bjh research paper

Prognostic indicators in primary plasma cell leukaemia: a multicentre retrospective study of 117 patients

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We report a multicentre retrospective study that analysed clinical characteristics and outcomes in 117 patients with primary plasma cell leukaemia (pPCL) treated at the participating institutions between January 2006 and December 2016. The median age at the time of pPCL diagnosis was 61 years. Ninety-eight patients were treated with novel agents, with an overall response rate of 78%. Fifty-five patients (64%) patients underwent upfront autologous stem cell transplantation (ASCT). The median follow-up time was 50 months (95% confidence interval [CI] 33; 76), with a median overall survival (OS) for the entire group of 23 months (95% CI 15; 34). The median OS time in patients who underwent upfront ASCT was 35 months (95% CI 24·3; 46) as compared to 13 months (95% CI 6·3; 35·8) in patients who did not receive ASCT ($P = 0{\cdot}001$). Multivariate analyses identified age ≥60 years, platelet count ≤100 × 10^9/l and peripheral blood plasma cell count ≥20 × 10^9/l as independent predictors of worse survival. The median OS in patients with 0, 1 or 2–3 of these risk factors was 46, 27 and 12 months, respectively ($P < 0{\cdot}001$). Our findings support the use of novel agents and ASCT as frontline treatment in patients with pPCL. The constructed prognostic score should be independently validated.

Keywords: myeloma, plasma cell leukaemia, therapeutic response, survival, prognosis.

 doi: 10.1111/bjh.15092

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Received 13 August 2017; accepted for publication 8 November 2017
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Plasma cell leukaemia (PCL) is a rare and aggressive disease associated with malignant proliferation of plasma cells (PCs) in the blood and bone marrow (Noel & Kyle, 1987), which was first described more than a century ago (Gluziński & Reichenstein, 1907). Current diagnostic criteria of PCL include absolute number of circulating PCs exceeding $2{\cdot}0 \times 10^9$/l or PC proportion >20% of the total leucocyte count (Jimenez-Zepeda & Dominguez, 2006). The overall incidence of PCL is very low, estimated at 0·04 cases per 100 000 per year (Fernández de Larrea *et al*, 2013). PCL can develop *de novo*, as primary PCL (pPCL), or evolve as a complication of late-stage multiple myeloma (MM), when it is referred to as secondary PCL (sPCL). The relative frequencies of pPCL and sPCL are estimated at 60–70% and 30–40%, respectively (Jurczyszyn *et al*, 2011).

With conventional chemotherapy, the survival of patients with pPCL is poor, with most of them dying within 1 year of diagnosis (Gonsalves *et al*, 2014; Royer *et al*, 2016). However, data from several single-institution retrospective studies and prospective trials suggest that upfront incorporation of novel agents and haematopoietic stem cell transplantation may positively impact response and survival in pPCL patients

(Mahindra *et al*, 2012; Reece *et al*, 2013; Musto *et al*, 2014; Royer *et al*, 2016). Due to the relative rarity of this condition, information about the clinical presentation and outcomes of pPCL is quite limited and originates primarily from retrospective single-institution series (Colovic *et al*, 2008; Tiedemann *et al*, 2008; Peijing *et al*, 2009; Pagano *et al*, 2011; Fernández de Larrea *et al*, 2013).

The aim of this multicentre retrospective study was to analyse the clinical characteristics, outcomes and prognostic factors in 117 patients with pPCL treated in the era of novel agents.

Materials and methods

Case selection

Between January 2006 and December 2016, patients with a pathological diagnosis of pPCL were identified from the medical records at the participating institutions. The diagnosis of pPCL was defined as an absolute PC count $>2 \times 10^9$/l or PC proportion >20% of the total white blood cell (WBC) count in a patient meeting the diagnostic criteria for multiple myeloma who had not been previously treated. The study protocol was reviewed and approved by the Institutional Review Board of each participating institution.

