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Comparison of autologous and allogeneic hematopoietic cell transplantation strategies in patients with primary plasma cell leukemia, with dynamic prediction modelling

Sarah Lawless*[1], Simona Iacobelli*[2], Nina Simone Knelange[3], Patrice Chevallier[4], Didier Blaise[5], Noel Milpied[6], Roberto Foà[7], Jan J. Cornelissen[8], Bruno Lioure[9], Ruben Benjamin[10], Xavier Poiré[11], Monique C. Minnema [12], Matthew Collin[13], Stig Lenhoff[14], John A. Snowden[15], Stella Santarone [16], Keith M. O. Wilson[17], Fernanda Trigo[18], Peter Dreger[19], Lara H. Böhmer[20], Hein Putter[21], Laurent Garderet[22], Nicolaus Kröger[23], Ibrahim Yaukoub-Agha[24], Stefan Schönland[25], Curly Morris[26].

*Denotes equal contribution to the manuscript

[1]Belfast City Hospital, Belfast, Northern Ireland, [2]Tor Vergata University, Rome, Italy, [3]EBMT Data Office Leiden, Leiden, The Netherlands, [4]CHU Nantes, Nantes, France, [5]ICRCM, INSERM, CNRS, AMU and Institut Paoli Calmettes, Marseille, France, [6]CHU Bordeaux, Pessac, France, [7]Univ.`La Sapienza`, Rome, Italy, [8]Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [9]Nouvel Hopital Civil, Strasbourg, France, [10]Kings College Hospital, London, UK, [11]Cliniques Universitaires St. Luc, Brussels, Belgium, [12]University Medical Center, Utrecht , Utrecht, The Netherlands, [13]Freeman Hospital, Newcastle, UK, [14]Skanes University Hospital, Lund, Sweden, [15]Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK, [16]Ospedale Civile, Pescara, Italy, [17]University Hospital of Wales, Cardiff Wales, UK, [18]Hospital Sao Joao, Porto, Portugal, [19]University of Heidelberg, Heidelberg, Germany, [20]Haga Teaching Hospital The Hague, The Netherlands, [21]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands, [22]Hospital

Saint Antoine, Paris, France, [23]University Hospital Eppendorf, Hamburg, Germany, [24]CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000 Lille, Lille, France, [25]University of Heidelberg, Heidelberg, Germany, [26]Queens University of Belfast, Belfast, Northern Ireland.

Corresponding Author:

Dr Stefan Schönland

University of Heidelberg, Heidelberg, Germany

Stefan.Schoenland@med.uni-heidelberg.de

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Abstract

Primary Plasma Cell Leukaemia (pPCL) is a rare and challenging malignancy. There is limited data regarding optimum transplant approaches. Therefore we undertook a retrospective analysis from 1998-2014 of 751 patients with Primary Plasma Cell Leukaemia (pPCL) undergoing one of four transplant strategies; single autologous transplant (single-auto), single allogeneic transplant (allo-first) or a combined tandem transplant either auto-allo or auto-auto. To avoid time bias multiple analytic approaches were employed including Cox models with time dependent covariates and dynamic prediction by landmarking. Initial comparisons were made between patients undergoing allo-first (n=70) versus auto first (n=681), regardless of subsequent administration of second transplant. The allo-first group had lower relapse rate (45.9%, 95%CI 33.2-58.6 vs. 68.4%, 64.4-72.4) but higher NRM (27%, 95%CI 15.9-38.1 vs 7.3%, 5.2-9.4) at 36 months.

Allo-first had remarkably higher risk in the first 100 days for both OS and PFS. Auto-allo (n=122) had no increased risk in the short term and significant benefit in PFS post-100 days compared to single auto (HR 0.69, 95%CI: 0.52- 0.92, p=0.012). Auto-auto (n=117) was an effective option for patients achieving CR prior to first transplant, whereas in patients without CR prior to transplant our modelling predicted that auto-allo was superior.

This is the largest retrospective study reporting on transplant in pPCL to date. We confirm significant mortality risk within the first 100 days for allo-first and suggest that tandem transplant strategies are superior. Disease status at time of transplant influences outcome, this knowledge may help guide clinical decisions on transplant strategy.

Introduction

Primary Plasma Cell Leukemia (pPCL) is a rare plasma cell disorder. It follows an aggressive clinical course with a median survival of 1-3 years[1.] Compared with multiple myeloma, pPCL is more likely to present with extramedullary involvement, thrombocytopenia, hypercalcemia, elevated serum β_2-microglobulin and lactate dehydrogenase levels[2]. Due to the infrequent incidence and fulminant course of pPCL, there is a paucity of prospective data to guide clinicians managing this challenging disorder.[3,4, 5.]

Analysis of the Surveillance, Epidemiology, and End Results (SEER) database of 445 pPCL patients between 1973 and 2009 shows an improvement in survival in recent years[5]. The use of novel agents bortezomib[6,7,8,9,10] and lenalidomide[11] have been shown to be effective in pPCL either alone or in combination[12,13,14,15] and may account for some of the improvements seen in recent years. Many of these reports also confirm the benefit of consolidation with hematopoietic stem cell transplantation (HSCT), although all modalities of transplantation including autologous, allogeneic and tandem approaches were generally considered together. Nevertheless, survival outcomes in pPCL patients in the SEER study are still inferior in comparison with multiple myeloma patients diagnosed during the same period when adjusted for gender and age[5].

The EBMT reported on the outcomes of 272 patients with pPCL undergoing autologous hematopoietic stem cell transplant (auto)[16]. This study confirmed that auto can improve outcome, but results were markedly inferior to those achieved in

patients with multiple myeloma. The CIBMTR have also demonstrated improvement in PFS and OS in pPCL following auto[17].

However, the role of allogeneic hematopoietic stem cell transplantation (allo) remains uncertain. In 2012 the CIBMTR compared outcomes of 147 patients undergoing auto or allo transplant between 1995-2006 and demonstrated that while allo patients had significantly lower relapse rates, their non-relapse mortality (NRM) was significantly higher with no overall survival (OS) benefit at 3 years[17].
In 2020 the CIBMTR reported a further analysis of 348 patients with pPCL transplanted between 2008-2015. An increase in HCT utilization was noted from 12% in 1995 to 46% in 2009 but outcomes remain poor with no increase in OS in the allo group when compared with their previous study[18].

This study utilized the largest cohort of patients with pPCL (751) undergoing HSCT to examine various transplantation strategies and determine how these may be of most benefit. This study included auto, allo and tandem transplants. To make statistically valid comparisons in this retrospective comparison of transplant strategies, nonstandard statistical methods were employed including the use of Dynamic Prediction Modelling.

Methods

A retrospective analysis was undertaken of the EBMT experience of patients with pPCL undergoing transplantation between 1998 and 2014. Only patients who had achieved Complete Response (CR), Partial Response (PR), Very Good PR (VGPR) or Stable Disease (SD) prior to transplantation were included. The objective was to compare patients undergoing a single autologous transplant (auto), a single allogeneic transplant (allo first) or a combined tandem approach with an allogeneic transplant following an autologous transplant (auto-allo) or a tandem autologous transplant (auto-auto) as consolidation in first line treatment. Tandem transplants were defined as given within 9 months in absence of disease progression. The main endpoints of interest were Overall Survival (OS) and Progression-Free Survival (PFS). Additionally we have illustrated Cumulative Incidence of Relapse (CIR) and Non-Relapse Mortality (NRM), and acute and chronic Graft Versus Host Disease (GvHD). The problem and approaches used to compare transplant strategies are illustrated in the Statistical Methods section and in the Supplement.

