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

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Abstract

Primary plasma cell leukemia (pPCL) is a rare and challenging malignancy. There are limited data regarding optimum transplant approaches. We therefore undertook a retrospective analysis from 1998-2014 of 751 patients with pPCL undergoing one of four transplant strategies; single autologous transplant (single auto), 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). 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 a subsequent second transplant. The allo-first group had a lower relapse rate (45.9%, 95% confidence interval [95% CI]: 33.2-58.6 *vs.* 68.4%, 64.4-72.4) but higher non-relapse mortality (27%, 95% CI: 15.9-38.1 *vs.* 7.3%, 5.2-9.4) at 36 months. Patients who underwent allo-first had a remarkably higher risk in the first 100 days for both overall survival and progression-free survival. Patients undergoing auto-allo (n=122) had no increased risk in the short term and a significant benefit in progression-free survival after 100 days compared to those undergoing single auto (hazard ratio [HR]=0.69, 95% CI: 0.52- 0.92; *P*=0.012). Auto-auto (n=117) was an effective option for patients achieving complete remission prior to their first transplant, whereas in patients who did not achieve complete remission prior to transplantation our modeling predicted that auto-allo was superior. This is the largest retrospective study reporting on transplantation in pPCL to date. We confirm a 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 to 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 the median survival of affected patients being 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.[3-5]

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] Novel agents, such as bortezomib[6-10] and lenalidomide,[11] have been shown to be effective in pPCL used either alone or in combination[12-15] and may account for some of the improvements seen in recent years. Many of the reports also confirm the benefit of consolidation with hematopoietic stem cell transplantation, although all modalities of transplantation including autologous, allogeneic and tandem approaches have generally been considered together. Nevertheless, survival outcomes of pPCL patients in the SEER study are still inferior to those of multiple myeloma patients diagnosed during the same period when the analysis is adjusted for gender and age of the patients.[5]

The European Society for Blood and Marrow Transplantation (EBMT) reported on the outcomes of 272 patients with pPCL undergoing autologous hematopoietic stem cell transplantation (auto).[16] This study confirmed that auto can improve outcome, but results were markedly inferior to those achieved in patients with multiple myeloma. The Center for International Blood and Marrow Transplant Research (CIBMTR) has also demonstrated improvements in progression-free survival (PFS) and overall survival (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 between 1995-2006 and demonstrated that while allo patients had significantly lower relapse rates, their non-relapse mortality (NRM) was significantly higher with no 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 hematopoietic cell transplant utilization was noted from 12% in 1995 to 46% in 2009 but outcomes remained poor with no increase in OS in the allo group when compared with that in the previous study.[18]

The present study utilized the largest cohort of patients with pPCL (n=751) undergoing hematopoietic stem cell transplantation to examine various transplantation strategies and determine how these may be of most benefit. The study includes auto, allo and tandem transplants. To make statistically valid comparisons in this retrospective comparison of transplant strategies, non-standard statistical methods were employed, including dynamic prediction modeling.

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 a complete response, partial response, very good partial response or stable disease 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 the absence of disease progression. The main endpoints of interest were OS and PFS. We also analyzed the cumulative incidence of relapse, NRM, and acute and chronic graft-*versus*-host disease. The problem and approaches used to compare transplant strategies are illustrated in the statistical methods section and in the *Online Supplementary Material*.

This study was conducted on behalf of the Chronic Malignancies Working Party of the EBMT. The EBMT represents more than 500 transplantation centers in and beyond Europe, which report minimum essential data on all transplants into a central database. EBMT centers are committed to obtain informed consent according to the local regulations applicable at the time of transplantation in order to report pseudonymized 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 defined as death from any cause and the first between death and progression, respectively. The occurrence of relapse or progression and of death was analyzed as mutually competing (generating cumulative incidence of relapse and NRM cumulative incidence curves). For acute and chronic graft-*versus*-host disease, traditionally defined as occurring respectively within and after 100 days from allogeneic transplantation, relapse or progression and death were considered competing events. The standard methods indicated in the EBMT statistical guidelines[19] were applied for the comparisons of groups according to the type of first transplant. Different approaches were applied for the comparison of single and tandem transplant strategies to avoid the risk of a time bias of retrospective analyses (*Online Supplementary Material S1*). A traditional landmark analysis is presented as a sec-

