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Hematological Malignancies

Plasma Cell Leukemia—Clinicopathological Profile from a Tertiary Care Center in Western India

Poornima Manimaran[1] Varnika Rai[1] Rahul Ranka[1] Jyoti Sawhney[2]

[1] Gujarat Cancer Research Institute, Ahmedabad, Gujarat, India
[2] Department of Oncopathology, Gujarat Cancer Research Institute, Ahmedabad, Gujarat, India

Address for correspondence Jyoti Sawhney, DM, Department of Oncopathology, Gujarat Cancer Research Institute, Ahmedabad, Gujarat 380016, India (e-mail: jyoti.sawhney@gcriindia.org).

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Abstract

Poornima Manimaran

Introduction Plasma cell leukemia (PCL) is very uncommon and aggressive neoplasm constituting 2 to 4% of all plasma cell dyscrasias. By definition, clonal plasma cells should make up 20% of peripheral blood or have an absolute plasma cell count of 2×10^9 cells/cu.mm. PCL can be primary or secondary. In this study, the clinicohematological features of PCL, and correlation of immunophenotypic profile and conventional therapies with overall survival was analyzed.

Materials and Methods This retrospective study involved PCL patients who were diagnosed across a 12-year period, from 2010 to 2021, at a tertiary care center in western India. Clinical, biochemical, peripheral smear, bone marrow aspirate, immunophenotyping, and molecular analysis were performed.

Results Total 39 PCL patients were included in the study among which 36 were primary PCL patients. Splenomegaly (10/27), hepatomegaly (6/26), and lymphadenopathy (5/23) were noted. At presentation, all patients had anemia (<11g/dL), thrombocytopenia (33/39), hypercalcemia (>11mg/dl) 10/33 (30.3%) and lytic lesions was noted in 18/26 (69.2%).

Immunophenotype of these patients showed CD 38 positivity, CD 138 positivity, CD56 positivity, and CD 117 negativity were 100, 62, 41.6, and 89%, respectively. Overall survival of our patients was 4.1 months and overall survival of patients treated with VTD (bortezomib, thalidomide, dexamethasone) and VCD (bortezomib, cyclophosphamide, dexamethasone) regimen was 3.4 and 4.1 months, respectively, which was not statically significant (*p*-value 0.816). CD117 and CD56 markers were also not having any prognostic significance (*p*-value 1.000 and 0.873, respectively).

Conclusion Because of rarity of the disease, prospective studies are very limited and hence management and outcome of the disease are difficult to analyze. The current treatment protocols have no survival advantage and hence newer therapeutic approach is mandatory to attain better outcome.

Keywords

- plasma cell leukemia
- immature plasma cells
- circulating plasma cells
- CD117
- CD56

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Introduction

Plasma cell leukemia (PCL) is an aggressive form of plasma cell dyscrasia and is very uncommon representing 2 to 4% of all plasma cell dyscrasias. primary PCL constitutes 60 to 70% and secondary PCL constitutes 30 to 40%.[1,2] First case of PCL was reported by Gulzinski and Reichenstein in 1906.[3] By definition, clonal plasma cells should constitute 20% in peripheral blood or absolute plasma cell count should be 2×10^9 cells/cu.mm. Revised diagnostic criteria have been proposed recently as some studies have shown that even more than or equal to 2%[4,5] or more than 5%[6,7] circulating plasma cells (CPC) have similar outcome to that of PCL with more than 20%CPC. PCL can be primary when it presents de novo without any evidence of previous multiple myeloma or secondary when there is leukemic transformation of already existing multiple myeloma.[8] Treatment and survival of patient partly depend on the presentation of disease whether it is primary or secondary. PCL has distinct clinical, immunophenotypic, and molecular features that separate it from plasma cell myeloma (PCM).[9]

This study evaluates the immunophenotypic profile, conventional treatments, and clinicohematological characteristics of PCL in relation to overall survival. We assessed the expression of CD56 and CDl17 on neoplastic plasma cells with overall survival. Also we evaluated the outcome of PCL patients treated with VCD (bortezomib, cyclophosphamide, dexamethasone) and VTD (bortezomib, thalidomide, dexamethasone) induction regimens.