This study was conducted on behalf of the Chronic Malignancies Working Party (CMWP) of the EBMT. The EBMT represents more than 500 transplantation centres in and beyond Europe, which report minimum essential data on all transplants into a central database. EBMT Centres commit to obtain informed consent according to the local regulations applicable the time of transplantation in order to report pseudonimysed data to the EBMT. The study was planned and approved by the Chronic Malignancies Working Party of the EBMT. In addition, the study protocol

was approved by the institutional review board at each site and complied with country specific regulatory requirements. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Statistical Methods

Events for OS and PFS were death for any cause and the first between death and progression respectively. The occurrence of Relapse or Progression and of death were analysed as mutually competing (generating CIR and NRM cumulative incidence curves). For GvHD the traditional definitions of Acute and Chronic occurring respectively within and after 100 days from allogeneic transplantation were used; relapse or progression and death were considered competing events. The standard methods indicated in the EBMT Statistical Guidelines[19] were applied for comparing groups according to the type of first transplantation. Different approaches were applied for the comparison of single and tandem transplant strategies to avoid the risk of time bias of a retrospective analysis (Supplementary Material 1). A traditional landmark analysis was presented as a secondary analysis (Supplementary Material 3) as it provides a partial view with some important limitations. An alternative landmark propensity score matched comparison (not shown) returned the same conclusions. The main analysis was done by Cox models including time-dependent covariates for the administration of the second transplant. Additionally, it was necessary to correct for the time-varying effect of an allogeneic transplant (both when given as first or as tandem) due to the higher early mortality. For simplicity, this time-dependent effect was modelled as being a stepwise constant in two periods measured from the time of allo transplant: from day 0 to day 100

("recent allo") and after 100 days ("past allo"). The effects of the transplant strategies are thus measured as Hazard Ratios (HR) with respect to single auto as baseline group (as seen in Table 4). Candidate adjustment factors for the models were patient sex, age, disease status and performance status at first transplant, time from diagnosis to first transplant, calendar year; only age and disease status were retained in the final models. A further insight on the effects on the probabilities of OS and PFS was obtained applying a method of dynamic prediction (Supplementary Material 4), illustrating the evolution during the first 36 months of follow-up of the conditional 3-yrs OS and 1-yr PFS (as seen in Figure 2). We applied the method of dynamic prediction by landmarking described by van Houwelingen and Putter[20] based on Cox models with the same structure for the effects of the transplant strategies and the same adjustment factors as the main analysis. A second set of dynamic prediction curves (as seen in Figure 3) was based on Cox models including interactions between patient's characteristics and type of transplant strategy.

Results

A total of 751 patients were included in our analysis. The Median OS of all patients irrespective of transplant type was 33 months and PFS 14 months respectively. The median follow up was 48.8 months.

Transplant strategies

Seventy patients received an allo-first and 681 patients received an auto as first transplant. With respect to tandem strategies 122 patients proceeded to a tandem auto-allo and 117 underwent tandem auto-auto leaving 442 patients receiving a single auto only.

Comparison of Auto versus Allo as first transplant

Initial comparisons were made between patients undergoing allo-first versus first auto (regardless of subsequent administration of second transplant). Characteristics are reported in Table 1. Patients having allo-first were predominantly male, significantly younger (median age 47.2 years versus 57.7 years for first auto, $p<0.001$), had a longer time from diagnosis to transplant ($p=0.005$) and a significantly higher proportion of patients both in CR and SD ($p<0.001$). The median OS was 17.5 months for allo-first versus 33.5 months for first auto, while the median PFS was 11.7 months for allo-first and 14.3 months for first auto (Fig1). The curves showed a clear crossing so that at 60 months the OS and PFS probabilities were roughly similar (OS: Allo 34.6% (95%CI 21.6 - 47.6), Auto 31.3% (95%CI 26.8 - 35.9); PFS: Allo 19.9% (95%CI 8.9 - 30.9), Auto 14.3% (95%CI 10.9 - 17.6)). Notably the NRM (Fig1 (d)) was 27% (95%CI 15.9-38.1) at 36 months for allo versus 7.3% (95%CI 5.2-9.4) for first auto while CIR at 36 months was lower in the allo-first group (45.9%, 95%CI 33.2-58.6) than in the auto group (68.4%, 95%CI 64.4-72.4).

Comparison of single and tandem transplant strategies

Characteristics of patients grouped according to the actual transplantations received are illustrated in Tables 2 and 3. Patients receiving a tandem auto-allo were slightly older and had shorter time from diagnosis to transplant and a higher proportion of matched unrelated donor transplants and reduced intensity conditioning than those who had allo-first (Table 3). They were also predominantly females and younger than the other patients with first auto.

The characteristics of allogeneic transplantations given as first transplant or as tandem auto-allo are shown Table 3. As previously noted, the administration of allo as first or second transplant was different in several characteristics. TBI was administered more frequently to allo-first patients than auto-allo patients if standard conditioning was used (47.1% allo-first versus 29.2% auto-allo), whereas TBI was given more frequently in auto-allo than allo if reduced intensity conditioning was used (42.3% allo-first versus 11.1% auto-allo).

Any differences in conditioning did not translate into any meaningful difference in GvHD. Table S1 (supplementary material) shows the incidence of acute and chronic GvHD which appears similar to that seen in patients receiving allo first or auto- allo. Only 13 patients who received an allo underwent DLI. They all belonged to the allo-first group. The median time to DLI was 5.7 months (range 2.7-46.1) with 6 patients receiving it before relapse and 7 patients receiving it post relapse.

In a preliminary approach, landmark analyses at 4 months were undertaken for OS, PFS, CIR and NRM (Supplementary Material 3; Fig S1) which showed no significant discrimination between transplant strategies, except a remarkably higher NRM for allo-first.

Due to the limitations of landmark analysis the main analysis was done using Cox models for OS and PFS. With single-auto as baseline, comparisons were made with first-allo, tandem auto-auto and tandem auto-allo, adjusting for age and disease status (Table 4). It can be seen that allo-first has the greatest risk in the first 100 days (OS: HR 5.74, 95%CI 2.66-12.40 $p<0.001$; PFS: HR 2.84, 95%CI 1.57-5.15

p=0.001). Being transplanted in CR conferred a significant benefit while the effect of being younger at transplantation may also conferred benefit. With consideration of the time-dependent effect after 100 days allo-first becomes comparable with other strategies. Tandem auto-allo had significant benefit in PFS after 100 days when compared to single-auto with a reduction of risk by 70% (HR 0.69, 95%CI: 0.52-0.92, p=0.012). Although some protective effect is seen also on OS (HR 0.80, 95%CI: 0.59-1.08, p=0.148), this did not reach significance. For auto-auto the HR for PFS and OS are also reduced (models without interactions: HR 0.81 95%CI: 0.61-1.08 p=0.114 and 0.86 CI: 0.67-1.11, p=0.254) respectively.

Conditional OS and PFS Probabilities

The difference of outcome of the 4 transplant strategies was further illustrated by dynamic prediction curves (Supplementary Material 4). Figures 2 (a) and (b) show respectively the projected 3-yrs OS and 1-year PFS starting from any time during the first 36 months for a 55 year-old patient not in CR at the time of first transplant (these being the median and the mode respectively of the two characteristics), according to the transplant strategy given. While it is clear that the OS outlook for the allo-first patients surviving the first 100 days is at least as good (or better) than any other strategy the high initial NRM is of concern. It can be seen that for 3-year OS there is no marked difference with respect to the transplant strategy used. A single auto is the least attractive option and is marginally improved by a second transplant, although the 1-year PFS is improved to a greater extent by an auto-allo than an auto-auto approach.

Effect of CR

Further modelling detected an interaction of the disease status with the transplant strategy auto-auto both for OS and for PFS (Table 4, last two lines; Figures 3 (a) and (b)). It can be seen that being in CR at first transplant corresponded to a marginal benefit when combined with an auto-allo strategy (orange curves) whereas CR at first transplant was of great benefit if employing an auto-auto strategy (green curves).

Discussion

Despite the improvements brought about by the use of novel agents pPCL remains a challenging disorder for clinicians to manage. This retrospective study provides evidence to help guide transplanting physicians in their decision-making process and offer patients an approach most suited to their circumstances following effective induction therapy.