ondary analysis (*Online Supplementary Material S3*) 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 (when given as a first transplant or in a tandem transplant strategy) due to the higher early mortality. For simplicity, this time-dependent effect was modeled as being a stepwise constant in two periods measured from the time of allo: 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 the baseline group. Candidate adjustment factors for the models were patients' sex, age, disease status and performance status at first transplant, time from diagnosis to first transplant, and calendar year. Only age and disease status were retained in the final models. A further insight into the effects on the probabilities of OS and PFS was obtained by applying a method of dynamic prediction (*Online Supplementary Material S4*), illustrating the evolution during the first 36 months of follow-up of the conditional 3-year OS and 1-year PFS. 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 was based on Cox models including interactions between patients' 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

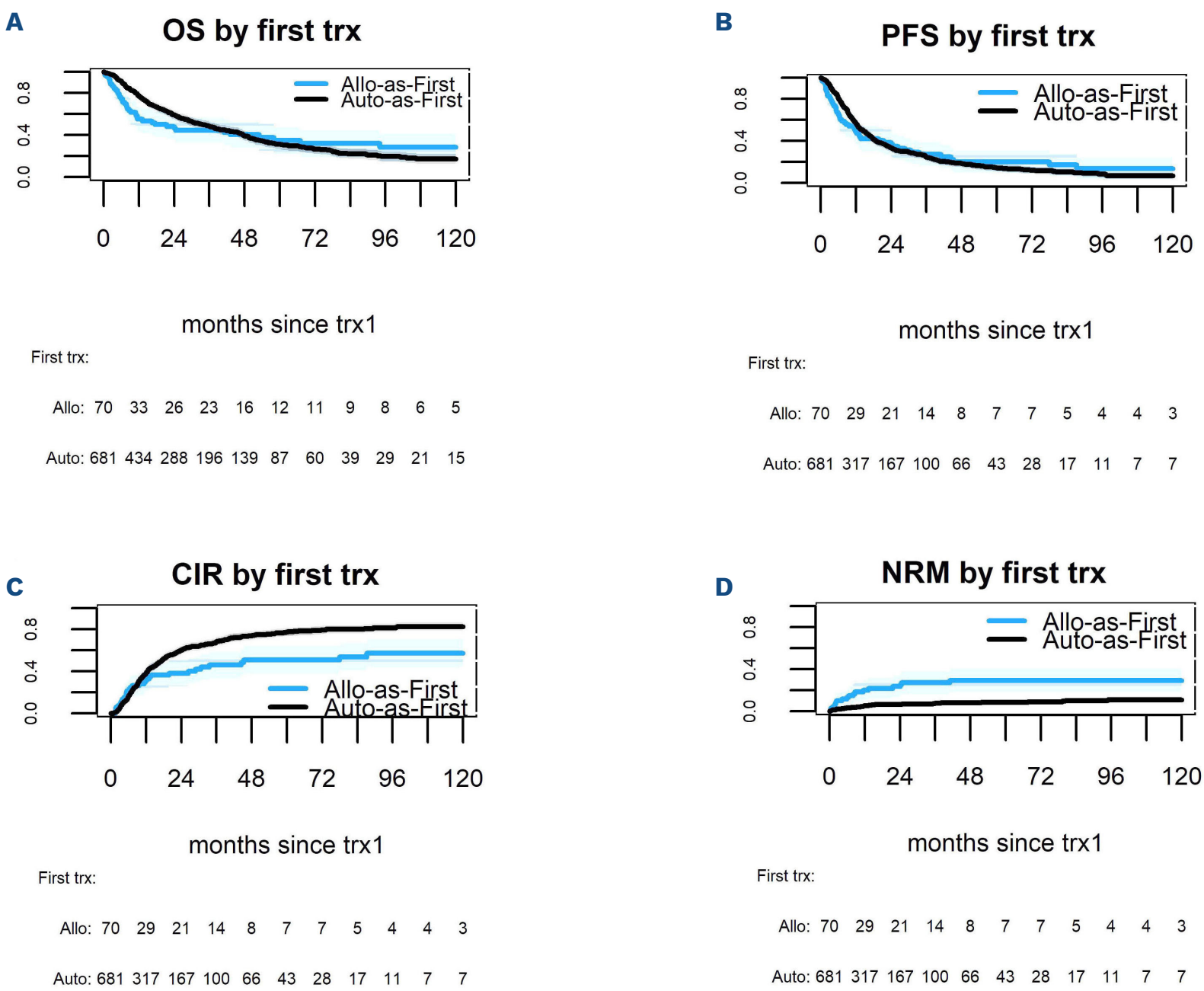

Figure 1. Comparison of outcomes by type of first transplant (autologous or allogeneic). (A) Overall survival. (B) Progression-free survival. (C) Cumulative incidence of relapse. (D) Non-relapse mortality. trx: transplant; trx1: first transplant; allo: allogeneic hematopoietic stem cell transplant; auto: autologous hematopoietic stem cell transplantation; OS: overall survival; PFS: progression-free survival; CIR: cumulative incidence of relapse; NRM: non-relapse mortality.