Designs Materials and Methods

Thirty-nine patients diagnosed with PCL over a period of 12 years from 2010 to 2021, from a tertiary care center in western India, were included in the study. These cases were retrospectively analyzed and its clinical, laboratory, immunophenotype, molecular, and treatment data were retrieved from electronic records. Institutional ethics committee approval was obtained. Peripheral smear and bone marrow aspirates were stained by Leishman stain in Mindray autostainer. Bone marrow biopsy sections were stained by hematoxylin and eosin. Serum total kappa and Lambda light chains were assessed using immunoturbidimetry (Cobas Pro 2 – module c503, Roche Diagnostics, Mannheim, Germany). Serum protein electrophoresis and immunofixation and serum electrophoresis were done using automated method (Sebia Capillary Octa3) (Sebia Lisses, France).

Immunophenotyping

Flow cytometric analysis was performed on 21 patients by FACSCanto flow cytometer in which for 16 cases it was done on bone marrow and for 5 patients it was done on peripheral blood. A panel of eight monoclonal antibodies directed against cell surface antigens of plasma cells were employed: CD38, CD138, CD56, CD20, CD79a, CD19, CD117, kappa and lambda light chains. In this study, we assessed the expression of CD56 and CD117 on neoplastic plasma cells with overall survival.

Immunohistochemistry

Immunohistochemical analysis was done on six patients in bone marrow biopsy sections by automated stainer (Ventana, Tucson AZ) for those patients in which bone marrow aspirate was diluted.

Cytogenetic Study

Karyotyping was done in bone marrow cells by G banding technique using unstimulated culture. ISH (fluorescence in-situ hybridization) was not done in any patient

Treatment Given

PCL patients were treated with either VCD (bortezomib [1.3 mg/m^2 weekly once], cyclophosphamide [300mg/m^2 weekly once] and dexamethasone [40 mg weekly once] for 4 weeks) or VTD (bortezomib [1.3 mg/m^2 weekly once), thalidomide [100–200 mg weekly once] and dexamethasone [40mg weekly once] for 4 weeks) induction regimens based on their renal function. We also evaluated the outcome of PCL patients treated with VCD and VTD induction regimens. None of the patients had undergone bone marrow transplant.

Statistical Analysis

The data are presented as median values with range (minimum variables). Independent risk factors for survival were examined in univariate and multivariate analysis using a Cox proportional hazards regression model. Computer-aided analysis was performed using IBM SPSS version 20.0.

Results

Of total 39 patients analyzed, 17 were male and 22 were female with a median age of 56 years. Thirty-six patients were diagnosed with primary PCL and 3 patients with secondary PCL that is evolved from PCM. Splenomegaly (10/27), hepatomegaly (6/26), and lymphadenopathy (5/23) were noted. At presentation, all patients had anemia (<11 g/dL), thrombocytopenia (33/39), and hypercalcemia (>11 mg/dL) was noted in 10/33 (30.3%).

Based on biochemical parameters the International Staging System for PCL, 96% of our patients are in stage 3 and 4% of patients in stage 2. Lytic lesions were observed in 18/26 (69.2%) patients. They were mainly in the following sites vertebra, skull and ribs. The treatment regimens were VTD in 12/26 (46.15%) patients and VCD in 14/26 (53.84%) patients.

Peripheral Smear

On peripheral smear, plasma cells are increased constituting more than 20%. It varies from mature plasma cells to plasmablasts. Sometimes, it resembles plasmacytoid lymphocytes.

Leukoerythroblastic blood picture with left shift, an occasional blast and nucleated RBCs were seen in few cases.

Bone Marrow Examination

Bone marrow aspirates and biopsy sections were diffusely replaced by mature and immature plasma cells in 82% of cases or plasmablasts in 2.5% of cases.

Serum Immunofixation

Immunofixation was done in 20 cases. Predominant type noted was immunoglobulin G (IgG) kappa (7/20). Other types like IgG lambda (4/20), IgA kappa (2/20), IgM kappa (1/20), IgA lambda (1/20), and lambda light chain (1/20) were less frequently noted. Oligosecretory or nonsecretory type was noted in 4/20 cases. These cases showed no monoclonal component in gamma region of serum protein electrophoresis and were also negative on serum immunofixation.

Cytogenetics

Karyotypic analysis was performed on 17 patients in which evaluable metaphases were obtained in 13 patients. Normal karyotype was noted in 11 patients. Only two cases showed chromosomal abnormality. One case showed t(11;14) and other case showed deletion **11**q13.