Data analysis

Clinical data were gathered from the medical records of patients meeting the inclusion criteria. The analysed parameters included age at diagnosis of pPCL, sex, paraprotein isotype, WBC count, platelet count, peripheral blood PC count, haemoglobin concentration and serum lactate dehydrogenase (LDH) level, International Scoring System (ISS), peripheral blood PC immunophenotype (CD117, CD56, CD45, CD38, CD138, CD20 and CD19 expression) and presence of cytogenetic abnormalities determined by means of fluorescence *in situ* hybridisation [FISH; del13q, del17p, t(11;14), t(14;16), t(4;14), gain 1q and t(14;20)] in bone marrow and/or circulating PCs, anti-pPCL treatments, therapeutic responses and overall survival (OS). Complex cytogenetics was defined as the presence of at least three cytogenetic abnormalities. Response to therapy was classified as complete response (CR), very good partial response (VGPR), partial response (PR) and no response (NR, both stable and progressive disease) (Durie *et al*, 2006). OS was defined as the time in months from pPCL diagnosis to last follow-up or death.

Statistical analysis

The chi-square and the rank-sum tests were used to compare categorical and continuous variables, respectively. For the survival analysis, the Kaplan–Meier method was used to generate survival curves, which were then compared using the log-rank test. The Cox proportional-hazard regression method was used to fit univariate and multivariate survival models for OS, the results of which are reported as hazard ratio (HR) with 95% confidence intervals (CI). Variables with >50% of missing data were not included in the survival analyses. Variables with significant *P*-values in the univariate analysis were then included in the multivariate analysis. All reported *P*-values are two-sided, and were considered significant if less than 0·05. Calculations and graphics were obtained using STATA SE 13·1 (StataCorp, College Station, TX, USA).

Results

One hundred and seventeen patients with an established diagnosis of pPCL were included in the analysis. The median age at the time of pPCL diagnosis was 61 years (range: 27–85 years). The median WBC count was $16{\cdot}5 \times 10^9$/l ($0{\cdot}9-12{\cdot}4 \times 10^9$/l), the median haemoglobin was 91 g/l (31–163 g/l), the median platelet count was 101×10^9/l ($9-290 \times 10^9$/l), the median PC count was $5{\cdot}7 \times 10^9$/l ($0{\cdot}6-81{\cdot}6 \times 10^9$/l) and the median PC percentage in peripheral blood was 40% (10–100%). Categorized clinical characteristics of the study subjects are listed in Table I.

At the time of pPCL diagnosis, 85/85 (100%) patients tested were positive for CD38/CD138 expression and 39/75 (52%) were positive for CD56 expression. t (11;14) was

Table I. Selected clinical characteristics of 117 patients with primary plasma cell leukaemia.

Characteristic	*n*/*N* (%)
Age ≥60 years	64/117 (55%)
Male sex	47/117 (40%)
WBC $>15 \times 10^9$/l	61/117 (52%)
Haemoglobin ≤10 g/dl	94/117 (80%)
Platelet count $\leq 100 \times 10^9$/l	57/117 (49%)
Plasma cell count (peripheral blood) $\geq 20 \times 10^9$/l	16/117 (14%)
Plasma cell percentage (peripheral blood) ≥40%	57/117 (49%)
Elevated LDH level	63/94 (67%)
Paraprotein isotype	
IgG	52/115 (45%)
Light chain only	34/115 (30%)
IgA	17/115 (15%)
Non-secretory	11/115 (10%)
Biclonal	1/115 (1%)
Region	
Europe	70/117 (60%)
United States	32/117 (27%)
Other*	15/117 (13%)
Year of diagnosis	
2006–2010	34/117 (29%)
2011–2016	83/117 (71%)

WBC, white blood cell count; LDH, lactate dehydrogenase.
*Other includes Brazil ($n = 6$), Israel ($n = 4$), Turkey ($n = 3$), Australia ($n = 1$) and Argentina ($n = 1$).

identified in 13/65 (20%) study subjects, and complex cytogenetics in 14/65 (22%). Selected pathological characteristics of the patients are shown in Table II.

