Primary plasma cell leukemia and autologous stem cell transplantation

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ABSTRACT

Background
Primary plasma cell leukemia is a rare disorder accounting for less than 5% of malignant plasma cell diseases. It has a poor prognosis compared to multiple myeloma, with a median survival of 8-12 months. The results of conventional therapy are disappointing though autologous stem cell transplantation may improve survival.

Design and Methods
A retrospective analysis was undertaken of the European Group for Blood and Marrow Transplantation experience of 272 patients with plasma cell leukemia and 20844 with multiple myeloma undergoing first autologous transplantation between 1980 and 2006. All patients were reported to the European Group for Blood and Marrow Transplantation registry using MED-A (limited data) or MED-B (extensive data) forms. All patients were included regardless of availability of complete data.

Results
There was no difference in type of graft or use of total body irradiation between patients with plasma cell leukemia and multiple myeloma, but the group with plasma cell leukemia was transplanted earlier after diagnosis (6.0 *versus* 7.7 months, *P*=0.000). Patients with plasma cell leukemia were more likely to enter complete remission after transplantation but their overall survival (25.7 months, 95% confidence interval 19.5-31.9 months) was inferior to that of patients with multiple myeloma (62.3 months, 95% confidence interval 60.4-64.3 months) (*P*=0.000), due to the short duration of their post-transplant response and increased non-relapse-related mortality.

Conclusions
This largest study ever reported on plasma cell leukemia suggests that autologous transplantation can improve outcome, although results are markedly inferior to those achieved in patients with multiple myeloma, highlighting the need for novel approaches to this aggressive disorder.

Key words: plasma cell leukemia, autotransplantation, overall survival.

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Introduction

Primary plasma cell leukemia (PCL) is a rare disorder, representing less than 5% of malignant plasma cell diseases,[1,2] and characterized by plasma cells circulating in the peripheral blood. Diagnostic criteria were defined by Kyle *et al.*[3] as an absolute plasma cell count of more than 2.0×10^9/L or a relative proportion of greater than 20% of the peripheral blood leukocyte count. Considered to represent advanced disease with a poor prognosis, the median survival of patients with PCL is reported to be 8 to 12 months,[1,2] which is significantly shorter than that for patients with multiple myeloma, even when the comparison is adjusted to compare only cases of multiple myeloma with a high tumor mass.[1] The disorder progresses rapidly with frequent early deaths; for example, 11 of a series of 40 patients with primary PCL died in the first month after diagnosis.[4] Patients are reported to present often with advanced stage, extramedullary involvement, raised lactate dehydrogenase and thrombocytopenia[1] while cytogenetic abnormalities, including hypodiploidy, pseudodiploidy, complex abnormalities and monosomy 13, have been described more frequently than in advanced myeloma.[2,4,5] Treatment of PCL with alkylating agent-based therapy is ineffective with no responding patients in a series of ten patients treated with melphalan and prednisolone[1] and a median survival of 2-3 months.[1,2] Polychemotherapy may offer significantly enhanced survival, with one study reporting a median survival of 18 months among patients treated in this way compared to 3 months among patients given alkylating agent therapy.[2] Prolonged survival has also been reported for individual cases after intensive chemotherapy and hematopoietic stem cell support. Here, we report an European Group for Blood and Marrow Transplantation (EBMT) registry study comparing presenting features and outcomes of 272 patients with primary PCL and 20844 patients with multiple myeloma undergoing autologous transplantation between 1980 and 2006.

Materials and Methods

A retrospective study was carried out of 20844 patients with common type multiple myeloma (58% IgG, 21% IgA and 19% light chain only types) and 272 patients with primary PCL who underwent first autologous transplantation between 1980 and 2006. All patients were reported to the EBMT registry using MED-A (limited data set) or MED-B (more extensive data set) forms. Consent appropriate to the time of transplant was obtained from all patients for the anonymized reporting of their data and the use of the data for retrospective studies. All autografted patients were included in the study, regardless of availability of complete MED-A or MED-B data. The proportion of patients that could be evaluated for each parameter was noted and the number of evaluable patients is included in the results.