Treatment Outcomes

Usually, PCL patients receive similar treatment regimen as that of PCM. The median overall survival of the patients was 119 days (►**Fig. 1**). The median survival of patients treated with VTD regimen was 3.4 months and the median survival of patients treated with VCD regimen was 4.1 months.

Among 39 patients, 12 patients received VTD regimen and 27 patients received VCD regimen. Complete remission was noted in seven patients among which five patients received VTD regimen. Relapse of the disease was noted in four patients among which two patients received VTD and another two received VCD regimen. Median follow-up of the patients was 119 days.

Prognostic Parameters

Immunophenotypic markers CD117 and CD56 and treatment regimens were analyzed as prognostic factors. Kaplan

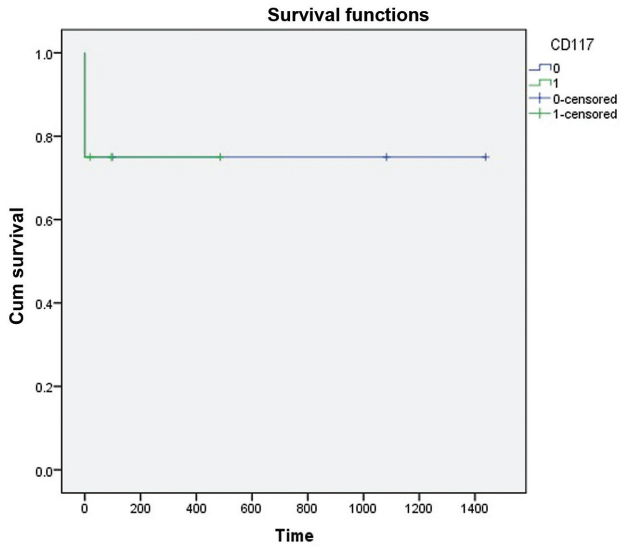

Fig. 2 Survival outcome with CD117.

Meier–log rank test did not show any prognostic significance for the above-mentioned parameters and the *p*-values for CD117, CD56, and treatment regimens were 1.000, 0.873, and 0.816, respectively (►**Figs. 2–4**).

Discussion

PCL is a very rare and has a fulminant disease course. The primary PCL accounts for 60 to 70% and secondary PCL accounts for 30 to 40% of all plasma cell dyscrasias. In our study, primary PCL constitutes 92% and secondary PCL constitutes 8%. This frequency is in accordance with other studies. The primary PCL presents with leucocytosis with