Data on treatment was available from 106 patients, of which 98 were treated with novel agents (immunomodulators and/or proteasome inhibitors, alone or combined with conventional chemotherapy). CR, VGPR, PR and NR rates were 21%, 22%, 36% and 22%, respectively, with an overall response rate (ORR) of 78%. Fifty-five patients (64%) underwent upfront autologous stem cell transplantation (ASCT) and 3 (5%) who received tandem ASCT. Sixteen patients (94%) who achieved CR before ASCT remained in CR after ASCT and 1 (6%) progressed. Four patients (33%) with VGPR before ASCT attained CR, five (42%) remained in VGPR, and three (25%) progressed. Seven patients (37%) who obtained PR before ASCT achieved CR and 5 (26%) reached VGPR, 3 (16%) remained in PR and 4 (21%) progressed. Two patients did not respond before ASCT; 1 (50%) achieved PR and 1 (50%) progressed. Overall, 75% of patients either maintained or deepened their response by undergoing ASCT following induction therapy. Response rates to induction therapy and ASCT are shown in Table III. Twelve patients (22%) underwent allogeneic stem cell transplantation (alloSCT), four of which were performed as first-line therapy. All were in CR and maintained the CR after alloSCT. Three are alive and 1 died of pulmonary graft-versus-host disease. Eight patients underwent alloSCT as second line, of which 5 relapsed and died of progressive disease.

The median follow-up time was 50 months (95% CI 33; 76). There were 74 deaths (61%), and the median OS for the entire group was 23 months (95% CI 15; 34) (Fig 1A). The estimated 5-year OS rate was 20% (95% CI 12%, 31%).

Table II. Selected pathological characteristics of 117 patients with primary plasma cell leukaemia.

Flow cytometry	Positive/tested (%)
CD38/CD138 expression	84/85 (99%)
CD56 expression	39/75 (52%)
CD45 expression	29/63 (46%)
CD117 expression	7/17 (41%)
CD20 expression	16/58 (28%)
CD19 expression	0/14 (0%)
Cytogenetic abnormalities	**Positive/tested (%)**
del13q	31/65 (48%)
del17p	22/65 (34%)
t(11;14)	13/65 (20%)
t(14;16)	13/65 (20%)
t(4;14)	13/65 (20%)
Gain 1q	11/65 (17%)
t(14;20)	0/65 (0%)
Poor risk*	38/65 (58%)
Complex cytogenetics†	14/65 (22%)

*Includes del17p, t(4;14) and t(14;16).
†Defined as 3 or more cytogenetic abnormalities.

pPCL patients were categorized in 5 groups according to PC count: 0–5 $\times$ 10^9/l, 6–10 $\times$ 10^9/l, 11–15 $\times$ 10^9/l, 16–20 $\times$ 10^9/l and >20 $\times$ 10^9/l. Using the group with PC count 0–5 $\times$ 10^9/l, PC count >20 $\times$ 10^9/l was the only category associated with a worse outcome. Median OS in patients younger than 60 years and those aged ≥60 years was 36 months (95% CI 23; 54) and 16 months (95% CI 9; 23), respectively (Fig 1B). Median OS in subjects with platelet counts up to 100 $\times$ 10^9/l and >100 $\times$ 10^9/l was 16 months (95% CI 9; 23) and 34 months (95% CI 23; 53), respectively (Fig 1C), and median OS in those with a platelet count less than 20 $\times$ 10^9/l and ≥20 $\times$ 10^9/l peripheral blood PCs in amounted to 31 months (95% CI 16; 36) and 19 months (95% CI 8; 23), respectively (Fig 1D).

