

# Prognostic impact of circulating plasma cells in patients with multiple myeloma: implications for plasma cell leukemia definition

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## ABSTRACT

The presence of circulating plasma cells in patients with multiple myeloma is considered a marker for highly proliferative disease. In the study herein, the impact of circulating plasma cells assessed by cytology on survival of patients with multiple myeloma was analyzed. Wright-Giemsa stained peripheral blood smears of 482 patients with newly diagnosed myeloma or plasma cell leukemia were reviewed and patients were classified into 4 categories according to the percentage of circulating plasma cells: 0%, 1-4%, 5-20%, and plasma cell leukemia with the following frequencies: 382 (79.2%), 83 (17.2%), 12 (2.5%) and 5 (1.0%), respectively. Median overall survival according to the circulating plasma cells group was 47, 50, 6 and 14 months, respectively. At multivariate analysis, the presence of 5 to 20% circulating plasma cells was associated with a worse overall survival (relative risk 4.9, 95% CI 2.6–9.3) independently of age, creatinine, the Durie-Salmon system stage and the International Staging System (ISS) stage. Patients with  $\geq 5\%$  circulating plasma cells had lower platelet counts (median  $86 \times 10^9/L$  vs.  $214 \times 10^9/L$ ,  $P < 0.0001$ ) and higher bone marrow plasma cells (median 53% vs. 36%,  $P = 0.004$ ). The presence of  $\geq 5\%$  circulating plasma cells in patients with multiple myeloma has a similar adverse prognostic impact as plasma cell leukemia.

## Introduction

Plasma cell leukemia (PCL) was originally defined by the presence of both  $>20\%$  circulating plasma cells (PCs) and an absolute count  $>2 \times 10^9/L$  PCs,<sup>1,2</sup> although in many studies the presence of only 1 of the above criteria was required.<sup>3-5</sup> PCL may be classified as primary when it presents *de novo* in patients without previous evidence of multiple myeloma (MM) or secondary when it is presented as a leukemic transformation of a previously recognized MM. Primary PCL is a rare entity with an incidence of 2 to 4% of MM<sup>6,8</sup> and is associated with a worse prognosis than MM. Its median survival, in a large epidemiological study, was only 4 months.<sup>7</sup> However, with the use of novel drugs upfront, median survival ranging from 18 to 36 months has been reported.<sup>9-15</sup>

The presence of circulating PCs, identified by cytology,<sup>16</sup> multiparameter flow cytometry<sup>17,18</sup> or slide-based immunofluorescence,<sup>19</sup> is also associated with a worse prognosis in myeloma patients not fulfilling the criteria of PCL. The presence of circulating PCs is also a risk factor of progression to active disease in patients with

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monoclonal gammopathy of undetermined significance<sup>20</sup> and smoldering MM.<sup>21</sup> It has been suggested that MM patients with circulating PCs, even below 20%, could have the same bad prognosis as patients with PCL. Indeed, a lower cutoff of  $\geq 5\%$  or  $\geq 0.5 \times 10^9/L$  of nucleated peripheral blood cells to redefine PCL has been proposed.<sup>3</sup> In the present study, the impact of the presence of circulating PCs assessed by cytology on the survival of patients with MM was analyzed.

## Methods

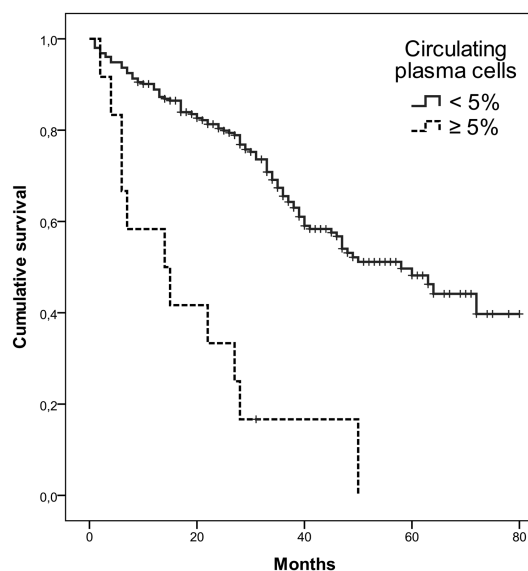
Requirements to enter the study were a diagnosis of symptomatic MM or primary PCL according to the International Myeloma Working Group (IMWG) criteria<sup>22</sup> between January 2008 and December 2013 in 5 University Hospitals from Catalonia, and to have peripheral blood smears at diagnosis available for review. The study was approved by the Ethic Committee of the Hospital de la Santa Creu i Sant Pau and was conducted according to the declaration of Helsinki. Clinical data including age, sex, myeloma isotype, percentage of bone marrow plasma cells, lactate dehydrogenase (LDH), Durie-Salmon and ISS stages, as well as initial treatment and follow up, were collected from medical records. Cytogenetic analysis was performed according to local policies and patients were treated according to regional protocols. Wright-Giemsa stained peripheral blood smears were reviewed by 5 experienced hematologists on peripheral blood cytology. A minimum of 100 nucleated cells per smear were systematically counted. Each sample was analyzed by a single morphologist, with each following the same common criteria.