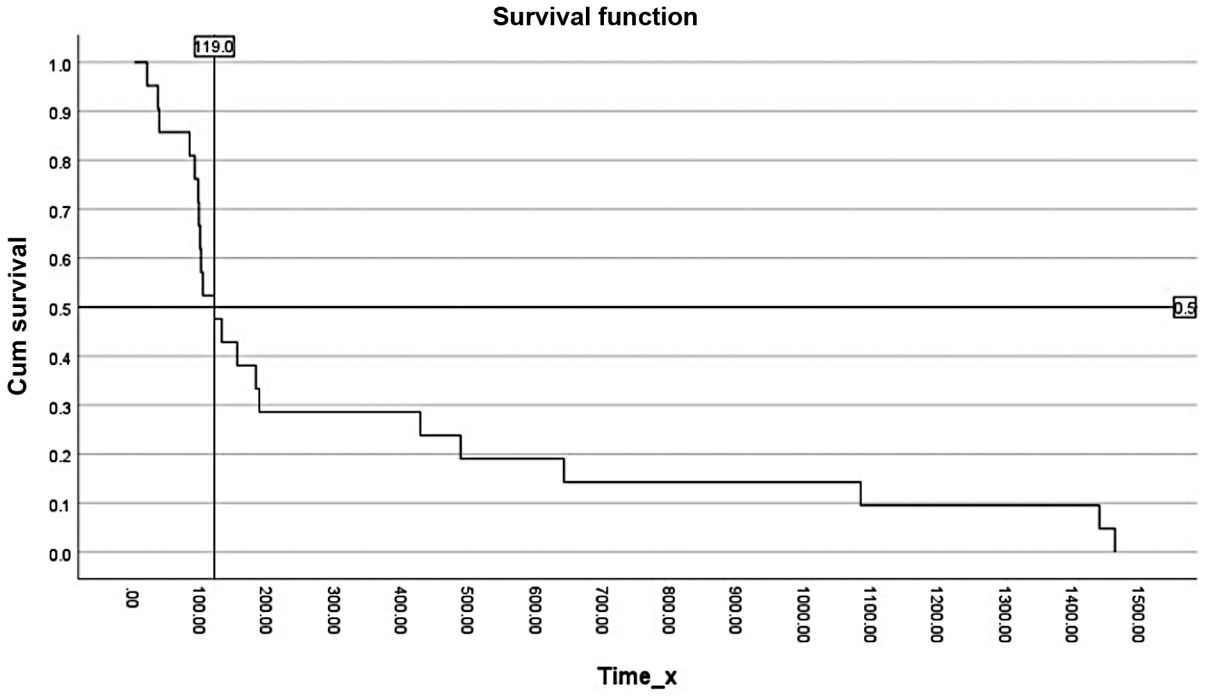

Fig. 1 Median overall survival.

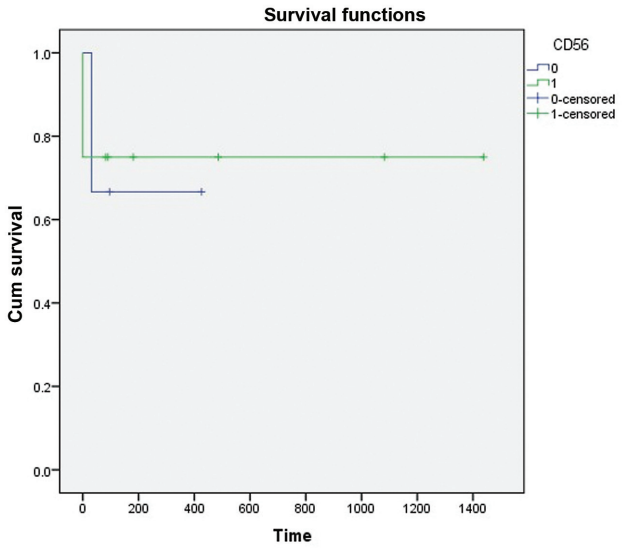

Fig. 3 Survival outcome with CD56.

neoplastic plasma cells in peripheral blood, anemia, and thrombocytopenia similar to acute leukemia.

Peijing et al described patients with PCL who had hepatomegaly (44%), splenomegaly (33%), or lymphadenopathy (22.7%).[10–12] In our series, 33% of patients had hepatomegaly, 37% had splenomegaly, and 21% had lymphadenopathy. Osteolytic lesions were less common in PC.[13–15]

In our study, 18/26 (69.2%) patients had lytic lesions that were predominantly involving vertebra, skull and ribs (►**Table 1**).

Bone marrow is diffusely replaced by malignant plasma cells that can be mature, immature, or plasmablastic. Colović et al described higher bone marrow infiltration with mature and immature plasma cells (80%). The most common morphology observed in bone marrow in our patients was mature and immature plasma cells (82%). Plasmablastic morphology

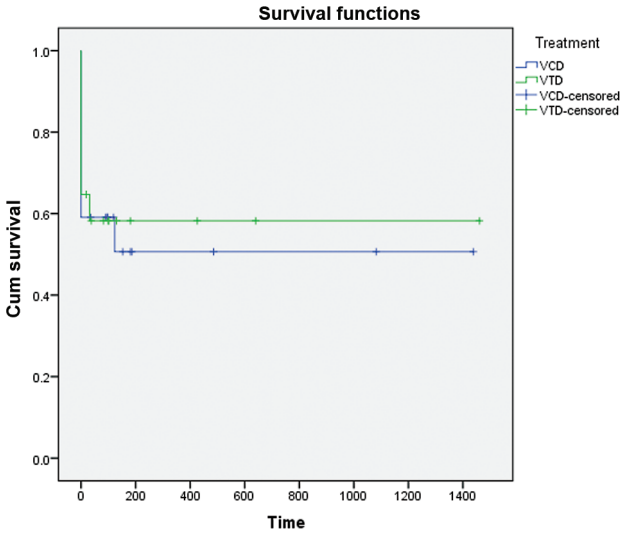

Fig. 4 Survival outcome in VTD (bortezomib, thalidomide, dexamethasone) and VCD (bortezomib, cyclophosphamide, dexamethasone) regimen.