Tandem transplants, both auto-auto and auto-allo have been used in multiple myeloma for the past two decades but without great clarity on their place in the treatment paradigm. Two major prospective studies of patients responding to therapy for newly diagnosed multiple myeloma compared auto-auto to auto-allo[21,22]. Although there was a dramatic improvement in NRM in the auto-allo approach compared an allo-first, this remained significantly higher than in auto-auto and it was only after five years follow-up that an advantage for the auto-allo approach became evident[22,23]. Our study indicates there may be a similar benefit in the auto-allo approach for patients with newly diagnosed pPCL in the longer term, particularly those not in CR at the time of first transplant. We provided curves of the expected conditional probabilities of OS and PFS (using a dynamic prediction approach) to better quantify

the differences in addition to the Hazard ratios provided by the Cox models. The predictions from this model suggests that if patients achieve CR prior to first transplant then auto-auto is an effective option with outcomes similar to auto-allo. This is an attractive option as it avoids the high NRM seen after allo and the potential morbidity and mortality of long-term graft versus host disease. However, if the patient does not achieve CR with induction therapy our model predicts that auto-allo is a superior approach regarding survival.

In one of the few prospective studies in pPCL, the IFM published results on 40 patients examining tandem auto-allo or tandem auto and maintenance therapy[23]. The PFS and OS were better in the tandem auto and maintenance group than in the auto-allo group. Median PFS for tandem auto-allo patients was 18.5 months and 50 months for tandem auto and maintenance group, and median OS was 39.3 months for the tandem auto-allo group and not reached in the tandem auto and maintenance group. Whilst we cannot draw direct comparisons between the IFM study and our findings it can be seen from the overall survival curves (supplementary material S1(a)) that the OS for the auto-allo group is comparable to the median OS in IFM study. The median PFS reported by the IFM is higher than what was observed in our study (supplementary material S1(b)) but the lack of maintenance in our cohort likely accounts for this.

There is growing evidence to indicate the consolidation and maintenance treatment improve PFS and OS in myeloma[24]. Maintenance therapy is now standard of care for patients with myeloma following an autologous transplant. In the IFM study although the data appears encouraging, the number of patients who received maintenance is

too small to draw firm conclusions on the role of maintenance therapy post-transplant in pPCL. This is an important area for future studies to consider and is currently being examined in the phase II EMN12/HOVON129 study, one of the few prospective clinical trials underway in patients pPCL. This trial is exploring the use of carfilzomib and lenalidomide induction (KRd), consolidation and maintenance in patients with pPCL in both young and elderly patients. The results of the first interim analysis included 33 patients under 65 years and 12 patients over 65 years old. It reported that KRd induced deep hematologic responses after 4 cycles of therapy ($\geq$ VGPR in 80% and $\geq$CR in 33%) without early death[25].

Whilst our findings have focused on younger transplant eligible patients the management of older and less fit patients not eligible for transplantation treatment should be scheduled for personalized, continuous treatments, aiming to keep patients on therapy for as long as possible[8].

The initial results from EMN12/HOVON 129 are encouraging regarding efficient and rapid disease control with KRd induction. The importance of bringing pPCL under control early is vital to avoid early mortality in this aggressive plasma cell disorder. Due to the high incidence of t(11;14) translocation in pPCL bcl-2 inhibitors may play a role in pPCL in the near future[26,27]. Monoclonal antibodies such as daratumumab and elotuzumab directed against CD38 and SLAMF7 respectively are currently widely used in multiple myeloma and may have a role in improving CR rates in pPCL as has been shown in multiple myeloma[8]. It is important to improve outcome of pPCL by combining highly effective (targeted) induction therapy to increase the chances of achieving CR prior to first transplant, followed by the selection of the

most appropriate transplant modality in accordance with the findings of the current analysis. Further international trials will be needed to determine the way forward, combining these agents with transplant strategies as outlined above.

As with all registry studies there are drawbacks in this work. The comparison of different transplant strategies could not be done based on information on intent-to-treat, thus although the analyses were adjusted for the main baseline characteristics related to the administration of elective second transplant (by use of Cox models or (not shown) propensity scores matching) we cannot exclude a residual indication bias. The Single Auto group is by construction likely to include all cases who experienced an early relapse, and this could in part account for worse outcome of the group compared to the tandem strategies; however the prevalence of relapse or progression as response post-transplant (Table S3) is limited (3.6%). There was also a wide heterogeneity in treatments, for example for allogeneic transplantation we have described differences in modalities including the use of TBI and DLI. While all of these factors may have relevance the potential number of subgroups generated would render statistical analysis meaningless. On the other hand it is unlikely that for this rare disease a series of interventional prospective studies could be set up to achieve strong evidence in favour of one of the multiple possible strategies. Our study is therefore an important source of background information for future studies. The use of proper statistical methodology to deal with the delayed definition of treatment groups was essential to avoid the time bias typically affecting retrospective comparisons. Additionally, our study did not assess the role of induction or maintenance therapy. However, most patients were unlikely to have received

maintenance treatment after their auto, since their first transplant was performed in 2014 or earlier.

Thus, in conclusion, this study reinforces the significant NRM seen in patients undergoing allo as first transplant. Patients require careful selection and individual risk assessment when considering allo transplant. Our study supports a tandem transplant approach of up front auto followed by either tandem allo or auto and our data suggests that remission status and especially CR prior to first transplant is an important determinant in selecting the optimal form of treatment for patients with pPCL.

References

1. Gavriatopoulou M, Musto P, Caers J, et al. European myeloma network recommendations on diagnosis and management of patients with rare plasma cell dyscrasias. Leukemia. 2018;32(9):1883-1898.

2. van de Donk, Lokhorst HM, Anderson KC, Richardson PG. How I treat plasma cell leukemia. Blood. 2012;120(12):2376-2389.

3. Suska A, Vesole DH, Castillo JJ, et al. Plasma Cell Leukemia – Facts and Controversies: More Questions than Answers? Clin Haematol Int. 2020;2(4);133-142.

4. Iriuchishima H, Ozaki S, Konishi J, et al. Primary Plasma Cell Leukemia in the Era of Novel Agents: A Multicenter Study of the Japanese Society of Myeloma. Acta Haematol. 2016;135(2):113-121.

5. Gonsalves WI, Rajkumar SV, Go RS, et al. Trends in survival of patients with primary plasma cell leukemia: a population based analysis. Blood. 2014;124(6)907-912.

6. D'Arena G, Valentini CG, Pietrantuono G, et al. Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: a retrospective study from GIMEMA Multiple Myeloma Working Party. Ann Oncol. 2012;23(6):1499-1502.

7. Musto P, Rossini F, Gay F, et al. Efficacy and safety of bortezomib in patients with plasma cell leukemia. Cancer. 2007;109(11):2285-2290.

8. Musto P, Statuto T, Valvano L, et al. An update on biology, diagnosis and treatment of primary plasma cell leukemia. Expert Rev Hematol. 2019;12(4):245-253.

9. Brink M, Visser O, Zweegman S, et al. First-line treatment and survival of newly diagnosed primary plasma cell leukemia patients in the Netherlands: a population based study, 1989-2018. Blood Cancer J. 2021;11(2):22.

10. Katodritou E, Terpos E, Delimpasi S, et al. Real-world data on prognosis and outcome of primary plasma cell leukemia in the era of novel agents: a multicenter national study by the Greek Myeloma Study Group. Blood Cancer J. 2018;8(3):31.

11. Musto P, Simeon V, Martorelli MC, et al. Lenalidomide and low dose dexamethasone for newly diagnosed primary plasma cell leukemia. Leukemia. 2014;28(1):222-225.

12. Mina R, Joseph NS, Kaufman J, et al. Survival Outcomes of Patients With Primary Plasma Cell Leukemia (pPCL) Treated With Novel Agents. Cancer. 2019;125(3):416-423.

13. Nandakumar B, Kumar S, Dispenzieri, et al. Clinical characteristics and ouctomes of patients with primary plasma cell leukemia in the era of novel agent therapy. Mayo Clin Proc. 2021;96(3):677-687.

14. Fernandez de Larrea C, Kyle RA, Durie B, et al. Plasma Cell Leukemia. Consensus Statement on Diagnostic Requirements, Response Criteria, and Treatment Recommendations by the International Myeloma Working Group. Leukemia. 2013;27(4):780-791.

