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Retrospective analysis of primary plasma cell leukemia in Kansai Myeloma Forum registry

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ABSTRACT

We retrospectively analyzed twenty-six patients with primary plasma cell leukemia (pPCL) registered from May 2005 until April 2015 by the Kansai Myeloma Forum. Twenty patients received novel agents (bortezomib or lenalidomide), and their median survival of was 34 months. The median survival of patients who underwent autologous stem cell transplantation (SCT) was 40 months, those undergoing allogeneic SCT 55 months, and those undergoing both types of SCT (auto–allo) 61 months; whereas for those who did not undergo SCT it was 28 months ($p = 0.845$). The only statistically significant risk factor identified by multivariate analysis was hypercalcemia.

1. Introduction

Primary plasma cell leukemia (pPCL), a rare aggressive form of plasma cell dyscrasia, is characterized by a fulminant clinical course and poor prognosis. It is defined by the presence of $>2 \times 10^9/\mu L$ peripheral blood plasma cells or plasmacytosis accounting for >20% of the differential white cell count. pPCL is also defined as *de novo* PCL without previous evidence of multiple myeloma (MM), whereas secondary PCL is defined as leukemic transformation in patients with end-stage MM. pPCL accounts for 1.3%–3.4% of plasma cell dyscrasias[1].

According to Surveillance, Epidemiology and End Results (SEER) analysis, the median overall survival (OS) of patients with pPCL is 6 months. However, OS was reportedly 4–6 months for patients diagnosed between 1973 and 2005, and 12 months for those diagnosed between 2006 and 2009. The introduction of novel agents (bortezomib or lenalidomide) as first-line therapy for pPCL has significantly improved the prognosis [2].

Because of the rarity of the disease, no prospectively randomized controlled trials have been performed; thus, the biological, clinical, and prognostic features of this disease have not been clearly determined. The clinical outcomes of pPCL in real-world settings also remain unclear and there is no consensus regarding how to treat it.

We therefore here retrospectively analyzed treatment strategies and outcomes of a real-world cohort of patients with pPCL registered with

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the Kansai Myeloma Forum (KMF), which is a registry study group for plasma cell dyscrasias.

2. Patients and methods

The Kansai Myeloma Forum (KMF), a study group comprising 73 facilities in the Kansai region of Japan, was established in 2012 to register clinical data of patients with all types of plasma cell dyscrasias with the aim of retrospectively analyzing treatment strategies and their outcomes. By April 2015, KMF had registered the clinical data of 2022 patients with plasma cell dyscrasias, of whom 26 had been diagnosed as having pPCL between May 2005 and April 2015 and registered in the KMF data base. We have here retrospectively analyzed their data.

OS was calculated as the period from the diagnosis to the time of death or last follow-up. Survival curves were created using the Kaplan–Meier method, and differences evaluated using the log-rank test. Multivariate analysis of survival was performed using the Cox proportional hazards model. All statistical tests were two-sided and statistical significance was set at $p < 0.05$. Additionally, 95% confidence intervals were calculated. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 2.13.0 (R Foundation, Vienna, Austria). More precisely, a modified version of R Commander (version 1.6–3), it is designed to incorporate the statistical functions frequently used in biostatistics. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Institutional Review Boards of all the institutes participating in the KMF.

3. Results

3.1. Patients' characteristics

From May 2005 until April 2015, 26 of the 2022 patients with plasma cell dyscrasias registered in the KMF data base had diagnoses of pPCL. Thus, the prevalence of pPCL was 1.2% in our cohort. Median follow up period was 22 (0.2–108) months. The clinical characteristics of the study patients are shown in Table 1. The median age of the 26 patients was 63.5 years (range: 21–82); 62% were men and 38% women. The frequencies of M-protein types were IgG (35%), IgA (11%), Bence-Jones protein (BJP) (35%), and IgD (11%). According to the International Staging System (ISS), 79% had ISS Stage 3 disease. Osteolytic lesions and extramedullary plasmacytoma were present in 38% and 15% of patients, respectively.