Age ≥60 years, platelet count ≤100 $\times$ 10^9/l and PC count in peripheral blood ≥20 $\times$ 10^9/l were associated with worse survival on both univariate and multivariate Cox regression analyses. Complete prognostic modelling is shown in Table IV. We evaluated collinearity between age, haemoglobin, platelet count, PC count and PC percentage as continuous variables using the variance inflation factor (VIF). All mean VIF values were <10, arguing against the presence of collinearity between these factors. Although CD20 expression was shown to be associated with worse OS on univariate analysis, this variable was not included in the multivariate model because CD20 expression status was available in less than 50% of the study subjects.

The three independent predictors of worse OS, i.e., age ≥60 years, platelet count ≤100 $\times$ 10^9/l, and peripheral blood PCs ≥20 $\times$ 10^9/l, had similar HRs and were used to develop a pPCL Prognostic Index (PCL-PI) by assigning 1 point per adverse prognostic factor. Our series included 26 patients (22%) with 0 risk factors, 51 (44%) with 1 risk factor and 40 (34%) with 2–3 risk factors. Median OS in patients with one risk factor (27 months, 95% CI 14; 41) and 2–3 risk factors (12 months, 95% CI 6; 20) was significantly worse than in those with no risk factors (46 months, 95% CI 33; not reached) (Fig 2). When compared with patients with a PCL-PI of 0, patients with PCL-PIs of 1 and 2–3 had HR 2·19 (95% CI 1·08–4·43; $P = 0·03$) and HR 5·78 (2·78012·0; $P < 0·001$), respectively. Internal validation of the PCL-PI was performed using the bootstrap method with 200 replications, which showed similar results. Patients with PCL-PIs of 1 and 2–3 had HR 2·19 (95% CI 1·02–4·69; $P = 0·04$) and HR 5·79 (95% CI 2·82–11·9; $P < 0·001$), respectively, when comparing with PCL-PI 0.

The median OS in patients who underwent upfront ASCT was 35 months (95% CI 24·3; 46) as compared to 13 months (95% CI 6·3; 35·8) in patients who did not undergo ASCT (Log-rank $P < 0·001$). Cox regression analysis evaluating ASCT in first remission as a time-varying covariate and adjusted for the PCL-PI showed a trend towards a beneficial effect on the survival in pPCL patients (HR = 0·98, 95% CI 0·96, 1·00, $P = 0·1$). In a subset analysis, ASCT in first remission appeared beneficial in the PCL-PI 1 group (HR 0·96, 95% CI 0·92, 1·00; $P = 0·05$) but not in the PCL-PI 0 (HR

Table III. Frontline treatment and response in 106 patients with primary plasma cell leukaemia who received frontline treatment and were evaluable for response.

Treatment	Number (%)	CR (%)	VGPR (%)	PR (%)	NR (%)
Chemotherapy only	8 (8%)	1 (12·5%)	1 (12·5%)	4 (50%)	2 (25%)
PI only	7 (7%)	0 (0%)	3 (43%)	1 (14%)	3 (43%)
IMID only	2 (2%)	1 (50%)	0 (0%)	1 (50%)	0 (0%)
Chemotherapy-PI	48 (45%)	12 (25%)	9 (19%)	17 (35%)	10 (21%)
Chemotherapy-IMID	17 (16%)	1 (6%)	3 (18%)	8 (47%)	5 (29%)
PI-IMID	15 (14%)	2 (13%)	4 (27%)	6 (40%)	3 (20%)
Chemotherapy-PI-IMID	9 (8%)	5 (56%)	3 (33%)	1 (11%)	0 (0%)
Single therapy	17 (16%)	2 (12%)	4 (24%)	6 (35%)	5 (29%)
Double therapy	80 (75%)	15 (19%)	16 (20%)	31 (39%)	18 (23%)
Triple therapy	9 (8%)	5 (56%)	3 (33%)	1 (11%)	0 (0%)
Prior to upfront ASCT	50 (47%)	17 (34%)	12 (24%)	19 (38%)	2 (4%)
After upfront ASCT	50 (47%)	27 (54%)	11 (22%)	4 (8%)	8 (16%)

ASCT, autologous stem cell transplant.; CR, complete response; IMID, immunomodulator; PI, proteasome inhibitor; PR, partial response; NR, no response; VGPR, very good partial response.