Tumor mass was defined as stage I, II or III according to the Durie-Salmon classification. Disease response to therapy was defined according to EBMT criteria [6] and bone structure at diagnosis was defined as normal, having minor lytic lesions, having major lytic lesions or showing osteoporosis using EBMT MED B criteria. Performance status at transplantation was described as good or poor.

Statistical analysis

Comparisons between the two groups were made using the χ^2 test for categorical data, and the Mann-Whitney test for continuous data. Overall survival was defined as the time between transplantation and death, with patients alive at last follow-up being censored. Progression-free survival was defined as the time between transplantation and progression of disease or death, regardless of response after transplantation, with censoring of patients alive without progression at last follow-up. The probabilities of overall survival and progression-free survival were calculated using the Kaplan-Meier method, and comparisons were made using the log-rank test. The probabilities of relapse/progression and death without relapse or progression (non-relapse mortality) were computed by the proper non-parametric estimator for outcomes with competing risks, and compared by Gray's test. These methods were also used to describe engraftment rates, considering death within 100 days as a competing event. The impact of complete remission on overall survival was investigated by a landmark analysis; in view of the short survival of PCL patients, we selected achievement of complete remission at 100 days, acknowledging that a greater proportion of myeloma patients may achieve complete remission by 1 year. All reported *P* values are from two-sided tests. The reported confidence intervals (CI) refer to 95% boundaries. All analyses were performed in SPSS 12.0 except for the application of methods for competing risks analysis, which was carried out in R 2.3.1 using the CMPRSK library by B. Gray.

Results

Factors at diagnosis

Age at diagnosis was similar between the groups, being 55.6 years and 55 years (P=0.088) for myeloma and PCL patients, respectively (Table 1). PCL patients were slightly younger at transplantation, the median age for the multiple myeloma patients and the PCL patients being 56.9 and 55.6 years, respectively (P=0.011). Gender, calcium and albumin levels were not significantly different between the groups for evaluable patients. Hemoglobin concentration was significantly lower in the PCL group, with the median hemoglobin being 11 g/dL and 9 g/dL in the

Table 1. Patients' characteristics at diagnosis.

Variable		Multiple myeloma	Plasma cell leukaemia	*P* value
Gender (male/female)		58.2/41.8	54.8/45.2	0.256
Age at diagnosis (years)		55.6	55	0.088
Age at transplantation (years)		56.9	55.6	0.011
Hemoglobin (g/dL)		11	9	0.000*
Creatinine (μmoL/L)		92	122.5	0.000*
Calcium (mmol/L)		2.38	2.43	0.180
Albumin (g/L)		37	36	0.169
Median β_2 microglobulin (mg/L)		3.1	6.8	0.000*
Percentage of patients with β_2 microglobulin > 4mg/L		52	78.4	0.000*
Disease stage	I	12.8	6.7	0.037*
	II	21.2	13.3	
	III	66.0	80.0	

*All values are expressed as median values. *denotes statistically significant* P *value.*

myeloma and the PCL patients, respectively (*P*=0.000). Creatinine levels were significantly higher in the patients in the PCL group, with a median creatinine of 92 μmol/L and 122 μmol/L in the myeloma and the PCL patients, respectively (*P*=0.000).

The level of β_2 microglobulin was significantly higher in the PCL group, with a median β_2 microglobulin of 3.1 mg/L and 6.8 mg/L in the multiple myeloma and PCL patients, respectively (*P*=0.000). At diagnosis, 78% of the PCL patients compared to 52% of the multiple myeloma patients had raised β_2 microglobulin (>4.0 mg/L) (*P*=0.000).

Disease stage at diagnosis was significantly different between the groups, with a trend to more advanced disease in the PCL group (80% of patients in stage III compared to 66% of multiple myeloma patients, *P*=0.037, Table 1).