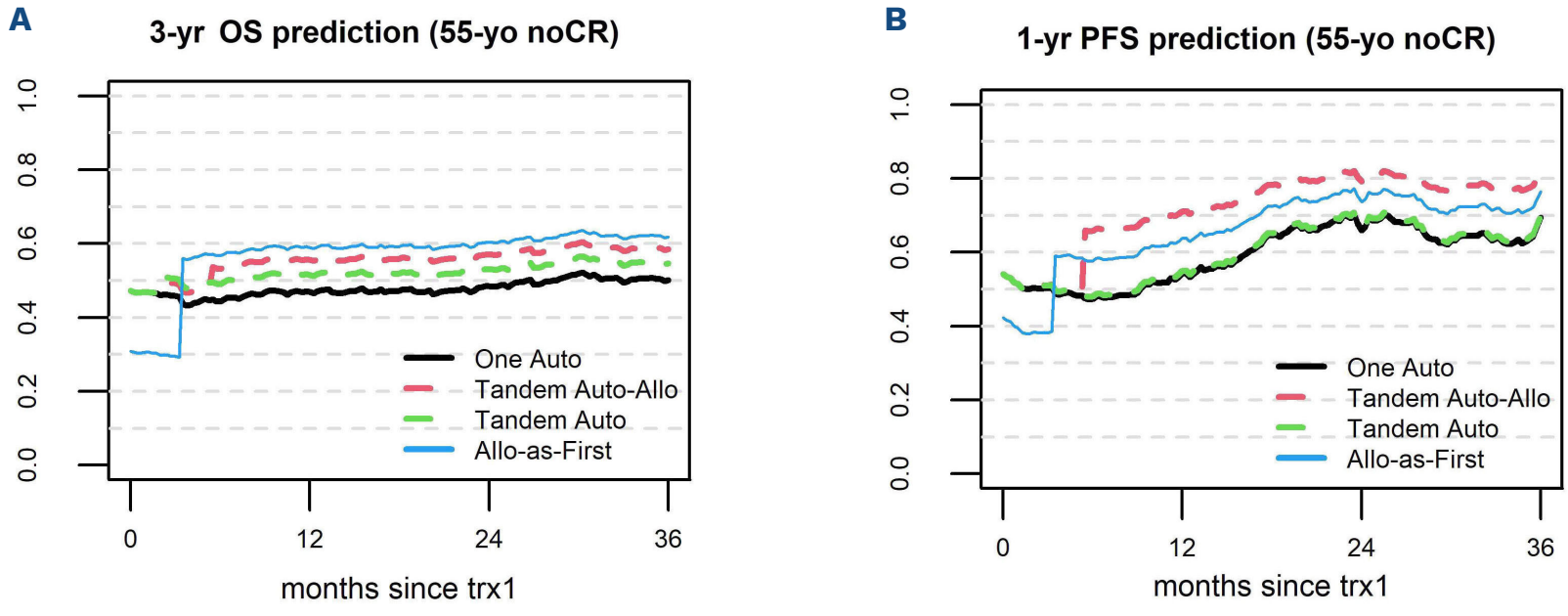

Figure 2. Conditional probabilities of overall and progression-free survival estimated by dynamic prediction models. (A) Three-year overall survival. For each prediction time during the interval 0-36 months from the first transplant (x axis) the 3-year overall survival probability (on the y axis) is re-estimated taking into account the previous transplants received. For example, a patient in the tandem autologous-allogeneic group has the same probability of surviving for at least the next 3 years as a patient who underwent a single autologous transplant until the day of allogeneic transplantation, at 2 months, when the curves separate. Vertical changes of the curves for the allogeneic transplant first and the tandem autologous-allogeneic transplant recipients are due to the end of the first 100-day high-risk period after allogeneic transplantation. (B) One-year progression-free survival. As for overall survival, but with a horizon time of 1 year. In both (A) and (B) the baseline characteristics were age 55 and not in complete remission at first transplant. OS: overall survival; PFS: progression-free survival; yr: years; yo: years old; noCR: not in complete remission; allo: allogeneic hematopoietic stem cell transplant; auto: autologous hematopoietic stem cell transplantation; trx1: time since first transplant.

Table 1. Characteristics of patients for all cases and split by the type of first transplant (autologous or allogeneic).

	All cases	First auto	Allo-first	*P* value
N of patients	751	681	70	
Age at 1st transplant, years				
Median	56.7	57.7	47.2	<0.001
Min-max	20-79	25-79	20-68	
Sex, N (%)				
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, N (%)				
≤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, N (%)				
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*, N (%)				
≥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°, N (%)				
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. First auto: an autologous transplant first (regardless of whether a second transplant was subsequently performed); allo-first: single allogeneic transplant.