The primary endpoint was overall survival (OS) measured from the date of diagnosis to the date of death or last follow up. Differences in demographics and baseline characteristics were compared using the two-sided Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Survival analysis was performed using the Kaplan-Meier method and differences were tested for statistical significance using the log-rank test. Multivariate analysis was conducted using the Cox proportional hazards model. All calculations were performed using the software SPSS® statistics version 22.

## Results

### Clinical characteristics

The study cohort included 482 patients diagnosed with MM between January 2008 and December 2013. The median age at diagnosis was 69 years (range 28 to 92 years). Two hundred and sixty (53.9%) of the patients were males. The median follow up was 28 months for the whole cohort and 38 months for the patients alive. Two hundred and thirty-one (47.9%) patients died during follow up. First-line therapy was based on bortezomib combinations in 230 (47.7%) patients, alkylating agents with glucocorticoids in 114 (23.7%) patients, vincristine, doxorubicin (adriamycin), and dexamethasone (VAD) or VAD-like chemotherapy in 60 (12.4%), immunomodulatory-based combinations in 26 (5.4%), high-dose dexamethasone in 4 (0.8%), and only palliative care in 48 (9.9%) patients. One hundred and fifty-six (32.4%) patients received autologous stem cell transplantation as part of their first-line treatment. Twelve (2.5%) patients received allogeneic stem cell transplantation during the course of the disease.



<5% PCs	253	191	92	33	2
≥5% PCs	12	5	1	0	0

Figure 1. Overall survival according to the circulating plasma cells (PCs) group in patients with multiple myeloma ( $P < 0.001$ ).

Clinical characteristics at diagnosis according to the circulating PCs group are summarized in Table 1. Differences in age, sex, myeloma isotope, LDH, Durie-Salmon and ISS stages between the 4 groups were not statistically significant. However, patients within the 5 to 20% circulating PCs group had lower platelet counts (median  $86 \times 10^9/L$  vs.  $214 \times 10^9/L$ ,  $P < 0.0001$ ) and a higher proportion of bone marrow PCs (median 53% vs. 36%,  $P = 0.004$ ).

The 5 patients with  $>20\%$  circulating PCs were initially treated with bortezomib and dexamethasone (2 patients); bortezomib, cyclophosphamide and dexamethasone (1 patient); melphalan and prednisone (1 patient); and bortezomib, melphalan and prednisone (1 patient). Of the 12 patients with 5-20% circulating PCs, 1 died the day after diagnosis and only received supportive care, the remaining 11 patients were initially treated as follows: bortezomib and dexamethasone (6 patients); bortezomib, thalidomide and dexamethasone (2 patients); VAD (1 patient); bortezomib, melphalan and prednisone (1 patient); and cyclophosphamide and steroids (1 patient). One patient with  $>20\%$  circulating PCs and 3 patients with 5-20% circulating PCs received an autologous stem cell transplantation as consolidation.

### Risk factors for overall survival in the overall cohort

According to the percentage of circulating PCs, 4 groups were considered for the analysis of survival: no circulating plasma cells, 382 (79.2%) patients; 1 to 4% circulating plasma cells, 83 (17.2%) patients; 5 to 20% circulating plasma cells, 12 (2.5%) patients; and classical PCL group ( $>20\%$  or  $>2 \times 10^9/L$  plasma cells), 5 (1%) patients. A patient with 15% circulating PCs but an absolute circulating PC count of  $2.7 \times 10^9/L$  was included in the classical PCL group.

The median OS of patients with no circulating PCs, 1 to 4%, 5 to 20% and  $>20\%$  were 47 (95%CI 38.6–55.4)

months, 50 (95%CI 31.0–68.9) months, 6 (95%CI 0.9–11.1) months and 14 (95%CI 9.7–18.3) months, respectively (Figure 1) ( $P < 0.001$ ).