Disease status and patients' performance status before transplantation

At the time of conditioning for transplantation, a higher proportion of patients with PCL than multiple myeloma patients were in complete remission (25.5% *versus* 11.9%, respectively; *P*=0.000). Further analysis showed that 91% of PCL patients achieved a partial response or better (myeloma 85%). No PCL patients were transplanted in relapse although 7% had progressive disease (myeloma 6%), but patients with untreated or primary refractory disease did not undergo transplantation (myeloma 0.6%).

There was no difference in performance status between the groups, with 93.9% of the myeloma patients and 92.5% of the PCL patients having good performance status prior to transplantation (*P*=0.47, Table 2).

Time to transplantation and conditioning

The median time from diagnosis to transplantation was significantly longer for the myeloma patients (7.7 months) than for those with PCL (6.0 months) (*P*=0.000). No difference was apparent in the type of graft used (bone marrow alone, peripheral blood stem cells alone or bone marrow plus peripheral blood stem cells) or the use of total body irradiation between the groups, with 7.8% of multiple myeloma patients and 9.1% of PCL patients receiving total body irradiation (*P*=0.44, Table 2).

Engraftment

The proportions of patients in whom the neutrophil count recovered to greater than 0.5×10^9/L and the platelet count to greater than 50×10^9/L in the first 100 days after transplantation were not significantly different between myeloma and PCL patients (*P*=0.138 for neutrophil recovery and *P*=0.161 for platelet recovery). The median time to neutrophil engraftment was 12 days for both PCL and multiple myeloma and 18 and 15 days, respectively, for platelet engraftment.

Response to transplant

PCL patients were more likely than myeloma patients to achieve complete remission after autologous transplantation (Figure 1): the probability of being in complete remission at 100 days post-transplantation was 28.2% for myeloma patients and 41.2% for PCL patients (*P*=0.000). Using a landmark analysis at 100 days, the proportion of patients converting from a less than complete remission to complete remission was approximately 10% in multiple myeloma and 25% in PCL; this conversion improved the overall survival of PCL patients [hazard ratio (HR), 0.59; CI, 0.34-1.05), although it remained significantly worse than patients with multiple myeloma achieving complete remission in the same period (HR, 3.18; CI, 2.55-3.96). Progression-free survival in PCL was improved in patients achieving a complete remission after transplantation (HR, 0.64; CI, 0.39-1.05).

The impact of the known prognostic factors β_2 microglobulin and hemoglobin were assessed in an adjusted sub-analysis of patients whose β_2 microglobulin and hemoglobin concentrations were known, utilizing myeloma patients in whom these variables were associated with a poorer prognosis to make an appropriate comparison with PCL patients. There was a larger difference between PCL and multiple myeloma patients for overall survival and progression-free survival than for the whole group (HR, 2.85; CI, 2.19-4.22 and HR, 2.05; CI, 1.42-2.94, respectively).

Table 2. Patients' status at transplantation and procedure-related factors.

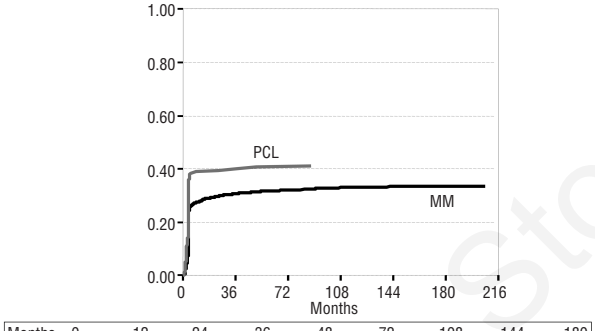
Variable	Multiple myeloma patients		Plasma cell leukemia patients		*P* value
Median time from diagnosis to transplantation (months)	7.66		6.01		0.000*
Disease response at stem cell mobilization	CR	8.7	CR	22.1	0.009*
	PR	74.9	PR	64.7	
	NR/MR	12.7	NR/MR	11.8	
	Rel/prog	3.2	Rel/prog	1.5	
Disease response at transplantation conditioning	CR	11.9	CR	25.5	0.000*
	PR	69.0	PR	58.7	
	NR/MR	12.3	NR/MR	8.9	
	Rel/prog	6.2	Rel/prog	6.9	
Performance status at transplantation	Good	93.9	Good	92.5	0.471
	Poor	6.1	Poor	7.5	
Graft type	BM	2.0	BM	0.8	Not valid
	BM/PBSC	1.1	BM/PBSC	1.5	
	PBSC	96.9	PBSC	97.7	
Total body irradiation included in conditioning	Yes	7.8	Yes	9.1	0.44
	No	92.2	No	90.9	