was 33 months and the median PFS was 14 months. The median follow-up was 48.8 months.

Transplant strategies

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

Comparison of autologous *versus* allogeneic as first transplant

Initial comparisons were made between patients undergoing allo-first *versus* first auto (regardless of subsequent administration of a second transplant). The characteristics of the patients are reported in Table 1. Allo-first patients were predominantly male, were significantly younger (median age 47.2 years *vs*. 57.7 years for first auto; $P<0.001$), had a longer time from diagnosis to transplant ($P=0.005$) and had a significantly higher proportion of patients both in complete remission and with stable disease ($P<0.001$). 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 (Figure 1). The curves show 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 (Figure 1D) 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 the cumulative incidence of relapse 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

The 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, had a shorter time from diagnosis to transplant, and had higher proportions of matched unrelated donors and reduced intensity conditioning than those who had allo-first (Table 3). They were also predominantly females and younger than the other patients undergoing first auto.

The characteristics of allogeneic transplants given as the first transplant or as part of a tandem auto-allo strategy are shown in Table 3. As previously noted, the administration of allo as a first or second transplant differed in several characteristics. Total body irradiation was administered more frequently to allo-first patients than to auto-allo patients if standard conditioning was used (47.1% allo-first *vs*. 29.2% auto-allo), whereas it was given more frequently in auto-allo than allo if reduced intensity conditioning was used (42.3% allo-first *vs*. 11.1% auto-allo).