Table 1
Patients' characteristics.

No. of patients	26
Median age, range (y/o)	63.5(21–82)
Male sex (%)	62
PS ≥ 2(%)	30
M protein(%)	
BJP(kappa/lamuda ratio)	35(2:1)
IgG	32
IgA	11
IgD	11
ISS(%)	
III	79
osteolytic bone lesion(%)	38
extramedullary plasmacytoma (%)	15
Chromosome abnormality (*n*)	
del(13q)	4
del(17p)	3
t(11;14)	1
t(14;16)	1

PS: Performance Status.
BJP: Bence Jones protein.
ISS: International Staging System.

3.2. Cytogenetic abnormalities

Fluorescence in situ hybridization (FISH) analysis was performed to identify cytogenetic abnormalities in 9 patients, out of which the commonest abnormality was deletion 13q ($n = 4$), following by deletion 17p ($n = 3$), $t(11;14)$ ($n = 1$), and $t(14;16)$ ($n = 1$).

3.3. Treatment

Conventional therapies were initially administered to 47%, of the study patients and novel agents (bortezomib- or lenalidomide-based therapies) to 42%; 11% of the patients were not treated because of deterioration of general condition. All the novel agent regimens contained bortezomib. The most frequently used regimen was bortezomib plus dexamethasone (VD) (19%), followed by bortezomib, cyclophosphamide and dexamethasone (VCD) (12%), bortezomib, doxorubicin and dexamethasone (PAD)(8%), and bortezomib, lenalidomide and dexamethasone (VRD)(3%). The most frequently used conventional regimen was dexamethasone (23%), followed by vincristine, doxorubicin and dexamethasone (VAD)(12%), and melphalan and prednisolone (MP)(12%).

The response rates were 92% in patients receiving the novel agent-containing regimens (CR: 0%, PR: 75%, SD: 17%) and 75% in those receiving the conventional agent regimens (CR: 8%, PR: 25%, SD: 42%).

3.4. Survival

The median survival from diagnosis to time of death or last follow-up of all patients was 29 months. The median OS of the patients who were not treated was 15 days. The median OS of the patients who were initially treated with conventional therapies was 29 months (95%CI: 6-NA), whereas it was 34 months for those treated with novel agents (95%CI: 5-NA) ($p = 0.943$) (Fig. 1(a)). The median OS of patients who were treated with novel agents (bortezomib or lenalidomide) throughout the entire treatment period was 29 months (95%CI: NA-NA) and was also 29 months for those who did not receive novel agents (95%CI: 6–57) ($p = 0.279$) (Fig. 1(b)).

3.5. Outcomes in patients who underwent transplantation

The median OS after all types of SCT was 56 months (95%CI: 12–61), whereas it was 28 months in patients who did not undergo SCT (95%CI: 5-NA) ($p = 0.089$) (Fig. 2(a)). Autologous SCT, allogeneic SCT, and both were performed in 23%, 8%, and 8% of patients, respectively. Median OS after autologous SCT was 40 months (95%CI: 12-NA), after allogeneic SCT 55 months (95%CI: 54-NA), and after both types of SCT 61 months (95%CI: NA-NA), whereas it was 28 months in patients who did not undergo SCT (95%CI: 5-NA) ($p = 0.845$) (Fig. 2(b)).

3.6. Prognostic factors

Univariate analysis was performed to identify risk factors associated with poor survival. Beta-2-microglobulin, lactate dehydrogenase (LDH), or white blood cells, and decreases in hemoglobin or platelet counts had no significant influence on OS. However, hypercalcemia was associated with poor survival (Table 2). Multivariate analysis identified only hypercalcemia remained as a significant factor affecting survival (hazard ratio: 11.85, 95%CI: 1.45–96.59, $p = 0.020$), whereas other factors were dropped out by backward stepwise selection.

4. Discussion

In this study, registry data were analyzed to determine the clinical features, therapeutic approaches, and clinical outcomes of pPCL in real-world settings. The prevalence of pPCL was 1.2%, the median age was