15. Levovic D, Zhang L, Alsina M, et al. Clinical outcomes of patients with primary plasma cell leukemia in the era or novel therapies and haematopoietic stem cell transplantation strategies: a single-institution experience. Clin lymphoma Myeloma Leukemia. 2011;11(6):507-511.

16. Drake MB, Iacobelli S, Morris C, et al. European Group for Blood and Marrow Transplantation and the European Leukemia Net. Primary plasma cell leukemia and autologous stem cell transplantation. Haematologica. 2010;95(5):804-809.

17. Mahindra A, Kalaycio ME, Vela-Ojeda J, et al. Hematopoietic cell transplantation for primary plasma cell leukemia: results from the Center for International Blood and Marrow Transplant Research. Leukemia. 2012;26(5):1091-109.

18. Dhakal, B, Patel S, Girnus S, et al. Hematopoietic Cell Transplantation Utilization and Outcomes for Primary Plasma Cell Leukemia in the Current Era. Leukemia. 2020;34(12):3338-3347.

19. Iacobelli S. Suggestions on the use of statistical methodologies in studies of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2013;48 Suppl 1:S1-37.

20. van Houwelingen HC, Putter H, Dynamic predicting by landmarking as an alternative for multi-state modeling: an application to acute lymphoid leukemia data. Lifetime Data Anal. 2008;14(4):447-463.

21. Gahrton G, Iacobelli S Bjorkstrand, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood. 2013;121(25):5055-5063.

22. Bruno B, Rotta M, Patriarca F, et al. A Comparison of Allografting with Autografting in Newly Diagnosed Myeloma. N Engl J Med. 2007;356(11):1110-1120.

23. Royer B, Diouf M, Roussel M, et al. Long term follow-up of hematopoietic stem cell transplantation (HSCT) for primary plasma cell leukemia (pPCL): final results of a prospective study of IFM group. Blood. 2016;128(22):4612.

24. Mohty M, Richardson PG, McCarthy PL, Attal M. Consolidation and maintenance therapy for multiple myeloma after autologous transplantation: where do we stand? Bone Marrow Transplant. 2015;50(8):1024-1029.

25. Van De Donk N, Van der Holt B, Schjesvold FH, et al. Treatment of Primary Plasma Cell Leukemia with Carfilzomib and Lenalidomide-Based Therapy: Results of the First Interim Analysis of the Phase 2 EMN12/HOVON129 Study. Blood. 2019;134(Supplement 1):653.

26. Naighranyan S, Singh AP and Schinke C. The combination of venetoclax, bortezomib and dexamethasone for the treatment of refractory primary plasma cell leukaemia. Am J Haematol. 2020;95(2):E34-E35.

27. Touzeau C, Maciag P, Amiot M, Moreau P. Targeting Bcl-2for the treatment of multiple myeloma. Leukemia. 2018;32(9):1899-1907.

Table 1. Characteristics of patients. All cases and split by type of first transplant (Auto or Allo)

		All cases	First Auto	Allo-first	p-value
	Nr of patients	751	681	70	
Age at 1st transplant (years)	Median (min-max)	56.7 (20-79)	57.7 (25-79)	47.2 (20-68)	<0.001
Sex	Male	378 (50.3%)	334 (49.0%)	44 (62.9%)	0.028
	Female	373 (49.7%)	347 (51.0%)	26 (37.1%)	
Time from diagnosis to 1st transplant	≤12 months	696 (92.7%)	637 (93.5%)	59 (84.3%)	0.005
	>12 months	55 (7.3%)	44 (6.5.%)	11 (15.7%)	
Disease status at 1st transplant	Complete response	247 (32.9%)	221 (32.5%)	26 (37.1%)	<0.001
	Partial response	460 (61.3%)	427 (62.7%)	33 (47.1%)	
	Stable disease	44 (5.9%)	33 (4.8%)	11 (15.7%)	
Karnofsky performance status at 1st transplant*	≥70	632 (96.3%)	571 (96.3%)	61 (96.8%)	0.046
	<70	24 (3.7%)	22 (3.7%)	2 (3.2.%)	
	(missing)	(95, 13%)	(88, 13%)	(7, 10%)	
Calendar period of 1st transplant°	1998-2003	153 (20.4%)	132 (19.4%)	21 (30.0%)	0.132
	2004-2007	143 (19.0%)	131 (19.2%)	12 (17.1%)	
	2008-2010	144 (19.2%)	133 (19.5%)	11 (15.7%)	
	2011-2012	149 (19.8%)	136 (20.0%)	13 (18.6%)	
	2013-2014	162 (21.6%)	149 (21.9%)	13 (18.6%)	

*Percentages computed among non-missing cases.
°Test for linear trends in time.

Table 2. Characteristics of patients according to transplant strategy

		Single Auto	Tandem Auto-Auto	Tandem Auto-Allo	Allo-first
	Nr of patients	44	117	122	70
Age at 1st transplant (years)	Median (min-max)	58.7 (25,79)	58.7 (37,75)	51.6 (33,70)	47.2 (20-68)
Sex	Male	224 (50.7%)	64 (54.7%)	46 (37.7%)	44 (62.9%)
	Female	218 (49.3%)	53 (45.3%)	76 (62.3%)	26 (37.1%)
Time from diagnosis to 1st transplant	≤12 months	403 (91.2%)	114 (97.4%)	120 (98.4%)	59 (84.3%)
	>12 months	39 (8.8%)	3 (2.6%)	2 (1.6%)	11 (15.7%)
Disease status at 1st transplant	Complete response	155 (35.1%)	28 (23.9%)	38 (31.1%)	26 (37.1%)
	Partial response	268 (60.6%)	79 (67.5%)	80 (65.6%)	33 (47.1%)
	Stable disease	19 (4.3%)	10 (8.5%)	4 (3.3%)	11 (15.7%)
Karnofsky performance status at 1st transplant*	≥70	366 (95.1%)	99 (98.0%)	106 (99.1%)	61 (96.8%)
	<70	19 (4.9%)	2 (2.0%)	1 (0.9%)	2 (3.2%)
	(missing)	(57, 13%)	(16, 14%)	(15, 12%)	(7, 10%)
Calendar period of 1st transplant	1998-2003	92 (20.8%)	27 (23.1%)	13 (10.7%)	21 (30.0%)
	2004-2007	77 (17.4%)	32 (27.4%)	22 (18.0%)	12 (17.1%)
	2008-2010	85 (19.2%)	14 (12.0%)	34 (27.9%)	11 (15.7%)
	2011-2012	96 (21.7%)	19 (16.2%)	21 (17.2%)	13 (18.6%)
	2013-2014	92 (20.8%)	25 (21.4%)	32 (26.2%)	13 (18.6%)
Disease status at 2nd transplant	CR/PR	*Not Applic*	116 (99.1%)	119 (97.5%)	*Not Applic*
	SD/MR	*Not Applic*	1 (0.9%)	3 (2.5%)	*Not Applic*

*Percentages computed among non-missing cases.

Table 3. Characteristics of Allo transplants (given as first transplant or as tandem auto-allo)

		Tandem Auto-Allo	Allo-first
	Nr of patients	122	70
Age at allo (years)	Median (min-max)	52.0 (33-71)	47.2 (20-68)
Disease status at allo	CR/PR	119 (97.5%)	59 (84.3%)
	SD/MR	3 (2.5%)	11 (15.7%)
Donor type	HLA matched sibling	58 (47.5%)	46 (65.7%)
	Matched unrelated donor	61 (50.0%)	20 (28.6%)
	Other donor	3 (2.5%)	4 (5.7%)
Source of stem cells	Bone marrow	14 (11.5%)	14 (20%)
	Peripheral blood	108 (88.5%)	56 (80%)
Conditioning*°	Standard	24 (19.8%)	51 (73.9%)
	– No TBI	17 (70.8%)	27 (52.9%)
	–TBI given	7 (29.2%)	24 (47.1%)
	Reduced intensity	97 (80.2%)	18 (26.1%)
	- No TBI	56 (57.7%)	16 (88.9%)
	– TBI given	41 (42.3%)	2 (11.1%)
T cell depletion*	Not given	50 (44.2%)	32 (54.2%)
	Given	63 (55.8%)	27 (45.8%)

*Percentages computed among non-missing cases. TBI information missing for 1 case in each group. T cell depletion missing in 9 (7.4%) and 11 (15.7%) cases respectively.
°For Conditioning, percentages of TBI not given/given are computed within the subgroups with Standard and Reduced Intensity regimen.