Any differences in conditioning did not translate into meaningful differences in graft-*versus*-host disease. *Online Supplementary Table S1* shows the incidences of acute and chronic graft-*versus*-host disease, which appear similar to those seen in patients receiving allo first or auto-allo. Only 13 patients who underwent an allo received donor lymphocyte infusion and all were in the allo-first group. The median time to donor lymphocyte infusion was 5.7 months (range, 2.7-46.1) with six patients receiving the treatment before relapse and seven patients receiving it after relapse. In a preliminary approach, landmark analyses at 4 months were undertaken for OS, PFS, NRM and cumulative incidence of relapse (*Online Supplementary Material S3; Online Supplementary Figure S1*) which showed no significant

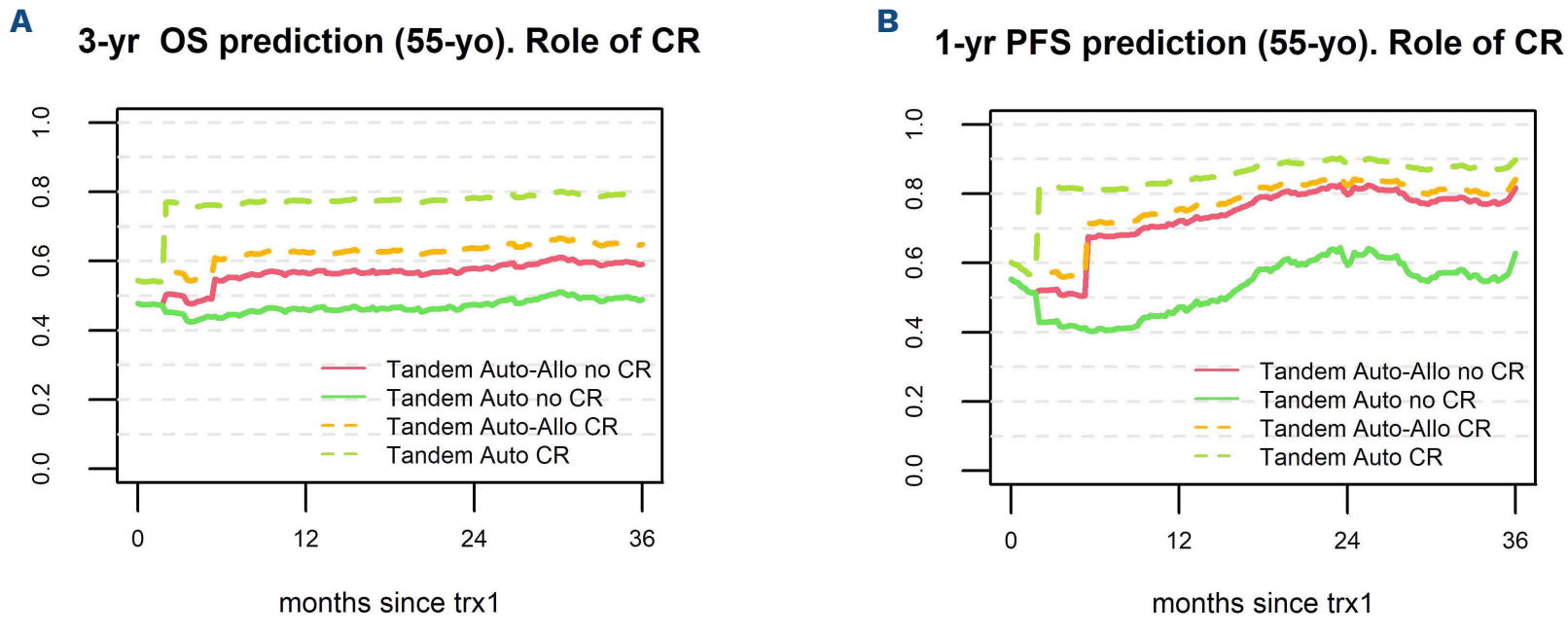

Figure 3. Conditional probabilities estimated by dynamic prediction models with interaction terms. Role of status at first transplant. (A) Three-year overall survival. (B) one-year progression-free survival. See the legend to Figure 2 for a general explanation of the graphs. OS: overall survival; PFS: progression-free survival; yr: years; yo: years old; CR: complete response; allo: allogeneic hematopoietic stem cell transplant; auto: autologous hematopoietic stem cell transplantation; trx1: time since first transplant.

