Plasma cell leukemia: another piece of the puzzle

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Primary plasma cell leukemia (pPCL) is the most aggressive plasma cell neoplastic disorder. It is characterized by intrinsic genomic instability, high proliferative activity, and co-existence of multiple, adverse clinical and laboratory features, which result in a poorer outcome when compared to that of multiple myeloma.[1] The introduction of proteasome inhibitors and immunomodulatory drugs into the treatment of pPCL has produced significant increases in overall (54-90%) and complete response (12-47%) rates compared to those achieved with previous "conventional" chemotherapy, although inducing only a moderate improvement in median overall survival (approximately 1 year for older patients, and 3 years for those who receive transplants).[1-5]

In this issue of *Haematologica*, Lawless and co-workers report an updated, retrospective European Blood and Marrow Transplantation Group (EBMT) analysis of 751 pPCL patients transplanted between 1998 and 2014, comparing four frontline transplant strategies: single autologous stem cell transplantation (auto-SCT), single allogeneic stem cell transplantation (allo-SCT), or a combined transplant, either tandem auto-SCT/allo-SCT or double auto-SCT (Table 1A, B).[6] With a median follow-up of approximately 4 years, the median progression-free survival and overall survival of all patients, irrespective of transplant type, were 14 and 33 months, respectively (Table 1A, B).

Three former retrospective registry studies in transplant-eligible patients, two from the EBMT and one from the Center for International Blood and Marrow Transplant Research (CBMTR), evaluated 780 pPCL patients undergoing auto-SCT between 1980 and 2009 (therefore with a limited use of novel agents)[7-9] (Table 1A). These surveys showed higher complete response rates in pPCL than in multiple myeloma, but also that auto-SCT was less effective in the long term due to increased non-relapse-related mortality and short duration of post-transplantation response. In particular, in the EBMT studies, the median overall survival was 26 months, while in the CBMTR study, 3-year overall survival was 56% *versus* 84% after single and double auto-SCT, respectively. More recently and expectedly, a positive effect on overall survival has been reported for maintenance therapy,[2,3] low-risk cytogenetics and achievement of complete remission after auto-SCT.[4] Two of the EBMT and CBMTR studies also compared allo-SCT in 112 patients, transplanted between 1995 and 2009, with similar populations treated with auto-SCT (Table 1B). The cumulative incidence of relapse was lower after allo-SCT than after auto-SCT, but the risk of non-relapse mortality was much higher, without any evidence of survival benefit. In the EBMT study overall survival at 5 years was 19% after reduced-intensity conditioning and 27% after myelo-ablative conditioning.[9] In the CBMTR study, 5-year overall survival following allo-SCT was 39% (32% for those undergoing myelo-ablative conditioning, 56% for those given reduced intensity conditioning).[8] A plateau phase at 20% was observed.

More recently, on behalf of the CBMTR, Dhakal *et al.* retrospectively reviewed 348 patients with pPCL receiving auto-SCT (n=277) or allo-SCT (n=71) between 2008 and 2015, thus after the introduction of novel drugs (Table 1A, B).[5] Four years after allo-SCT or auto-SCT the progression-free survival (19% *vs*. 17%), non-relapse mortality (12% *vs*. 7%), relapse rate (69% *vs*. 76 %) and overall survival (31% *vs*. 28%) were similar in the two groups, confirming no differences in outcome.

Notably, only two prospective trials have been published regarding transplant-eligible pPCL patients, one by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA)[10] and one by the Intergroupe Francophone du Myelome (IFM).[11] Lenalidomide + demamethasone or alternating bortezomib, doxorubicin, dexamethasone (PAD)/bortezomib, cyclophosphamide, dexamethasone (VCD) induction, followed by low-dose lenalidomide or alternate bortezomib, lenalidomide, dexamethasone (VRD)/lenalidomide maintenance after auto-SCT were used, respectively. With a median follow-up of 34 and 28 months, the median overall survival was not reached after single or double auto-SCT in either study (Table 1A), while it was 36 months in the IFM trial patients with a suitable donor, who were planned to undergo auto-SCT followed by reduced intensity conditioning allo-SCT (Table 1B).

What, therefore, does the new EBMT study add to our knowledge (Table 1A, B)? Albeit with several important limitations that the authors correctly report, the study by Lawless *et al.* sheds some light on an important, still

Table 1. Selected studies evaluating the role of autologous (A) and allogeneic (B) stem cell transplantation in primary plasma cell leukemia. Excluding the GIMEMA and IFM prospective trials, all other reports are retropective, registry studies.