Table IV. Univariate and multivariate analyses for overall survival in patients with primary PCL.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age ≥60 years	2·32 (1·41–3·83)	0·001	2·50 (1·51–4·12)	<0·001
Male sex	1·01 (0·61–1·66)	0·98		
WBC ≥15 × 10^9/l	1·34 (0·83–2·17)	0·23		
Haemoglobin ≤10 g/dl	1·50 (0·76–2·96)	0·24		
Platelet count ≤100 × 10^9/l	2·09 (1·28–3·41)	0·003	2·08 (1·27–3·42)	0·004
Plasma cell count ≥20 × 10^9/l	1·92 (1·01–3·68)	0·04	2·33 (1·20–4·56)	0·01
Plasma cell percentage ≥40%	1·05 (0·64–1·71)	0·85		
Elevated LDH level	1·26 (0·69–2·28)	0·45		
Non-IgG isotype	1·09 (0·67–1·76)	0·73		
ISS stage 3 vs. ISS stage 2	0·84 (0·46–1·53)	0·57		
CD56 expression	0·89 (0·48–1·65)	0·71		
CD20 expression	2·64 (1·19—5·84)	0·02	Not included*	
Poor cytogenetics	1·78 (0·86–3·68)	0·12		
Complex cytogenetics	1·67 (0·83–3·34)	0·15		
Years 2011–2016	0·63 (0·38–1·05)	0·08		

95% CI, 95% confidence interval; HR, hazard ratio; IgG, immunoglobulin G; ISS, International Staging System; LDH, lactate dehydrogenase; WBC, white blood cell count.
Region and year of diagnosis were not included in the survival analysis.
*CD20 expression status was available in less than 50% of the subjects.

0·97, 95% CI 0·94, 1·01; $P = 0·13$) or PCL-PI 2-3 groups (HR 1·02, 95% CI 0·96, 1·10; $P = 0·41$).

The median follow-up in patients who received single, double and triple therapy was 108 (95% CI 20; -), 51 (95% CI 43; 74) and 13 months (95% CI 5; 32), respectively. Median OS in patients treated with a single therapy was 27 months (95% CI 10·9; 45·3), and 1- and 2-year OS rates were 77% (95% CI 50; 90) and 58% (95% CI 31; 77), respectively. Median OS in the subset of patients who received a double therapy was 23 months (95% CI 15·4; 32·6), with 1- and 2-year OS rates of 69% (95% CI 58; 78) and 46% (95% CI 34; 57), respectively. Due to small sample size, we were unable to estimate median OS in patients treated with a triple therapy. However, 1- and 2-year OS rates in this subset were 89% (95% CI 43; 98) and 71% (95% CI 23; 92), respectively. Cox regression analysis did not show a survival benefit associated with the use of a double or triple therapy when compared with single therapy (double therapy: HR = 1·07, 95% CI 0·57; 2·01, $P = 0·82$; triple therapy: HR = 0·45, 95% CI 0·10–2·03, $P = 0·30$).