Table 4. Cox models for comparison of transplant strategies

		OS			PFS	
	HR	95%CI	p-value	HR	95%CI	p-value
Age: Effect of +1 yr	1.01	1.00-1.02	0.064	1.01	1.00-1.02	0.146
Disease status: No CR vs CR	1.31	1.06-1.62	0.014	1.31	1.08-1.58	0.005
Allo-first, effect within 100 days	5.74	2.66-12.4	<0.001	2.84	1.57-5.15	0.001
Allo-first, effect after 100 days	0.92	0.61-1.38	0.677	0.83	0.57-1.20	0.317
Tandem auto-allo, effect within 100 days	0.89	0.45-1.79	0.751	1.01	0.62-1.64	0.967
Tandem auto-allo, effect after 100 days	0.80	0.59-1.08	0.148	0.69	0.52-0.92	0.012
Tandem auto-auto	0.81	0.60-1.08	0.144	0.86	0.67-1.11	0.254
In a model with interactions°:						
- Tandem auto-auto, No CR	0.94	0.68-1.28	0.678	1.08	0.82-1.42	0.602
- Tandem auto-auto, CR	0.44	0.21-0.91	0.026	0.39	0.21-0.73	0.003

°Models with interaction terms: only the HR for Tandem Auto combined with Disease status are shown. The p-value for the interaction was 0.060 for OS and 0.003 for PFS.

Table 5. List of abbreviation

Abbreviation	Meaning
pPCL	Primary plasma cell leukemia
Single auto	Patient who received an autologous transplant only
Allo-first	Patient who received an allogeneic transplant as first transplant
Auto-allo	Patient who received a tandem transplant-first an autologous transplant followed by an allogeneic transplant
Auto-auto	A patient who received tandem autologous transplants
NRM	Non relapse/progression mortality
OS	Overall survival
PFS	Progression free survival
CR	Complete response
PR	Partial response
VGPR	Very good partial response
SD	Stable disease
CIR	Cumulative incidence of relapse
Recent allo	Allo transplant within last 100 days
Past allo	Allo transplant more than 100 days before

Figure Legends

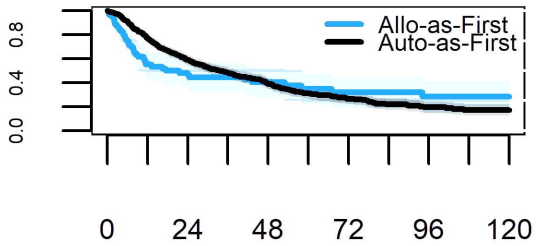
Figure 1. Comparison of outcomes by type of first transplant, Auto or Allo. (a) Overall Survival (b) Progression-Free Survival (c) Cumulative Incidence of Relapse (d) Non-Relapse Mortality.

Figure 2. Conditional probabilities estimated by dynamic prediction models. (a) 3-yrs OS (b) 1-yr PFS. Panel (a): For each prediction time during the interval 0-36 months from the administration of first transplant (X axis) the 3-yrs OS probability (on the Y axis) is re-estimated taking into account the previous transplants received. For example, a patient of the tandem auto-allo group has the same probability of surviving for at least the next 3 years as a single auto patient until the day of allo, at time 2mo, when the curves depart. Vertical changes of the curves for the allo-first and the tandem auto-allo patients are due to the end of the first 100dd high-risk period post allo. Panel (b): Similarly, with horizon time 1 year. In both (a) and (b) the baseline characteristics were age 55 and no CR status at first transplant.

Figure 3. Conditional probabilities estimated by dynamic prediction models with interaction terms. Role of status at first transplant. (a) 3-yrs OS (b) 1-yr PFS. (See Figure 2 for a general explanation of the graphs).

A

OS by first trx



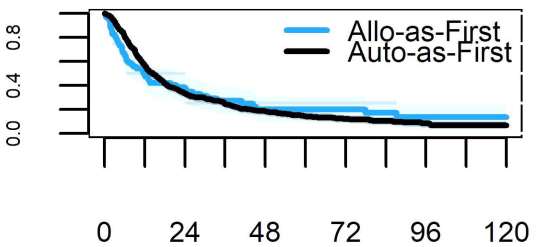
months since trx1

First trx:

Allo:	70	33	26	23	16	12	11	9	8	6	5
Auto:	681	434	288	196	139	87	60	39	29	21	15

B

PFS by first trx



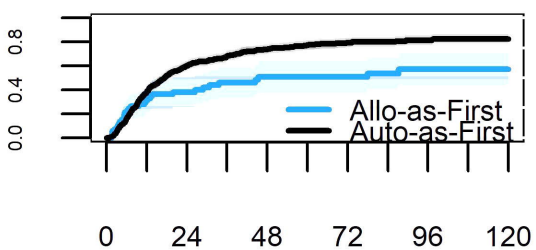
months since trx1

First trx:

Allo:	70	29	21	14	8	7	7	5	4	4	3
Auto:	681	317	167	100	66	43	28	17	11	7	7

C

CIR by first trx



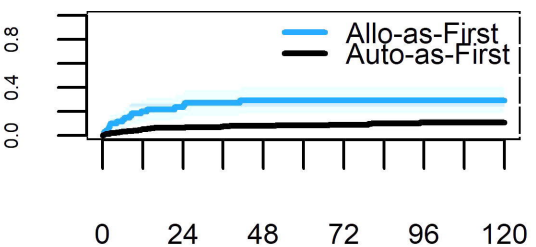
months since trx1

First trx:

Allo:	70	29	21	14	8	7	7	5	4	4	3
Auto:	681	317	167	100	66	43	28	17	11	7	7

D

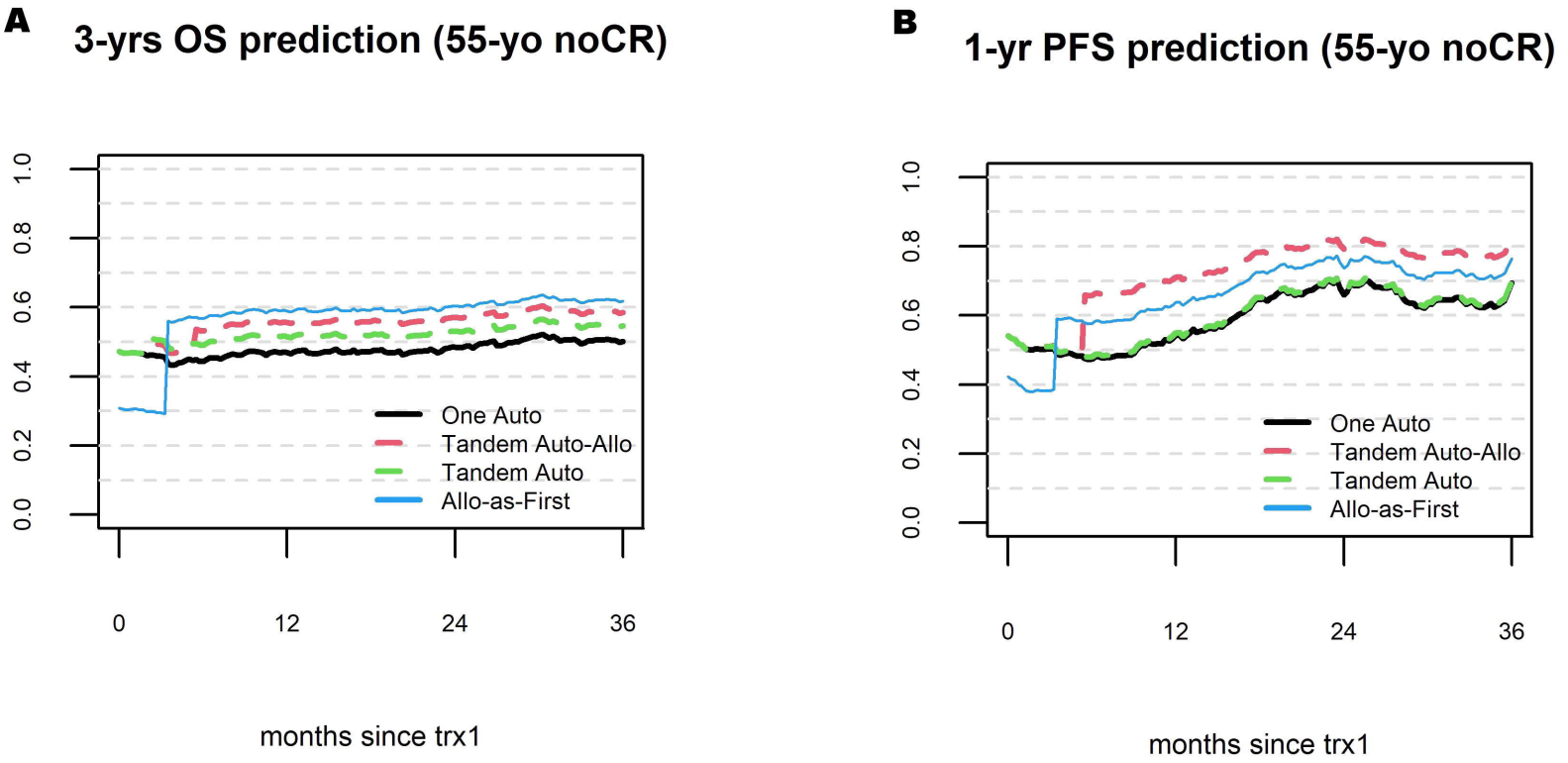
NRM by first trx



months since trx1

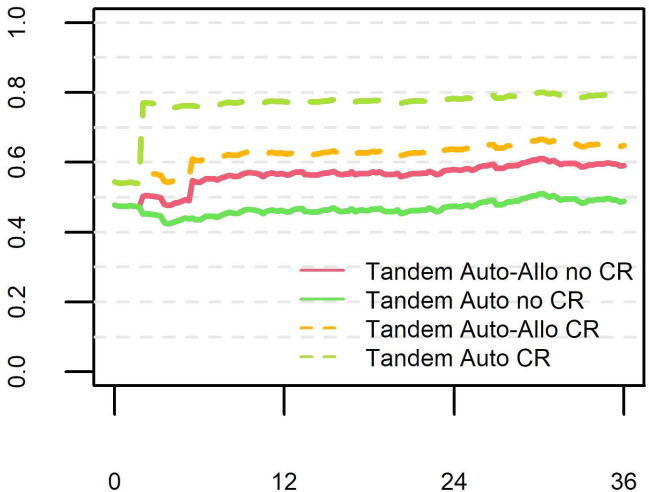
First trx:

Allo:	70	29	21	14	8	7	7	5	4	4	3
Auto:	681	317	167	100	66	43	28	17	11	7	7


A
3-yrs OS prediction (55-yo noCR)
1.0
0.8
0.6
0.4
0.2
0.0
One Auto
Tandem Auto-Allo
Tandem Auto
Allo-as-First
0
12
24
36
months since trx1
B
1-yr PFS prediction (55-yo noCR)
1.0
0.8
0.6
0.4
0.2
0.0
One Auto
Tandem Auto-Allo
Tandem Auto
Allo-as-First
0
12
24
36
months since trx1

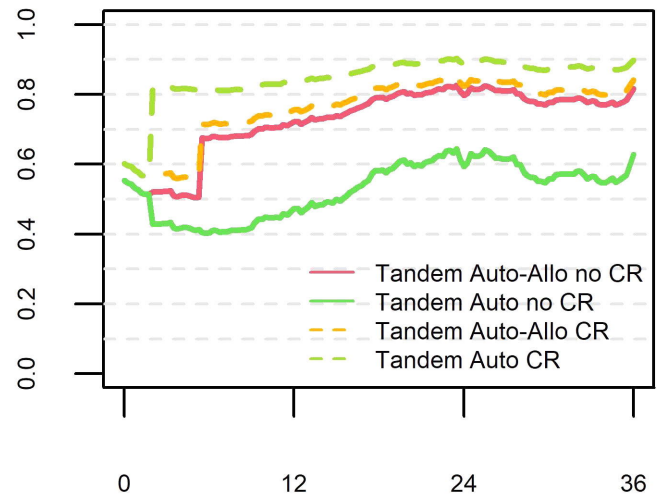
A

3-yrs OS prediction (55-yo). Role of CR



B

1-yr PFS prediction (55-yo). Role of CR



Supplementary Material for the Comparison by transplant strategy

1. Methodology: Time bias and possible approaches

2. Table-Graft versus Host Disease and Response

3. Landmark analysis (Methods and Results)

4. Dynamic prediction method

1. Methodology: “Immortal” time bias and possible approaches

Time bias is likely to affect analyses comparing treatment strategies given in two or more steps in non-interventional studies, as in this one considering tandem Auto-Allo and tandem second Auto. The problem arises as groups cannot be defined and compared as if they were known at time 0 (here, the day of first transplant). For example, in this study at time 0 it is not known whether a patient who got Auto as first transplant will receive a tandem second Auto or a tandem Allo, or remain a “Single Auto” case. Importantly, in order to receive a tandem second transplant, this patient must survive relapse-free during the first months after first transplant; ignoring this “waiting time” and classifying cases from time 0 (by using information from their follow-up records) would systematically include the cases who fail early (or, too early to receive the second transplant) into the “Single auto” group, associating it to poor outcome by construction.

Immortal time bias is often overcome by assessing the differences between treatment strategies in a Cox model with time-dependent covariates; this was done in our study (results shown in Table 4). The main limitation is that the differences are thus evaluated as hazard ratios, while the associated survival probabilities are also of clinical relevance.

A simple way to show survival curves (or cumulative incidence curves) in this situation is to choose a “landmark” time when classifying the patients according to the treatment received up to that time and starting the comparison of outcomes. The results of this analysis in our study are reported in section S3. The landmark analysis has clearly a limitation in that it is affected by the choice of the landmark time (LT), which is in general arbitrary. Picking an early LT can leave a large proportion of patients not yet classified in the correct group, for example in our study at LT=1month most of the patients have received only the first auto transplant: the two groups of the tandem strategies are very small, and the Single Auto group is an heterogeneous collection of cases with many who later will receive the second transplant. On the other hand, a late LT implies a strong case selection, as patients failed before LT are excluded from the comparison. In our study we fixed LT=4month being close to the median time to second transplant, but in particular the resulting Allo-as-First group is heavily selected, including only the patients who survived the high risk of death of the first 100 days post allogeneic transplantation. However, this problem would occur even with a different choice of the LT time, making the use of landmark analysis particularly unsatisfactory in our study.

More complex statistical methods to estimate survival curves from Cox models with time-dependent covariates in presence of treatment strategies given in two or more steps are multi-state modelling [19] and dynamic prediction by landmarking [20]. The latter was applied in our study (results shown in Figures 2 and 3) and it is further illustrated in section S4.

2. Graft versus Host Disease

Table S1. Graft versus Host Disease

		Tandem Auto-Allo	**Allo-first**
Acute GvHD*	No aGvHD	56 (47.9%)	32 (48.5%)
	Grade I	26 (22.2%)	14 (21.2%)
	Grade II	23 (19.7%)	10 (15.2%)
	Grade III	6 (5.1%)	6 (9.1%)
	Grade IV	4 (3.4%)	4 (6.1%)
Chronic GvHD°	Cum. Inc. At 36 mo	56.2% (45.4, 67.0)	41.6% (26.8, 56.3)
	Cum. Inc. At 60 mo	58.1% (47.2, 69.1)	54.7% (39.1,70.3)
	% Extensive cGvHD	45%	64%

*Acute GvHD: number of cases and %. Percentages computed among non-missing cases. AGvHD information missing in 3 (2.5%) and 4 (5.7%) cases respectively.