CR: complete remission, PR: partial remission; NR/MR: no response or minimal response; Rel/prog: relapse or progression; BM: bone marrow; PBSC: peripheral blood stem cells.

Survival post-transplantation

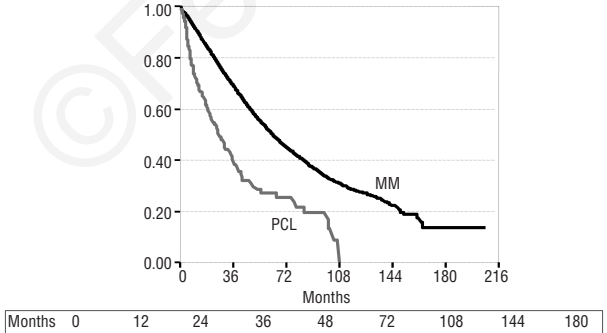
The median post-transplant overall survival for the myeloma patients was 62.3 months (CI, 60.4–64.3 months) and for the PCL patients 25.7 months (CI, 19.5–31.9 months) (P=0.000), as shown in Figure 2. The proportion of myeloma patients surviving at 1 year was 89.6% (CI, 89.2–90.1%), at 2 years 79% (CI, 78.3–79.6%), at 3 years 69% (CI, 68.2–69.9 %), at 5 years 51.6% (CI, 50.5–52.7%) and at 10 years 28% (CI, 26.2–30%). The proportion of PCL patients alive at 1 year was 69.3% (CI, 63.4–75.7%), at 2 years 54.1% (CI, 47.3–61.8%), at 3 years 39.5% (32.3–48.2%), and at 5 years 27.2 (20.2–36.8%).

The median overall survival was not significantly different whether patients did or did not achieve complete remission in either of the groups. For the myeloma group, the median overall survival was 59 *versus* 61 months for patients who did or did not achieve complete remission, respectively, in the first 100 days post-transplant (HR, 0.91; CI, 0.82–1.01). For the PCL group, the median overall survival was 21 *versus* 30 months for those who did or did not achieve complete remission, respectively (HR, 0.77; CI, 0.46–1.29).



Months	0	12	24	36	48	72	108	144	180
MM	20,844	4,837	2,477	1,392	770	279	51	15	1
PCL	272	32	13	8	4	2			

Figure 1. Complete response after autologous transplantation in multiple myeloma (MM) and plasma cell leukemia patients (PCL). Probability of complete response at 100 days post-transplant in MM was 28.2% and in PCL 41.2% (P=0.000).



Months	0	12	24	36	48	72	108	144	180
MM	20,844	12,196	8,221	5,650	3,772	1,524	328	44	3
PCL	272	123	76	42	25	14			

Figure 2. Overall survival after autologous transplantation in multiple myeloma (MM) and plasma cell leukemia patients (PCL). Median overall survival 62.3 months for MM and 25.7 months for PCL patients (P=0.000).