Discussion

The results of our retrospective study suggest a high response rate to novel agents in patients with pPCL. Additionally, the use of ASCT following induction therapy appears associated with deeper response and an improved survival. Our study also suggests the adverse prognostic value of older age, lower

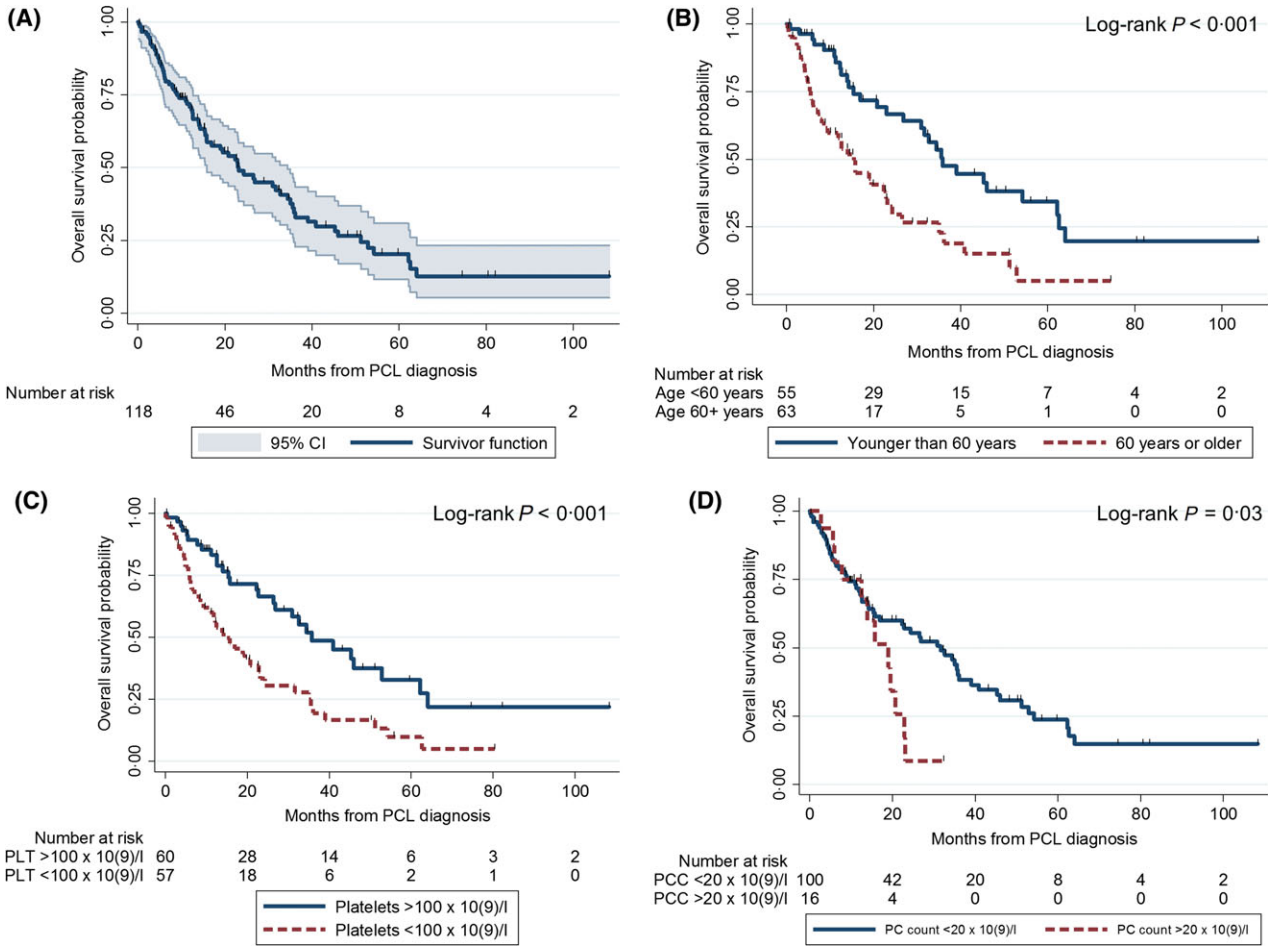

Fig 1. Overall survival estimates in 117 primary plasma cell leukaemia patients for the entire cohort (A), by age (B), platelet count (C) and plasma cell count in peripheral blood (D). 95% CI, 95% confidence interval; PCC, plasma cell count; PCL, plasma cell leukaemia; PLT, platelet count. [Colour figure can be viewed at wileyonlinelibrary.com]