° Chronic GvHD: cumulative incidence estimates at different time points, with 95% confidence interval. Competing events: death and relapse or progression. N=30 (15.6%) cases could not be evaluated due to missing info (19, 15.6%, and 11, 15.7% respectively in the two groups). The % of Extensive cGvHD is computed among all cases who experienced cGvHD.

Table S2. Response post-transplant

Transplant strategy			Frequency	Percent
Single Auto	Valid	CR	214	54.7
		VGPR/PR	158	40.4
		MR/SD	5	1.3
		Rel/Prog	14	3.6
		Total	391	100.0
	Missing	NA/NE	51	11.5
	Total		442	
Tandem Auto-Allo	Valid	CR	57	48.3
		VGPR/PR	58	49.2
		MR/SD	3	2.5
		Total	118	100.0
	Missing	NA/NE°	4	3.3
	Total		122	
Tandem Auto-Auto	Valid	CR	50	43.5
		VGPR/PR	64	55.7
		MR/SD	1	0.9
		Total	115	100.0
	Missing	NA/NE°	2	1.7
	Total		117	
Allo-as-First	Valid	CR	35	62.5
		VGPR/PR	18	32.1
		Rel/Prog	3	5.4
		Total	56	100.0
	Missing	NA/NE	14	20.0
	Total		70	

The % of Not Available / Not Evaluable is computed over the total of the group. The % of CR, VGPR or PR, Minimal Response or Stable disease, and of Relapse/Progression are computed over the total of cases available in the group.

°Based on information collected at 2nd transplant, we know that the 4 missing in the Tandem Auto-Allo group and the 2 missing in the Tandem Auto-Auto group had either CR or VGPR or PR.

3. Landmark analysis

Statistical methods

The approach and its limitations were introduced in the section S1. The landmark time LT was 4 months; for each endpoint (OS, PFS, CIR and NRM) the number of cases evaluable (alive event-free at 4mo) and the distribution according to the treatment received up to LT are reported in the tables. Unadjusted analyses were based on Kaplan-Meier probability estimates and Log-Rank test for OS and PFS, and on crude cumulative incidence and Gray test for CIR and NRM (Figure S1). Table S3 reports outcome estimates at time 60mo from 1st transplant with 95%CI limits and test p-values. Adjusted analysis was based on Cox models. Because of the strong bias affecting the Allo-first group, unadjusted tests were repeated and the Cox models were applied excluding this group. In the models, the baseline treatment group is Single Auto (Table S4).

Results

Table S3. Landmark analysis. Unadjusted.

	OS (N=663)		PFS (N=612*)		CIR	NRM
	N	estimate at 60mo (95%CI)	N*	estimate at 60mo (95%CI)	estimate at 60mo (95%CI)	estimate at 60mo (95%CI)
Single Auto	449	32.1% (26.7-37.5)	404	13.4% (9.2-17.5)	79.8% (75.1-84.5)	6.8% (4.0-9-6)
Tandem Auto-Allo	84	38.7% (25.6-51.8)	84	30.8% (19.4-42.2)	59.2% (47.2-71.2)	10.0% (3.4-16.5)
Tandem Auto-Auto	77	29.4% (15.8-42.9)	76	15.0% (4.5-25.5)	79.4% (67.0-90.9)	5.6% (0.0-11.8)
Allo-first	53	41.2% (26.3-56.1)	48	25.9% (12.0-40.0)	48.9% (33.5-64.3)	25.1% (12.1-38.1)
p-value (excluding Allo-1st)		0.591 (0.525)		0.309 (0.353)	0.002 (0.073)	0.001 (0.244)

*Same sample size for CIR and NRM

Table S4. Landmark analysis. Adjusted.

	OS	PFS	CIR	NRM
Single Auto	1	1	1	1
Tandem Auto-Allo	0.85 (0.62-1.19)	0.83 (0.62-1.11)	0.77 (0.56-1.05)	1.49 (0.67-3.30)
Tandem Auto-Auto	1.00 (0.72-1.38)	0.99 (0.73-1.33)	1.01 (0.74-1.38)	0.71 (0.21-2.37)

Effects expressed as HR (with 95%CI) versus Single Auto as baseline. Cases of the 1st trx Allo excluded. Adjustment factors: Age and Disease Status at first transplant (not shown).

Figure S1 (a). Landmark OS curves.

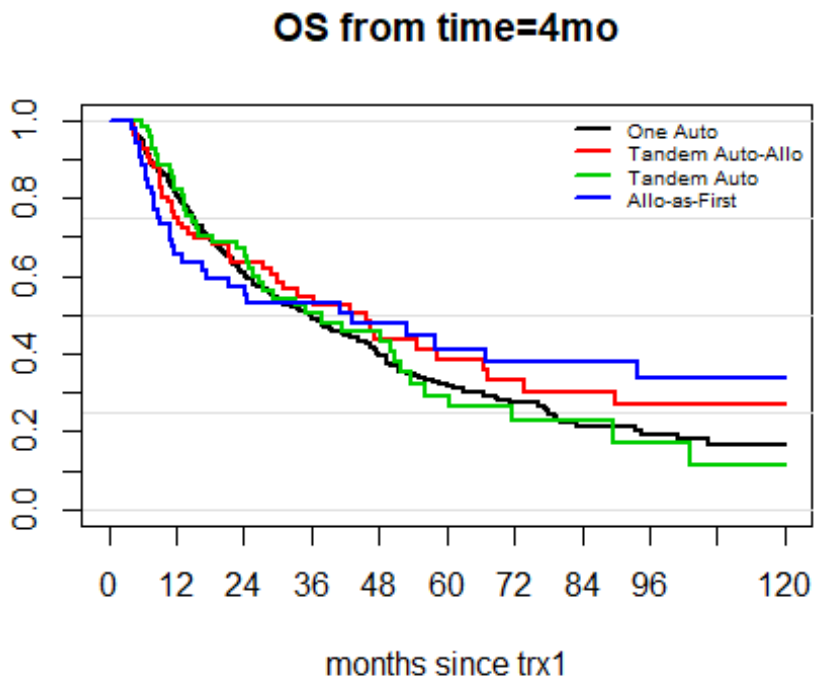


Figure S1 (b). Landmark PFS curves.

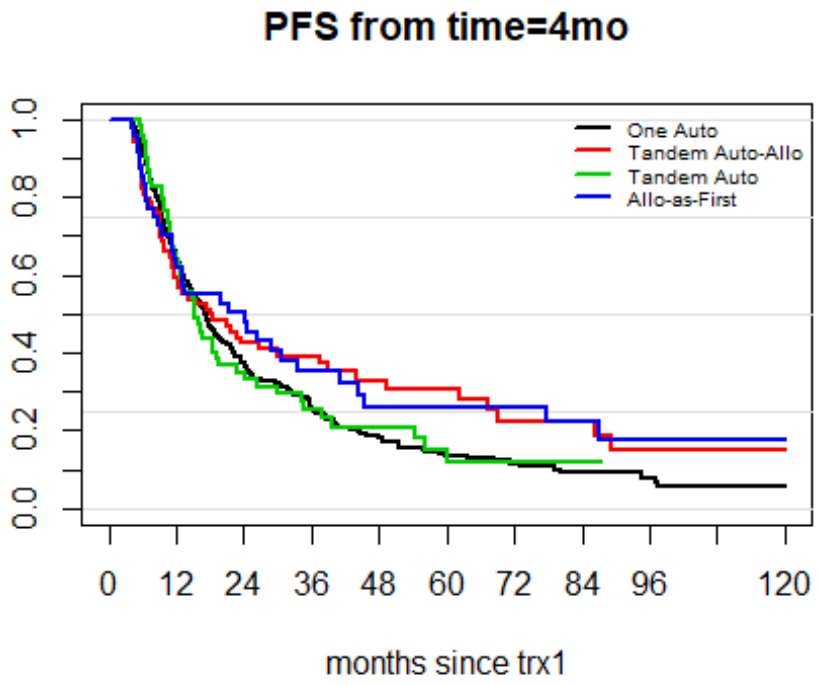


Figure S1 (c). Landmark CIR curves.