A

Auto-SCT	N of patients (median age in years)	Study group (period of analysis)	NRM	PFS	OS
Lawless *et al.*[6°] (current study)	Total 559 Single 442 (58.8) Double 117 (58.7)	EBMT (1998-2014)	Frontline auto-SCT NRM=7.3%	Frontline auto-SCT mPFS=14.3 months Frontline auto-SCT 5-year PFS=14.3%	Frontline auto-SCT mOS= 33.5 months Frontline auto-SCT 5-year OS=31.3%
Drake *et al.*[7]*	272 (55)	EBMT (1980-2006)	Unspecified, but reported as increased with respect to registered myeloma patients	mPFS=14.3 months	mOS=25.7 months 1-year OS=69.3% 3-year OS=39.5% 5-year OS=27.2%
Morris *et al.*[9]*	411 (55.9)	EBMT (1984-2009)	Unspecified, but reported lower than in 62 similar pPCL patients undergoing allo-SCT	1-year PFS= 51% 5-year PFS= 10%	1-year OS= 73% 5-year OS= 25%
Mahindra *et al.*[8]**	Total 97 (56) Single 68 Double 25	CIBMTR (1995-2006)	3-year NRM=5%	3-year PFS=34% Single=36% Double=37%	3-year OS=64% Single=56%, Double=84%
Dakhal *et al.*[5]	Total 277 (60) Single 249 Double 28	CIBMTR (2008-2015)	Cumulative 4-year NRM =7%	Cumulative 4-year PFS=17%	Cumulative 4-year OS=28%
Musto *et al.*[10§]	Total 8 (58) Single 4 Double 4	GIMEMA (2009-2011)	Cumulative NRM=0%	Cumulative mPFS=27 months	Cumulative OS=NR
Royer *et al.*[11^] (2010-2013)	7 (57)	IFM (2010-2013)	NA	mPFS=NR	mOS=NR

B

Allo-SCT	N of patients (median age in years)	Study group (period of analysis)	NRM	PFS	OS
Lawless *et al.*[6°] (current study)	Single allo-SCT 70 (47.2) Tandem auto-SCT/allo-SCT 122 (51.6)	EBMT (1998-2014)	Frontline allo-SCT NRM=27%	Frontline allo-SCT mPFS =11.7 months Frontline allo-SCT 5-year PFS=19.9%	Frontline allo-SCT mOS= 17.5 months Frontline allo-SCT 5-year OS= 34.6%
Mahindra *et al.*[8]	Total 50 (48) MAC 34 NMA/RIC 16	CIBMTR (1995-2006)	3-year NRM MAC=41% NMA/RIC= 42%	3-year PFS=20% MAC=21% NMA/RIC=18%	3-year OS=39% MAC=32% NMA/RIC=56%
Morris *et al.*[9]	Total 66 MAC 49 (45.9) RIC 17 (52.9)	EBMT (1998-2009)	Unspecified, but reported higher than in 411 similar pPCL patients undergoing auto-SCT	1-year PFS MAC=39% RIC =43% 5-year PFS MAC=19% RIC=11%	1-year OS MAC=46% RIC=59% 5-year OS MAC=27% RIC =19% Plateau phase seen at 20%
Royer *et al.*[11°°]	16 (57)	IFM (2010-2013)	NRM=12%	mPFS=17.9 months	mOS=36.3 months
Dakhal *et al.*[5]	Total. 71 (56) Single allo-SCT 43 Tandem auto-SCT/allo-SCT 28	CIBMTR (2008-2015)	Cumulative NRM=12%	Cumulative 4-year PFS=19%	Cumulative 4-year OS=31%

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*Single auto-SCT. **Four patients underwent tandem auto-SCT/allo-SCT. §Prospective study with a median follow-up of 34 months. ^Prospective study with a median follow-up of 28.7 months; all patients received double auto-SCT. °Frontline auto-SCT included single auto-SCT, double auto-SCT and tandem auto-SCT/allo-SCT. Comparing single and double/tandem transplant procedures, patients undergoing frontline allo-SCT had the greatest risk of death in the first 100 days (but not later). Being transplanted in complete remission conferred significant benefit for both progression-free survival and overall survival after double auto-SCT, with respect to after single auto-SCT. Tandem auto-SCT/allo-SCT positively influenced progression-free survival (but not overall survival) in patients not achieving complete remission after induction therapy. °°Prospective study with a median follow-up of 28.7 months; all patients received tandem auto-SCT/allo-SCT. Allo-SCT: allogeneic stem cell transplantation; auto-SCT: autologous stem cell transplantation; CIBMTR: Center for International Blood and Marrow Transplant Research; EBMT: European Group for Blood and Marrow Transplant; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; IFM: Intergroupe Francophone du Myélome; MAC: myeloablative conditioning; mOS: median overall survival; mPFS: median progression-free survival; NA: not available; NMA/RIC: non-myeloablative/reduced intensity conditioning; NR: not reached; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; pPCL: primary plasma cell leukemia; RIC reduced intensity conditioning.