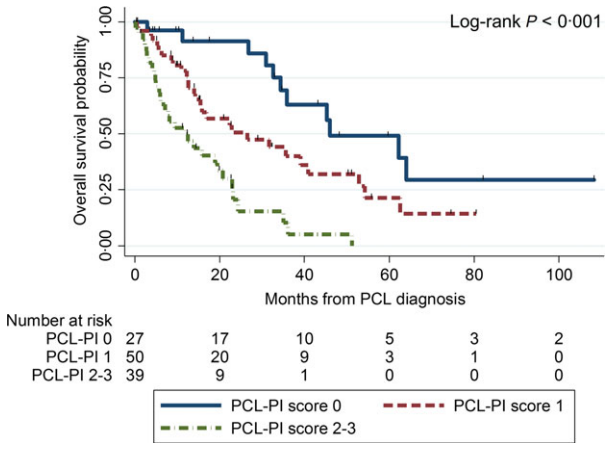

Fig 2. Overall survival estimates in 117 patients with primary plasma cell leukaemia by pPCL Prognostic Index. PCL, plasma cell leukaemia; PCL-PI, plasma cell leukaemia prognostic index. [Colour figure can be viewed at wileyonlinelibrary.com]

platelet counts and higher absolute PC counts in patients with pPCL, with the formulation of a novel and easy-to-use pPCL prognostic index.

Historically, the prognosis in pPCL has been poor. Although recent evidence suggests that upfront incorporation of ASCT and novel-agent therapies may provide survival benefits in patients with this condition, available data in this matter are still limited. The largest study analysing the outcomes of ASCT in pPCL was the retrospective report by the European Group for Blood and Marrow Transplantation, including data on 272 patients. The study demonstrated that individuals subjected to ASCT were more likely to enter complete remission, with median OS of 26 months (95% CI 19·5; 31·9) (Drake *et al*, 2010). Another large study, conducted by the Centre for International Blood and Marrow Transplant Research, included 147 patients, subjected to either ASCT or alloSCT. After 3 years of follow-up, the OS rates for these two groups were 64% and 39%, respectively (Mahindra *et al*, 2012). These encouraging findings were reflected in the consensus statement of the International

Myeloma Working Group, which recommend intensification of pPCL treatment with high-dose therapy followed by ASCT whenever age and clinical condition of the patient do not preclude this approach (Fernández de Larrea *et al*, 2013). However, the previously mentioned studies were retrospective, registry-based and did not have a comparator group. Our study provides additional semi-comparative data supporting the use of ASCT in pPCL.

Single-institution studies demonstrated that implementation of a proteasome inhibitor, bortezomib, may increase ORR up to 78%, and prolong median OS to 18–28 months (Esparís-Ogando *et al*, 2005; Musto *et al*, 2007; Lebovic *et al*, 2011; D'Arena *et al*, 2012; van de Donk *et al*, 2012). Also, lenalidomide, an immunomodulatory drug, was shown to be effective for pPCL in small retrospective studies (Benson & Smith, 2007; Musto *et al*, 2008; Olivieri *et al*, 2009). Additional promising results have also been reported from single-institution prospective trials. In a prospective phase II study conducted by the Intergroupe Francophone du Myélome, 40 patients with pPCL received four alternating cycles of bortezomib, dexamethasone plus doxorubicin or cyclophosphamide, followed by ASCT. The ORR to induction therapy was 69%, and the median OS was 37 months (95% CI 25·6; not reached) (Royer *et al*, 2016). Also, the only reported prospective trial of lenalidomide confirmed the efficacy of this agent in combination with low-dose dexamethasone in a group of 23 patients with pPCL (Musto *et al*, 2014). The ORR for the whole study group was 74%, and the median OS time 28 months. A better survival was reported in the subset of patients who underwent ASCT following lenalidomide and dexamethasone induction (Musto *et al*, 2014).