Table 1 Clinical and laboratory features

Parameter	Median (range) or number (%)
Age	54 (35–64)
Male/female	17/22
Lytic lesions	18/26 (69.2%)
Hemoglobin (g/dL)	8 (4–11.3)
Thrombocytopenia ($< 1.5 \times 10^9$/L)	33/39 (84.6%)
Leucocytosis ($>11 \times 10^9$/L)	30/39 (77%)
Albumin (3.5–5.5 g/dL)	13 (37%)
Albumin (<3.5 g/dL)	22 (68.25%)
Albumin >5.5 g/dL	Nil
Percentage of plasma cells in bone marrow	41(13–95%)
LDH (>190 IU/L)	24/39 (61.5%)
Creatinine (mg/dL)	1.63 (0.57–8.65)
Beta2-microglobulin (>5.5 mg/L	24/25 (96%)
Beta2-microglobulin (3.5–5.5 mg/L)	1/25 (4%)
Beta2-microglobulin (<3.5 mg/L)	Nil
International staging system	
Stage 1	0%
Stage 2	1/25 (4%)
Stage 3	24/25 (96%)
Serum immunoglobulins	
Serum IgG (700–1,600 mg/dL)	9/16 (56.25%) more than 1600 mg/dL
Serum IgM (40–230 mg/dL)	2/15(13.33%) more than 230 mg/dL
Serum IgA (70–400 mg/dL)	1/16 (6.25%) more than 400 mg/dL
Serum total kappa light chains (138–375 mg/dL)	7/17 (41%) more than 375 mg/dL
Serum total lambda light chains (80–225 mg/dL)	5/17 (29%) more than 225 mg/dL
Myeloma protein type (serum immunofixation)	
Monoclonal band (normal range: 0.8–1.4 g/dL)	Median value 3.3 (range: 0.2–8.3 g/dL)
IgG	11/20 (55%)
IgA	3/20 (15%)
IgM	1/20 (5%)
Cell morphology	
Plasmablastic	2.5%
Mature and immature plasma cell	82%

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase.

was very rare. In our study, 2.5% of cases presented with a plasmablastic morphology. These cases can occasionally be confused with acute myeloid leukemia especially those that have a monoblastic morphology (►**Figs. 5** and **6**). Most of the

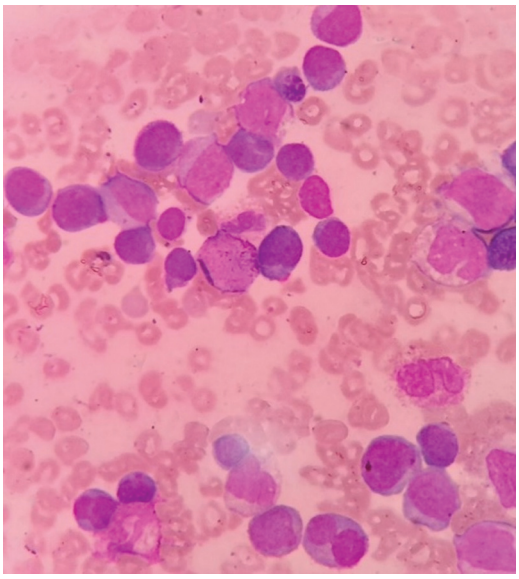

Fig. 5 Mature and immature plasma cells in bone marrow aspirate.

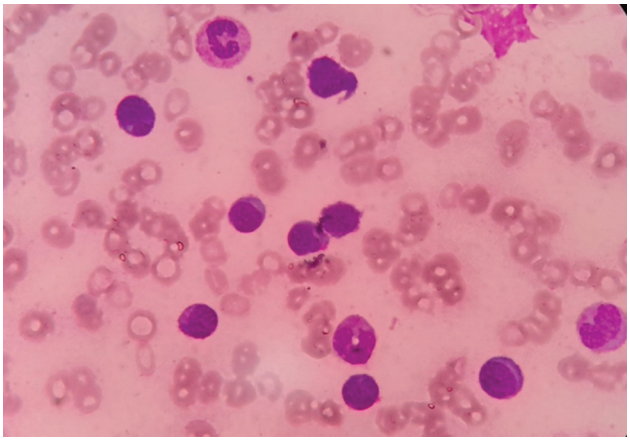

Fig. 6 Plasma cells in peripheral smear.