unmet clinical need. Given that all previous studies clearly demonstrate the need for transplant(s) in pPCL patients who are eligible for such a procedure, which is the best option to use? Based on the data presented, the answer seems to be quite (and perhaps unexpectedly) clear, helping to guide clinical decisions on transplant strategy.

First, the allo-SCT group had a lower relapse rate, but also a remarkable non-relapse mortality (particularly during the first 100 days) that, overall, negatively affected both progression-free and overall survival, at least for the first 2-3 years after transplantation. Interestingly, a plateau phase involving approximately a quarter of patients seemed to be present after 5 years. Although still based on a limited number of patients, this last observation constitutes a not negligible result in terms of a possible “cure” of the disease, which would warrant being discussed very thoroughly with eligible patients.

Regarding tandem transplant strategies, double auto-SCT represented an effective option for patients achieving complete remission prior to their first transplant, while, on the other hand, tandem auto/allo-SCT reduced the short-term risk of non-relapse mortality following first-line single allo-SCT and showed a significant overall survival benefit when compared to single auto-SCT and double auto-SCT in patients without a complete response prior to the transplant. Thus, in these patients, disease status at the time of transplant may influence the outcome significantly. This is another important message for clinical practice, suggesting that the results achieved with transplant strategies may depend upon the efficacy of induction treatment. As a consequence, highly active initial therapies should be pursued before proceeding with transplant procedures.

According to currently available recommendations,[12] first-line therapy for younger, transplant-eligible pPCL patients, should be oriented toward a short (2-3 cycles) induction phase with proteasome inhibitor and immunomodulatory drug-based triplet, considering the addition of chemotherapy (i.e. hyperfractionated cyclophosphamide, vincristine, doxorubicin, and prednisolone [hyper-CVAD] or cisplatin, doxorubicin, cyclophosphamide, and etoposide [PACE]) if rapid cytoreduction is required. The treatment should include double auto-SCT, consolidation, and maintenance therapy. The pros and cons of possible frontline allo-SCT should be carefully discussed with eligible patients, who are younger individuals with poor prognostic characteristics at baseline and have achieved a good response to first-line induction.

However, the paradigm of first-line treatment in multiple myeloma is changing rapidly and, as a consequence, pPCL therapy will probably change as well, including new drugs (particularly monoclonal antibodies) in induction and in maintenance therapies after auto-SCT. In this setting, mature results of the recently concluded phase II, EMN12/HOVON129 study for newly-diagnosed pPCL, exploring carfilzomib and lenalidomide-based induction/maintenance therapy, integrated with double auto-SCT or tandem auto/allo-SCT in eligible patients, are eagerly awaited. Venetoclax, an oral inhibitor of BCL-2, may also represent an attractive option, either as a single agent or in combination with novel drugs, for patients with pPCL, given the high prevalence (30-50%) of the t(11;14) in the background of complex genomic characteristics in this population. Highly active new immunotherapies, currently employed in advanced multiple myeloma, such as chimeric antigen receptor T cells, and immuno-conjugated or bispecific antibodies, also warrant investigation for a desirable early use in the setting of pPCL. Further treatments, possibly based on recently recognized genomic characteristics of pPCL, could also be identified. Finally, the emerging role of measurable residual disease in multiple myeloma could be similarly useful in pPCL, i.e., for directing patients toward autologous and/or allogeneic procedures, in the near future.

On this basis, pPCL patients should always be considered for a clinical trial. As a rare disease, pPCL is, however, often excluded from studies performed in multiple myeloma. The new International Myeloma Working Group’s definition of pPCL, lowering the circulating plasma cells from 20% to 5%,[13] seems to be one correct move to meet the goal of broader clinical trial availability for pPCL patients in great need of better therapies. It is therefore hoped that these patients will be enrolled in future multiple myeloma trials, with devoted endpoints, predefined plans to extrapolate specific data, and *ad hoc* analyses for pPCL populations. Such approaches could provide novel biological and clinical information in a short time, which would be useful to speed up the journey along the “long and winding road” of pPCL management.

Disclosures

No conflicts of interest to disclose.

Contributions

PM and RW wrote the manuscript.

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