Non-relapse mortality

The higher overall mortality in the PCL group was partially accounted for by increased non-relapse related mortality in this group compared to in the myeloma group (P<0.0001). A review of available data at 100 days, 1 year and 2 years showed a higher rate of infectious deaths in PCL patients but the database does not indicate whether this was related to concomitant relapse. Following their autologous transplant a higher proportion of PCL patients (10.3%) than myeloma patients (5.3%) received an allogeneic transplant; not unexpectedly these patients seemed to have a higher rate of transplant-related mortality.

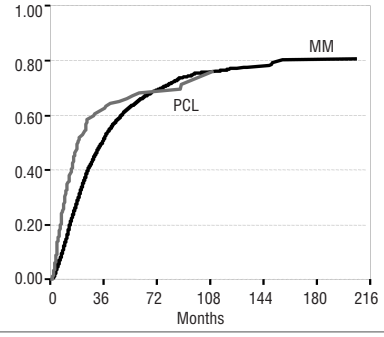
Relapse in patients with plasma cell leukemia

Post-transplant response in PCL patients was typically of short duration. The median progression-free survival was 14.3 months for PCL patients, compared to 27.4 months for patients with multiple myeloma (P=0.0000), as shown in Figure 3.

Discussion

PCL is a rare plasma cell dyscrasia with a highly aggressive course and frequent early mortality due to disease progression. There is, therefore, scant literature on the disease, particularly with regard to therapeutic options. Most clinical data are derived from case reports and small series, with only three reviews featuring at least 25 cases.[1,2,7] This study of patients undergoing first autograft, including 272 PCL and 20844 multiple myeloma patients, therefore comprises the largest series of patients with PCL described to date.

Our data largely accord with those of previous observers, who have noted that PCL at presentation is more frequently associated than multiple myeloma with advanced disease stage, marrow failure, raised β_2 microglobulin and renal impairment.[1,2,7] Although primarily a transplant study, the median age of 55 years of the PCL patients in this study reflects the reported median age range of 53 to 57 years,[8] which is approximately 10 years younger than the median age of patients with multiple myeloma at presentation.[9] Lytic bone disease is less com-



Months	0	12	24	36	48	72	108	144	180
MM	20,844	10,531	5,811	3,453	2,053	751	143	22	2
PCL	272	102	48	30	17	8	1		

Figure 3. Progression-free survival after autologous transplantation in multiple myeloma (MM) and plasma cell leukemia (PCL) patients. Median progression-free survival was 14.3 months in PCL and 27.4 months in MM (P=0.000)

mon than in multiple myeloma,[8] and has been related by one author to the lower expression of malignant plasma cells in PCL of CD56 or neural cell adhesion molecule; it has been suggested that CD56 may facilitate formation of nodules of plasma cells which may prove more aggressive to bone trabeculae and that plasma cells with weak CD56 expression favor leukemic expansion.[10]

PCL has been compared to acute leukemia, requiring urgent control of clinical manifestations, and responding better to increased intensity polychemotherapy than to conventional melphalan-based therapy. Intensification of therapy using high dose melphalan was reported in PCL around the same time as application of this regime in multiple myeloma.[11] There have been several case reports[12-17] as well as descriptions of one[2] and five[1] patients in two previously reported series of patients with PCL describing the value of melphalan or other high-dose therapy when combined with autologous transplantation. In general, patients received induction with aggressive combination chemotherapy and the median survival after autografting ranged from 3 to 59 months.

In this, the first large series of patients with PCL treated with high-dose therapy and autologous transplantation, it appears that autologous transplantation produces modest improvement of outcome by consolidation of the response to polychemotherapy, though durable responses are uncommon. Nevertheless, overall survival of this cohort of PCL patients is markedly inferior to the comparative group of myeloma patients, despite their younger age, similar performance status, shorter period from diagnosis to transplantation and likely pre-selection through early mortality from complications of the disease or therapy. This is in part due to higher transplant-related mortality, particularly in the early post-transplant period. The reasons for the higher transplant-related mortality in PCL patients compared to in myeloma patients are not clear but may be related to tissue damage inflicted by the aggressive early course of the disease, causing a higher rate of infectious complications; furthermore, it is noted that the rate of allogeneic transplantation in PCL patients is approximately twice that in myeloma patients and that complications associated with allogeneic transplantation seemed very frequent.