discrimination between transplant strategies, except for 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 the 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 patients had 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 complete remission conferred a significant benefit and the effect of being younger at transplantation may also confer a benefit. With consideration of the time-dependent effect, after 100 days the outcomes of allo-first became comparable to those of other strategies. Tandem auto-allo had a significant benefit on 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 was also seen on OS (HR=0.80, 95% CI: 0.59-1.08, *P*=0.148), this did not reach statistical significance. For auto-auto the hazard ratios for PFS and OS were also reduced (models without interactions: HR=0.81 95% CI: 0.61-1.08, *P*=0.114 and HR=0.86, 95% CI: 0.67-1.11, *P*=0.254, respectively).

Table 2. Characteristics of patients according to transplant strategy.

	Single auto	Tandem auto-auto	Tandem auto-allo	Allo-first
N of patients	442	117	122	70
Age at 1st transplant, years				
Median	58.7	58.7	51,6	47.2
Min-max	(25,79)	(37,75)	(33,70)	(20-68)
Sex, N (%)				
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, N (%)				
≤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, N (%)				
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*, N (%)				
≥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, N (%)				
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, N (%)				
Complete/partial response	na	116 (99.1)	119 (97.5)	na
Stable disease/minimal response	na	1 (0.9)	3 (2.5)	na

*Percentages computed among non-missing cases. Single auto; single autologous hematopoietic stem cell transplant; Tandem auto-auto; tandem autologous hematopoietic stem cell transplants; Tandem auto-allo; autologous hematopoietic stem cell transplant followed by an allogeneic transplant; Allo-first: single allogeneic transplant; na: not applicable.

Conditional overall and progression-free survival probabilities

The difference of outcomes of the four transplant strategies was further illustrated by dynamic prediction curves (*Online Supplementary Material S4*). Figure 2A and 2B show respectively the projected 3-year OS and 1-year PFS starting from any time during the first 36 months for a 55 year-old patient not in complete remission at the time of the 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 as (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.

Table 3. Characteristics of allogeneic transplants (given as first transplant or in a tandem autologous-allogeneic strategy).

	Tandem auto-allo	Allo-first
N of patients	122	70
Age at allo, years		
Median (min-max)	52.0 (33-71)	47.2 (20-68)
Disease status at allo, N (%)		
CR/PR	119 (97.5)	59 (84.3)
SD/MR	3 (2.5)	11 (15.7)
Donor type, N (%)		
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, N (%)		
Bone marrow	14 (11.5)	14 (20)
Peripheral blood	108 (88.5)	56 (80)
Conditioning*°, N (%)		
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*, N (%)		
Not given	50 (44.2)	32 (54.2)
Given	63 (55.8)	27 (45.8)

*Percentages computed among non-missing cases. Information on total body irradiation is missing for one case in each group. T-cell depletion data are missing for nine (7.4%) and 11 (15.7%) cases, respectively. °For conditioning, the percentages for total body irradiation not given/given are computed within the subgroups of the standard and reduced intensity regimens. Tandem auto-allo; allogeneic hematopoietic stem cell transplant following an autologous transplant; Allo-first: single allogeneic transplant; allo: allogeneic hematopoietic stem cell transplant; CR: complete response; PR: partial response; SD: stable disease; MR: minimal response; HLA: human leukocyte antigen; TBI: total body irradiation.