Our findings are consistent with the above-mentioned results. In our study, 78% of pPCL patients showed at least PR to upfront therapy, with a median OS of 23 months, and 80% of the patients either maintained or improved their response after ASCT following induction. Furthermore, median OS in patients who received an upfront ASCT was nearly three times longer than in those who did not (35 vs. 13 months). Patients who underwent ASCT were more likely to be aged <60 years (67% vs. 29%; $P = 0{\cdot}001$) and to have PC >40% (61% vs. 34%; $P = 0{\cdot}02$). No other differences were seen in sex, WBC, haemoglobin, platelet, PC count, poor or complex cytogenetics. Due to the small size and heterogeneity of the sample, we were unable to analyse the effects of each agent separately. Nevertheless, although the follow-up time for the subset of patients receiving the triple therapy (chemotherapy, proteasome inhibitor, and immunomodulatory drug) was too short (median follow-up about 1 year), there is encouraging evidence that the estimated 1- and 2-year OS rates in this group might be higher than with single or double therapy.

We identified three independent adverse prognostic factors in patients with pPCL: age ≥60 years, platelet count $<100 \times 10^9$/l, and peripheral blood PC count $\geq 20 \times 10^9$/l. The median OS for individuals without any risk factors was approximately 4 years, which was nearly four times longer than for patients with 2–3 risk factors. Published evidence regarding prognostic factors in pPCL is generally sparse and inconclusive. The value of some parameters with prognostic impact in MM, e.g. cytogenetic abnormalities, remains unclear in pPCL, primarily due to the small size and heterogeneity of examined samples (Jelinek *et al*, 2015). Nevertheless, both published evidence and our unpublished clinical experience suggest that the identified prognostic indicators are linked to pPCL biology. PC count is a diagnostic criterion of PCL and a measure of its severity (Jimenez-Zepeda & Dominguez, 2006). In turn, the fact that younger subjects included in our series had longer OS probably reflected their better performance status, which has already been shown to be a favourable predictor of survival in pPCL (Vela-Ojeda *et al*, 2002; Colovic *et al*, 2008). Furthermore, younger patients are more likely to undergo ASCT following induction therapy (Jelinek *et al*, 2015; Gonsalves, 2017). Finally, the negative prognostic value of lower platelet count in pPCL has been demonstrated in previous single-institution studies (Colovic *et al*, 2008; Katodritou *et al*, 2014).

Our findings have important clinical implications. First, using the 3-variable pPCL-PI, we were able to identify a subset of patients who may particularly benefit from more intensive therapy. Second, all three variables included in the index can be easily determined at the time of pPCL diagnosis, in comparison to PC immunophenotype or cytogenetic abnormalities, especially in the community. Finally, all these observations derive from a large series of 117 patients from three continents, minimizing the bias of ethnic background of the study subjects.

Potential limitations of this study include its retrospective character, lack of protocol standardization, and incomplete clinical and laboratory data, particularly regarding the immunophenotypic and cytogenetic characteristics of PCs. Thus, we were unable to include other potential variables of importance in the survival regression models, or to formulate any firm conclusions regarding the immunophenotypic and cytogenetic profiles of pPCL. Another important inherent weakness of a retrospective study is selection bias. We have minimized this bias by including consecutive patients at each of the participating institutions.

In conclusion, our study confirmed that the prognosis in pPCL could be improved with the implementation of novel therapies, such as proteasome inhibitors and immunomodulators as well as ASCT. Of significant clinical interest in future management of patients with PCL is the availability of anti-CD38 monoclonal antibodies as single agents or in combination. The PCL-PI reported here should be independently validated.

Author contributions

AJ, DHV and JJC designed the study and drafted the initial manuscript. All the authors provided patient data for the study, provided critical input and approved the final manuscript.

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