The shorter overall survival of PCL patients compared to myeloma patients is in contrast to the higher post-autograft complete remission rate in the former group. It is, however, clear that many of the complete remissions obtained are of short duration with rapid relapse of disease. Success of initial therapy in PCL has been previously reported as dependent upon rapid clearance from the peripheral blood of circulating plasma cells and failure to clear such plasma cells identified unresponsive disease.[1] This suggests that achievement of a low disease burden is necessary for durable response but that complete remission, as defined by conventional criteria, is associated with an appreciable burden of minimal residual disease in many PCL patients after autografting. This is in keeping with our finding that achievement of complete remission by 100 days does not have a significant impact on the overall survival of PCL patients and is also supported by existing reports on PCL patients treated with autologous transplantation. We accept that our use of landmark analyses on day 100 may be to the disadvantage of myeloma patients who may not achieve complete remission until 6 months or later; however, the use of a later time for these analyses would lead to an underestimation of the relapse rate in PCL. Hovenga *et al.*[13] reported on a patient who achieved complete remission as assessed by conventional means but who relapsed 3 months after an autograft, while other authors described patients surviving for more than 11 months,[15] more than 24 months,[16] and 59 months[17] but found to be in molecular remission post-transplantation.

Various causes for the aggressive nature of PCL compared to myeloma have been suggested, including the high incidence of poor prognosis cytogenetic factors, such as hypodiploidy, chromosome 13, or complex cytogenetic abnormalities[2] and mutations of the *NRAS*, *KRAS*[18,19] and *P53* oncogenes.[19,20] Identification of these variables is outside the range of this study due to limitations of registry data but our results highlight the need for further investigation of disease etiology, in the hope that novel therapeutic strategies can be identified. While rapid reduction in tumor mass appears key to achieving disease control, adequate consolidation of response is likely to require further intensification than provided by a conventional autograft. Tandem autotransplantation may have a role but has been reported as relatively ineffective in myeloma with chromosome 13 abnormalities,[21] which are reported in 70-80% of PCL cases. Allogeneic transplantation offers the possibility of enhanced intensity and a graft-*versus*-plasma cell effect, but must be approached with caution in view of the higher non-relapse mortality seen in PCL after a single autograft. Reduced intensity allogeneic transplantation may improve the non-relapse mortality, but it is unclear whether the aggressive nature of PCL will lead to early loss of disease control.

Another possible approach, after autografting or combined with more intensive options, is the use of maintenance therapy. Suitable drugs include interferon, which has been described to prolong remissions in myeloma following autografting.[22,23] Malignant cells are more frequently CD20-positive in PCL than in myeloma[2] which may indicate a role for anti-CD20 monoclonal antibody in initial or maintenance therapy. Thalidomide has been used in induction therapy alone and in combination[24] and may be a useful maintenance agent after autologous transplantation. Responses to antibody to interleukin-6 have been reported in patients with advanced PCL.[25,26] Newer anti-myeloma agents, including the group of immunomodulating drugs and proteasome inhibitors, also offer promise, with one small series reporting responses in four patients.[27] Interestingly, this series included a patient who experienced tumor lysis syndrome, which was also described in one case report.[28] In conclusion, our series highlights inadequacies in the current management of PCL and emphasizes the need for new and cooperative approaches to this rare but highly aggressive disorder.

Authorship and Disclosures

MBD designed the study, analyzed the statistical output and drafted the manuscript. SI performed the statistical analysis and contributed to the interpretation of data and drafting the manuscript. AvB prepared the data set for analysis. CM and JFA conceived the study and CM contributed to drafting the manuscript.

All authors reviewed the manuscript and reported no potential conflicts of interest.

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