In the univariate analysis, the other factors associated with a worse survival together with circulating PCs were age older than 65 years at diagnosis, creatinine  $> 2$  mg/dL, treatment with new drugs upfront (proteasome inhibitors or immunomodulatory drugs), and Durie-Salmon and ISS advanced stages. Cytogenetic data was not included in the survival analysis due to the lack of such data in most patients. The 5 patients with classical PCL were excluded from the multivariate analysis. The finding of 5 to 20%

circulating plasma cells, age older than 65 years, Durie-Salmon III, creatinine  $> 2$  mg/dL, and ISS 3 retained their significance in the multivariate analysis (Table 2).

#### Risk factors for overall survival in patients treated with novel agents upfront

Two hundred and sixty five of the 482 (54.9%) patients were treated upfront with proteasome inhibitors and/or immunomodulatory drugs. Of these, 192 (72.5%) patients had 0% circulating PCs, 61 (23.0%) patients had 1 to 4% circulating PCs, 9 (3.4%) patients had 5 to 20% circulating PCs and 3 (1.1%) patients had a diagnosis of classical PCL. One hundred and ten (41.5%) patients treated with novel

**Table 1.** Clinical characteristics according to the number of circulating plasma cells group.

Circulating plasma cells	0%	1-4%	5-20%	>20%
N (% overall)	382 (79.2)	83 (17.2)	12 (2.5)	5 (1.0)
Male, n (%)	218 (57.1)	33 (39.7)	5 (42)	4 (80)
Age, y. median (range)	70.1 (32-92)	68 (28-88)	65 (48-85)	62 (49-80)
Heavy chain, n (%):				
Ig G	230 (60.2)	46 (55.4)	6 (50)	3 (60)
Ig A	92 (24.1)	18 (21.7)	2 (17)	0
light chain only	57 (14.9)	18 (21.7)	4 (33)	2 (40)
IgD or IgM	3 (0.7)	1 (1.2)	0	0
Light chain, n (%):				
$\kappa$	247 (64.6)	54 (65.1)	5 (42)	2 (40)
$\lambda$	135 (35.3)	29 (34.9)	7 (58)	3 (60)
Hemoglobin, g/L. Median (range)	104 (56–171)	99 (68–139)	92 (65–144)	103 (40–129)
WBC. $\times 10^9/L$ . Median (range)	6.2 (1.7–22.6)	5.9 (0.9–16.2)	6.3 (3.7–7.0)	24 (63–8)
Platelets. $\times 10^9/L$ . Median (range)	214 (50–558)*	223 (58–493)	86 (24–174)*	138 (28–242)
Calcium, mg/dL. Median (range)	9.3 (7.2–14.8)	9.4 (7.3–14.2)	10.1 (8.6–15.8)	9.4 (9.0–11.4)
Creatinine, mg/dL. Median (range)	1.1 (0.3–11.9)	1.1 (0.5–12.2)	1.5 (0.6–8.0)	1.1 (0.6–6.8)
Lytic lesions. n (%):				
None	172 (45.0)	39 (46.9)	7 (58)	3 (60)
One to 3	186 (48.7)	43 (51.8)	4 (33)	1 (20)
More than 3	24 (6.3)	1 (1.2)	1 (8)	1 (20)
D-S stage. n (%):				
I	55 (14.4)	7 (8.4)	1 (8)	2 (40)
II	156 (40.8)	41 (49.4)	3 (25)	0
III	171 (44.7)	35 (42.2)	8 (67)	3 (60)
B (creat $> 2$ mg/dL)	64 (16.7)	18 (21.7)	5 (42)	
$\beta 2$ -m, mg/L. median (range)	4.6 (1–48)	5.0 (1.7–35.1)	5.8 (2.9–31)	6.7 (4.9–7)
Albumin, g/L. median (range)	37.0 (15–48.9)	35.7 (20–43)	31 (24–45)	38.1 (29–47)
ISS stage. n (%):				
I	85 (22.2)	13 (15.7)	1 (8)	0
II	132 (34.6)	28 (33.7)	4 (33)	1 (20)
III	137 (35.8)	36 (43.4)	7 (58)	3 (60)
NA	28 (7.3)	6 (7.2)		1 (20)
LDH UNL, n (%)	59 (15.4)	11 (13.2)	4 (33)	2 (40)
Bone marrow PCs, %. median (range)	36 (1–100)**	48 (2–100)	53 (38–90)**	43 (18–95)
Extramedullary disease, n (%)	77 (20.1)	11 (13.2)	3 (25)	1 (20)
Cytogenetics, n/assessed (%)				
t(4;14)	7/164 (4.2)	5/31 (16.1)	0/4 (0)	0/3 (0)
del 17p.	17/177 (9.6)	3/39 (7.7)	1/8 (12)	1/3 (33)

\* $P < 0.001$ . \*\* $P = 0.006$ . WBC: White blood cells; D-S: Durie-Salmon;  $\beta 2$ -m: beta 2 microglobulin; ISS: International Staging System; LDH: Lactate dehydrogenase; UNL: Upper normal limit; PCs: plasma cells.