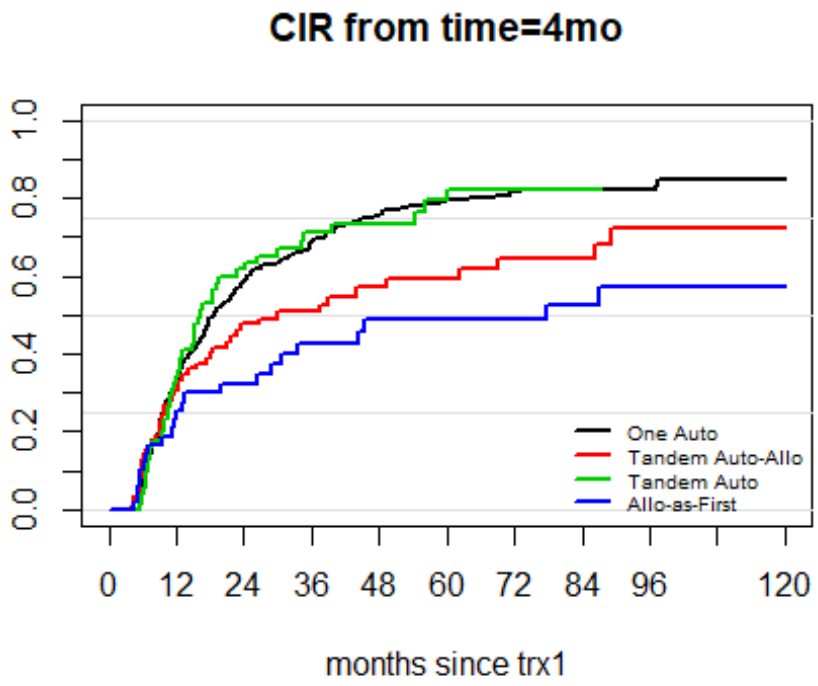
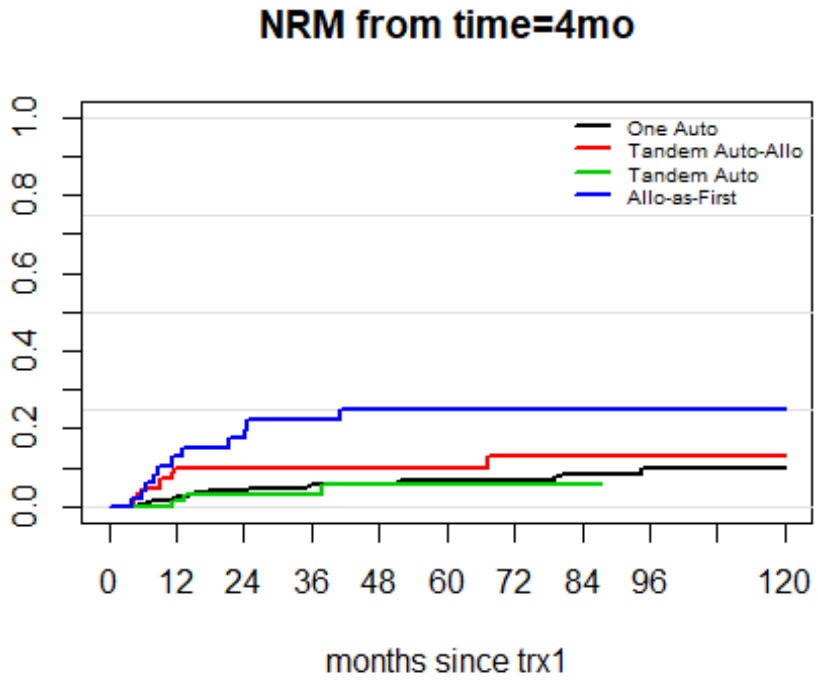


Figure S1 (d). Landmark NRM curves.

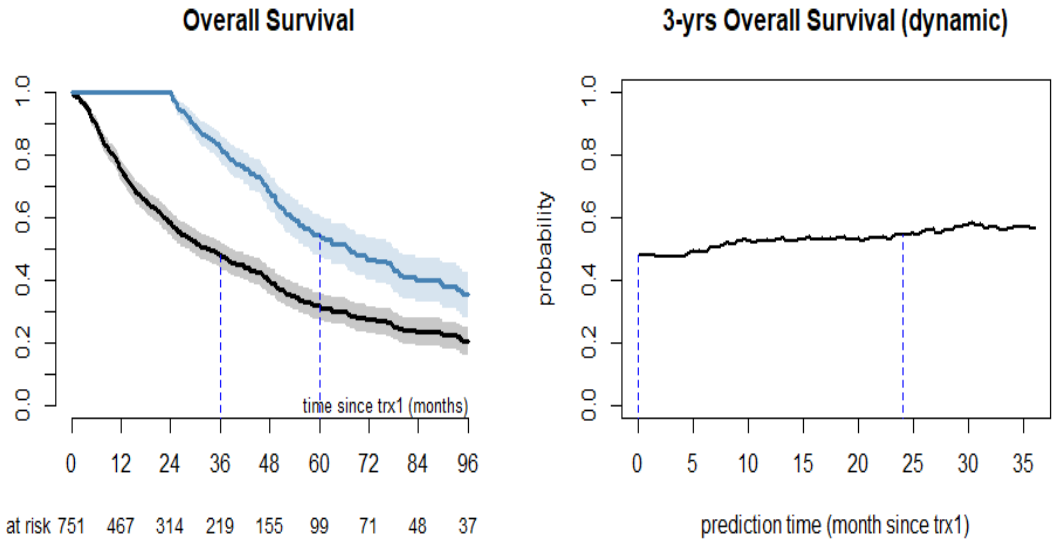


4. Dynamic prediction

The landmark analysis is the analysis of conditional probabilities for the patients who are still failure-free at the landmark time LT. It is interesting in itself, but limited by the choice of LT. Ideally, LT should be varied along an interval, say from t_0 to t_P, to appraise how the survival probabilities change according to the course of the disease. For example in our study moving the prediction time LT would allow to classify more and more patients with first transplant autologous into the groups of tandem Auto-Allo and Auto-Auto, and thus to evaluate the impact of these treatments. This is the intuitive principle of the dynamic predictions obtained by the method of “landmarking” (van Houwelingen, Putter[20]).

In this approach the focus is on estimating the survival probability after a certain “horizon” time since LT. In our study we considered of interest the probability of 3-yrs OS and of 1-yr PFS. We estimated these predicted probabilities moving LT from t_0=0 (the day of first transplant) to t_P=36mo. The graph below illustrates this concept using the Kaplan-Meier estimator. The method proposed by van Houwelingen and Putter estimates the dynamic prediction values from a “supermodel” which in intuitive terms combines the different landmark Cox models for each LT time.

Figure S2. Illustration of dynamic prediction curves.



Left panel: The black curve is the standard OS Kaplan-Meier curve estimated at time t_0=0 for all 751 patients included in the study. The blue curve is the landmark OS Kaplan-Meier curve estimated at time LT=24mo for the 314 patients still alive by that time. The focus is on the probability of surviving for 3 years after the prediction time, which on the black curve it is the value corresponding to time=36 (48%), and on the blue curve it is the value corresponding to time=60 (=24+36) (55%). Right Panel: These two probability values are reported on the curve for prediction time t_0=0 and LT=24mo respectively. The dynamic prediction curve joins the predicted 3-yrs OS probabilities from a number of landmark curves, showing the improvement of the 3-yrs OS for the PCL patients surviving during the first 36mo from first transplant.

In detail, we based our dynamic prediction estimates on 121 different landmark times. The supermodel was stratified on LT. The analysis was performed in R v. 3.5 using the library “dynpred”.