Effect of complete response

Further modeling detected an interaction of the disease status with auto-auto transplant strategy for both OS and PFS (Table 4, last two lines; Figure 3A, B). It can be seen that being in complete remission at the time of the first transplant provided a marginal benefit when combined with an auto-allo strategy (orange curves) whereas complete remission 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 transplant 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 with newly diagnosed multiple myeloma responding to therapy compared auto-auto to auto-allo.[21,22] Although there was a dramatic improvement in NRM with the auto-allo approach compared with allo-first, the NRM remained significantly higher than with auto-auto and it was only after 5 years of follow-up that an advantage for the auto-allo approach became evident.[22,23] Our study indicates that there may be a similar benefit from the auto-allo approach for patients with newly diagnosed pPCL in the longer term, particularly those not in complete remission at the time of the 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 dynamic model suggest that if patients achieve a complete response prior to their first transplant then auto-auto is an effective option with outcomes similar to those of 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 have a complete response to induction therapy our model predicts that auto-allo is a superior approach with regard to survival.

In one of the few prospective studies in pPCL, the Intergroupe Francophone du Myélome (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. The median PFS was 18.5 months for the tandem auto-allo patients and 50 months for the tandem auto and maintenance group, while the median OS was 39.3 months for the tandem auto-allo group and not reached in the tandem auto and maintenance group. Although we cannot draw direct comparisons between the IFM study and our findings it can be seen from the OS curves (*Online Supplementary Material S1A*) that the OS for the auto-allo group is comparable to the median OS in the IFM study. The median PFS reported by the IFM is higher than that observed in our study (*Online Supplementary Material S1B*) but the lack of maintenance in our cohort likely accounts for this.

There is growing evidence to indicate that 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. Although the findings in the IFM study appear encouraging, the number of patients who received maintenance is too small to draw firm conclusions on the role of maintenance therapy after transplantation 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 with pPCL. This trial is exploring the use of carfilzomib and lenalidomide induction (KRd), consolidation and maintenance in both young and elderly pPCL 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 four cycles of therapy (very good partial response or better in 80% and complete response in 33%) without early deaths.[25]

Our findings have focused on younger, transplant-eligible patients; older and less fit patients not eligible for transplantation treatment should be scheduled for personalized, continuous treatments, aiming to keep the 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 complete response rates in pPCL as has been shown in multiple myeloma.[8] It is important to improve the outcomes 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

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 year	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 hazard ratios for Tandem autologous transplants combined with Disease status are shown. The P value for the interaction was 0.060 for overall survival and 0.003 for progression-free survival. HR: hazard ratio; 95% CI: 95% confidence interval; CR: complete response; Allo-first: single allogeneic transplant; Tandem auto-allo; autologous hematopoietic stem cell transplant followed by an allogeneic transplant; Tandem auto-auto; tandem autologous hematopoietic stem cell transplants.

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 an elective second transplant (by use of Cox models or, not shown, propensity score matching) we cannot exclude a residual indication bias. The single auto group is, by construction, likely to include all patients who experienced an early relapse, and this could in part account for the worse outcome of this group compared to the groups of patients undergoing tandem transplants; however, the prevalence of relapse or progression as post-transplant response is limited (3.6%) (*Online Supplementary Table S3*). There was also a wide heterogeneity in treatments, for example for allogeneic transplantation we have described differences in modalities including the use of total body irradiation and donor lymphocyte infusion. 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 a series of interventional prospective studies could be set up for this rare disease such as to achieve strong evidence in favor 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 that typically affects 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 that significant NRM occurs in patients undergoing allo as a first transplant. Patients require careful selection and individual risk assessment when considering an allo. Our study supports a tandem transplant approach of upfront auto followed by either tandem allo or auto and our data suggest that remission status and especially a complete response prior to first transplant is an important determinant in selecting the optimal form of treatment for patients with pPCL.

Disclosures

No conflicts of interest to disclose.

Contributions

All authors submitted data and approved the manuscript. SI was responsible for the statistics. SL, SI, SS and CM designed the study and wrote the manuscript.

Data-sharing statement

The final analysis dataset will be available upon specific request to the Working Party, which can be sent to the corresponding author.

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