**Table 2.** Risk factors for overall survival, overall cohort.

	Univariate*			Multivariate*		
	RR	95% CI	P	RR	95% CI	P
5-20% circulating PCs	4.0	2.1 – 7.3	<.001	4.9	2.6 – 9.3	<0.001
>65 years	2.1	1.6 – 2.8	<.001	2.0	1.5 – 2.8	<0.001
D-S stage III	1.6	1.2 – 2.0	0.001	1.7	1.2 – 2.2	<0.001
Creatinine >2mg/mL	1.7	1.3 – 2.3	0.001	1.5	1.1 – 2.1	0.010
ISS II or III	2.4	1.6 – 3.5	<.001	1.7	1.1 – 2.6	0.014
New drugs upfront	1.5	1.1 – 2.0	<.001	1.6	1.2 – 2.2	<0.001
LDH UNL	1.3	0.9 – 1.9	0.07	1.4	0.9 – 1.9	0.09

\*Cox model. RR: relative risk; CI: confidence interval; PCs: plasma cells; D-S: Durie-Salmon; ISS: International staging System; LDH: lactate dehydrogenase. UNL: Upper normal limit.

agents upfront died during follow up and their median OS was 50 (95% CI 38–61) months.

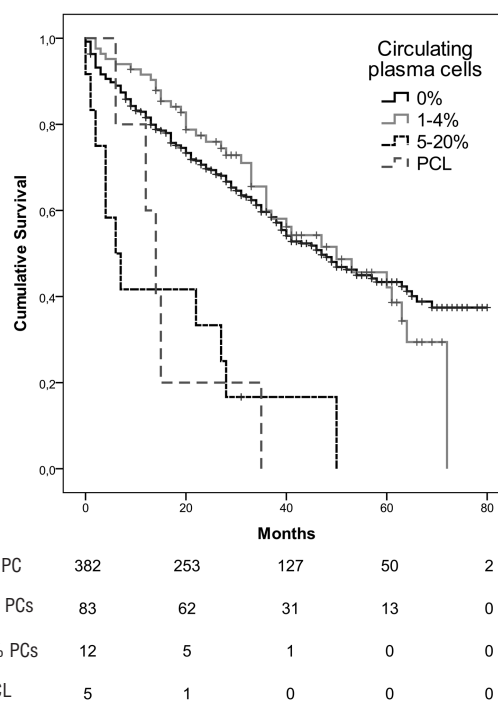
In patients treated with novel agents upfront, the median OS in cases with 0%, 1 to 4%, 5 to 20% and PCL were 58 (95% CI NR) months, 60 (95% CI 33–86) months, 22 (95% CI 0–65) months and 14 (95% CI 1–26) months, respectively. When only 2 groups were considered, <5% and ≥5% circulating PCs, median OS were 58 (95% CI 46 – 69) months and 14 (95% CI 0.4 – 27) months (Figure 2).

Together with the percentage of circulating PCs, the other factors associated with a worse OS in univariate analysis were creatinine >2mg/dL and ISS stage II or III. A trend was observed in patients >65 years old and Durie-Salmon stage III. Taking into account the aforementioned variables, having ≥5% circulating PCs alone was the only fact which maintained statistical significance in the multivariate analysis (Table 3). LDH was not included in the multivariate analysis due to the lack of statistical significance or even a trend in univariate analysis (RR 1.1, 95% CI 0.7–1.9,  $P=0.467$ ).

## Discussion

This study aimed to address the impact of circulating PCs on the survival of patients with MM. Seventeen per cent of patients had between 1 and 4% circulating plasma cells. That finding was not associated with other clinical characteristics and had no impact on survival. There was a completely different picture for the 2.5% of patients with 5 to 20% circulating PCs. Such patients had lower platelet counts, higher bone marrow infiltration and, importantly, a shorter survival independent of other known clinical prognostic factors. In fact, the median OS of 6 months observed in these patients is closer to that of patients with the “classical” definition of PCL. When the analysis was restricted to patients treated with novel agents upfront, the impact of circulating PCs was consistent with the whole cohort. The differences in OS observed between patients with 5-20% circulating PCs and >20% circulating PCs (6 vs. 14 months) may be explained by the low number of cases in both groups.