PCL described in literature were light chain only and IgD type.[16] In our study, IgG kappa is predominantly noted followed by IgG lambda. One weakness of our study was that we do the total light chain assay rather than free light chain assay; there may be a few cases of light chain myeloma that could have been missed.

Flow cytometry plays an important role in confirming the neoplastic nature of plasma cells. Also, it helps in excluding other lymphoproliferative disorders showing plasmacytic differentiation. As florid reactive polyclonal plasmacytosis can be seen in many conditions like autoimmune disorders, drugs, and human immunodeficiency virus infection, monoclonality of plasma cells is established by either kappa or lambda light chain restriction.

Plasma cell markers CD38 and CD138 are expressed both in PCL and PCM. [17–19] Similarly in our study, there was significant expression of CD38 and CD138. Low CD19 expression was noted in abnormal plasma cells when compared to normal plasma cells. In this study, none of the cases showed CD19 expression.[20] This feature helps to differentiate it from non-Hodgkin lymphoma with plasmacytic differentiation as more than 90% of lymphomas with clonal plasma cells will express CD19 unlike PCM and PCL. Frequent CD20 expression and lower CD56 expression are observed in PCL and it is vice versa in PCM.

In this study, CD20 expression was noted in 9.5% cases and CD56 in 28.5% cases. CD56 antigen is a neural cell adhesion molecule that is involved in anchoring of plasma cells to the bone marrow stroma. In the majority of the cases, there was lack of CD56, which results in release of plasma cells in to the peripheral blood. CD117 is less frequently expressed in PCL. Only one case showed CD117 expression. Lack of expression of CD56 and CD 117 is noted as bad prognostic factors in a case series by Tembhare et al [21] (►**Tables 2** and **3**). But in our study, we found that there is no significant prognostic value for CD 56 and CD 117 (►**Figs. 2** and **3**).

Most important prognostic factor in PCL is response to treatment. Current treatment protocols for PCL are similar to multiple myeloma. Most of the treatment regimens are bortezomib based.[22] Musto showed that there was no significant difference in overall response rate to conventional regimens or novel regimens. Similarly in our study, there was no significant difference in overall survival with VCD or VTD regimen (►**Fig. 4**).

Various studies described different karyotypic abnormalities. But in our study, most of the patients had normal karyotype except two cases that showed translocation t (11;14) and deletion llq13. Gowin K and Mosca et al described chromosome 11 aberration like translocation t (11;14) and 11q13 deletion in primary PCL.[23,24]

Table 2 Panel of immunophenotype

Phenotype expression	Number (%)
CD 38 positive	21/21 (100%)
CD 138 positive	13/21 (62%)
CD 20 positive	3/14 (21.4%)
CD 19 negative	12/12 (100%)
CD 56 positive	5/12 (41.6%)
CD 117 negative	8/9 (89%)
Kappa positive	13/21 (62%)
Lambda positive	6/21 (28.5%)

Abbreviation: CD, cluster differentiation.

Table 3 Immunohistochemistry ($n = 6$)

Immunohistochemistry markers	Number (%)
CD38 positive	3/6 (50%)
CD138 positive	4/6 (66.6%)
CD45 negative	4/4 (100%)
CD20 negative	4/5 (80%)
Kappa positive	2/2 (100%)
Lambda negative	2/2 (100%)

Abbreviation: CD, cluster differentiation.

Conclusion

Because of rarity of the disease, prospective studies are very limited and hence management and outcome of the disease are difficult to analyze. Other factors like genomics and tumor microenvironment are implicated in the dismal outcome of these patients. Detection of even more than 1% CPC by Wright-stained peripheral smear or flow cytometry portends a poor prognosis. Intensive chemotherapy regimens like VTD/RVD-PACE (bortezomib, thalidomide or lenalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide) or hyper-CVAD-RV (cyclophosphamide, vincristine, doxorubicin, dexamethasone, lenalidomide, bortezomib) can be used for rapid cytoreduction.

There is need for new clinical trials, targeted therapies, and other alternative therapies, like recently described Venetoclax, a potent Bcl-2 inhibitor (BH3 mimetics), daratumumab, anti-CD38 antibody, CAR-T therapy (chimeric antigen receptor-T cell) for better management of these patients.

Conflict of Interest

None declared.

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