In addition, renal failure is more common in pPCL, which can be partly explained by the higher incidence of light-chain disease.[1,4,14,23] Furthermore, hypercalcemia, anemia, thrombocytopenia, elevated plasma cell labeling index, increased LDH, and GEP defined high-risk disease are more frequent at presentation in pPCL compared with MM.[1-2,4,6-7,14,25,27] In our series, none of our patient had renal failure at the beginning but developed over course of disease in all. All our patients had Lambda light chain disease only, with high degree of thrombocytopenia, moderate anemia and high LDH. Peripheral blood examination in pPCL shows circulating tumor cells and typically a leuko-erythroblastic blood picture in up to 67% of patients.[4,25] BM biopsy typically demonstrates extensive BM involvement, disrupting normal hematopoiesis. In some cases, tumor resembles normal plasma cells, whereas in others, lympho-plasmacytoid or immature plasma cells predominate.[28-30] our

series also highlighted presence of plasma-blastic or immature plasma cells both in blood and bone marrow. The most striking immune-phenotypic feature is increased expression of CD20 and CD23 and down-regulation of CD56 may be related to the high incidence of t(11;14) in pPCL.[1,31-33] Tumor cells are positive for CD38 and CD138 in both PCL and MM.[1,16,28] We also demonstrated similar results in our series with high expression of CD38/138 and loss of CD56. There is a paucity of literature on the treatment of pPCL, and no randomized trials have been reported exclusively for patients with pPCL. The prognosis of pPCL after conventional chemotherapy without novel agents is poor, with median OS of ~ 7 months.[1,4,6,12,23,30,34] The introduction of immune-modulatory drugs and proteasome inhibitors has significantly improved survival of MM patients.[35-36] Increasing evidence suggests that these agents also improve outcome of pPCL, but the benefit may be less pronounced compared with classic MM. A retrospective analysis performed by the Inter-groupe Francophone du Myélome showed that pPCL patients treated with novel agents had a survival of 15 months compared with 8 months for patients who did not receive novel agents as part of their treatment.[37]Several case reports and small case series suggest that bortezomib, alone or in combination with other agents, is effective in newly diagnosed pPCL and may also be active in refractory pPCL or sPCL.[5,34,38-43] In pPCL, the efficacy of combinations of novel agents, such as lenalidomide, bortezomib, and dexamethasone (RVD),[44] bortezomib, thalidomide, and dexamethasone (VTD),[5,34,37] or melphalan, prednisone, bortezomib, and thalidomide (VMPT),[5] appears very promising. In our series, we treated all patients with borteozomib and dexamethasone, all were transplant ineligible based on their performance status. Initially till 8 weeks of therapy, all our patients responded evidence by interim assessment, but subsequently all progressed fast with deterioration in renal functions and superadded infections. The median survival we documented was 5 months and longest survival of 8 months. There were some peculiarities in our patients. All were young, had moderate anemia with critical thrombocytopenia. All had high LDH and β2 microglobulin with high degree of plasmacytosis in bone marrow and blood. All our patients had lambda light chain disease with suppressed other immunoglobulin's. Response to treatment was very short lived and median survival was lower than evidenced by modern treatment strategies, partly due to different genetics in our patients.

Conclusion

Primary plasma cell leukemia is very aggressive disease and should be picked up early and treated aggressively. Since authors have recommended that at-least 20% of plasma cells to be seen in PBF, to diagnose this condition. As aggressiveness of this disease is concerned, these criteria's need to be revised and less threshold of monoclonal plasma cells percentage to be seen in PBF for its diagnosis. Further work need to be done for classifying this leukemia, refining its staging and refining its treatment.

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