Although the presence of circulating PCs has been previously associated with survival, conventional cytology has been used for their assessment in only one study.<sup>16</sup> In that case, patients with circulating plasma cells constituted 14.1% of the overall series and had a median survival of 25 months. The results of the present study are consistent with the ominous prognostic impact of peripheral blood



**Figure 2.** Overall survival according to the circulating plasma cells (PCs) in patients with multiple myeloma and plasma cell leukemia (PCL) treated with novel drugs upfront ( $P<0.001$ ).

plasmacytosis; however, the definition of a high-risk group found was different; ≥2% circulating PCs in the study by An *et al.* and ≥5% circulating PCs in the study herein.

Using multiparameter flow cytometry, the presence of circulating PCs has also been associated with survival.<sup>17,18,23</sup> In the study from the Mayo Clinic,<sup>17</sup> 24% of patients had more than 400 circulating PCs. Such patients had a median OS of 32 months *versus* not reached in patients with 400 or less circulating PCs. In another study from the same institution, which in this case used slide-based immunofluorescence microscopy for plasma cell quantification,<sup>19</sup> 54% of patients with >4% PCs were identified. These patients had a median survival of 2.4 years compared to 4.4 years in patients with fewer circulating PCs. The aforementioned studies used much more sensitive techniques than those used in the present; this may explain the different percentages of patients with circulating PCs identified

**Table 3.** Factors associated with overall survival in patients treated with novel drugs upfront.

	Univariate*			Multivariate*		
	RR	95% CI	P	RR	95% CI	P
≥5% circulating PCs	4.8	2.5 – 9.1	<0.001	4.5	2.4 – 8.8	<0.001
>65 years	1.4	0.9 – 2.1	0.060	1.3	0.8 – 1.9	0.186
D-S stage III	1.3	0.9 – 1.9	0.102	1.3	0.9 – 2.0	0.132
Creatinine >2mg/mL	1.8	1.2 – 2.8	0.007	1.5	0.9 – 2.4	0.082
ISS II or III	1.9	1.1 – 3.3	0.010	1.6	0.9 – 2.7	0.092

\*Cox model. RR: relative risk; CI: confidence interval; PCs: plasma cells; D-S: Durie-Salmon; ISS: International staging System; LDH: lactate dehydrogenase.

in those studies in comparison with the present one.

Despite these findings, the definition of PCL has been based on standard morphological examination of peripheral blood.<sup>3</sup> In comparison with flow cytometry and immunofluorescence, conventional cytology identifies a smaller number of patients with an extremely poor prognosis. Additionally, conventional cytology has the advantage of being a simple and inexpensive technique that can be applied in any clinical laboratory worldwide. However, it has a limitation; conventional cytology is not able to identify the clonality of PCs, as can be achieved by flow cytometry and immunofluorescence. This may hamper the specificity of conventional cytology since polyclonal reactive PCs may be rarely detected in some patients with MM.<sup>24,25</sup>

The presence of t(4;14), del(17p), amp(1q21) and del(1p21) in malignant PCs are adverse prognostic factors in MM.<sup>26,27</sup> Indeed, adverse cytogenetics together with ISS 3 and/or high LDH identifies a group of patients with an ultra-high risk of MM.<sup>28</sup> Several of these genetic abnormalities, particularly del(17p)9 and chromosome 1 alterations<sup>29</sup> are more frequent in PCL than in MM. In the series presented herein, del(17p) by fluorescence *in situ* hybridization (FISH) was observed in 1 of 7 patients with 5 to 20% circulating PCs and 1 of 2 patients with >20% circulating PCs. A limitation of the present study is that, due to the lack of cytogenetic data in most patients, the prognostic impact of unfavorable cytogenetic abnormalities and the revised ISS<sup>28</sup> could not be analyzed.

As highlighted in the last consensus by IMWG,<sup>3</sup> the diagnosis of PCL has been classically done on the basis of the presence of >20% circulating PCs and/or an absolute count >2 × 10<sup>9</sup>/L PCs. However, lower peripheral blood PC counts, as showed in our study (that is, ≥5% peripheral blood plasma cells), should be considered as a diagnostic criteria of PCL (“PCL-like” myeloma or early PCL), due to the independent and strong prognostic impact. Prospective multicenter analysis with translational and correlative studies into the biology of these patients is encouraged as well as risk-oriented therapeutic strategies.<sup>30,31</sup> Careful examination of peripheral blood by conventional microscopy should be done for all patients with MM in daily clinical practice.

In conclusion, the presence of ≥5% circulating PCs by conventional cytology easily identifies a group of patients with myeloma with a prognosis as poor as that of PCL, suggesting that the diagnosis of PCL should be revisited. If confirmed in other series, especially in prospective studies of uniformly treated patients, such patients may benefit from a distinct and more intensified therapeutic approach.

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