Outcomes of unrelated cord blood transplantation in patients with multiple myeloma: a survey on behalf of Eurocord, the Cord Blood Committee of Cellular Therapy and Immunobiology Working Party, and the Chronic Leukemia Working Party of the EBMT

Annalisa Paviglianiti,[1,2]* Erick Xavier,[1,2]* Annalisa Ruggeri,[1,2,3] Patrice Ceballos,[4] Eric Deconinck,[5] Jan J. Cornelissen,[6] Stephanie Nguyen-Quoc,[7] Natacha Maillard,[8] Guillermo Sanz,[9] Pierre-Simon Rohrlich,[10] Laurent Garderet,[3] Fernanda Volt,[1,2] Vanderson Rocha,[1,2,11] Nicolaus Kroeger,[12] Eliane Gluckman,[1,2] Nathalie Fegueux,[4]* and Mohamad Mohty[3,13]*

[1]Eurocord, APHP, University Paris Diderot, Hôpital Saint Louis, Paris, France; [2]Monacord, Centre Scientifique de Monaco, France; [3]Service d'Hématologie et Thérapie Cellulaire, Hôpital Saint Antoine, AP-HP, Paris, France; [4]Département d'Hématologie Clinique, CHU Lapeyronie, Montpellier, France; [5]Department Hematology, CHU Besancon, France; [6]Department of Hematology, Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, the Netherlands; [7]Department Hematology, University Paris IV, Hôpital la Pitié-Salpêtrière, Paris, France; [8]Bone Marrow Transplant Unit Clinical Hematology, Hôpital La Miletrie, Poitiers, France; [9]Servicio de Hematologia, Hospital Universitario y Politecnico La Fe, Valencia, Spain; [10]Hematologie Clinique, CHU - Hôpital de l`ARCHET I, Nice, France; [11]Department Hematology, Churchill Hospital, Oxford, UK; [12]Dept. Stem Cell Transplantation, University Hospital of Hamburg, Germany; and [13]INSERM, UMRs 938, Paris, France

AP and EX, and NF and MM contributed equally to this work.

Haematologica 2016
Volume 101(9):1120-1127

Correspondence:

annalisa.paviglianiti@gmail.com

Received: November 13, 2015.

Accepted: May 24, 2016.

Pre-published: May 26, 2016.

doi:10.3324/haematol.2015.138917

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/101/9/1120

ABSTRACT

Although allogeneic stem cell transplantation is not a standard therapy for multiple myeloma, some patients can benefit from this intense therapy. There are few reports on outcomes after umbilical cord blood transplantation in multiple myeloma, and investigation of this procedure is warranted. We retrospectively analyzed 95 patients, 85 with multiple myeloma and 10 with plasma cell leukemia, receiving single or double umbilical cord blood transplantation from 2001 to 2013. Median follow up was 41 months. The majority of patients received a reduced intensity conditioning. The cumulative incidence of neutrophil engraftment was 97%±3% at 60 days, and that of 100-day acute graft-*versus*-host disease grade II-IV was 41%±5%. Chronic graft-*versus*-host disease at two years was 22%±4%. Relapse and non-relapse mortality was 47%±5% and 29%±5% at three years, respectively. Three-year progression-free survival and overall survival were 24%±5% and 40%±5%, respectively. Anti-thymocyte globulin was associated with decreased incidence of acute graft-*versus*-host disease, higher non-relapse mortality, decreased overall and progression-free survival. Patients with high cytogenetic risk had higher relapse, and worse overall and progression-free survival. In conclusion, umbilical cord blood transplantation is feasible for multiple myeloma patients.

Introduction

The current standard of care for patients with multiple myeloma (MM) is the use of drugs such as bortezomib, thalidomide and lenalidomide followed by autologous stem cell transplantation (ASCT).[1,2] Although this combined treatment has markedly improved prognosis, disease recurrence remains high in MM patients. The Intergroupe Francophone du Myelome[3] was the first to demonstrate, in a large randomized trial, the long-term benefits in survival of double ASCT in comparison

with single transplants. Since then, other randomized trials[4] and registry studies[5,6] have shown less recurrence and long-term disease control in patients treated with double ASCT.[4,7] However, relapse remains the main reason for treatment failure after ASCT, due to the presence of non-detectable residual disease in the patient, the graft, or both.[8] Conversely, allogeneic stem cell transplantation (alloSCT) is a potentially curative alternative, offering a tumor-free graft along with the benefit of a graft-*versus*-MM (GvM) effect.[9] Nevertheless, the role of alloSCT in MM patients is still controversial.[10-12] Several studies have shown elevated rates of molecular remission after myeloablative conditioning regimen (MAC) alloSC.[13] This regimen is characterized by high morbidity and mortality, especially in elderly patients with co-morbidities due to previous treatments, for whom less intensive conditioning regimens are preferable. The use of reduced intensity conditioning (RIC) extends the indication of hematopoietic stem cell transplantation to a higher number of patients who may benefit from an aggressive, but less toxic therapy than MAC, while maintaining the GvM effect. However, the efficacy of RIC on MM outcome remains uncertain. Different studies comparing tandem ASCT to alloSCT/RIC have given discordant results, with some of them failing to demonstrate the benefit of alloSCT/RIC.[10,14,15] There is, therefore, a general hesitancy in recommending up-front alloSCT. Consequently, most of the time alloSCT is offered as a salvage therapy post-ASCT relapse or for refractory disease. Outcomes after matched unrelated donor (MUD) transplantations for MM have been reported to be similar to those with HLA identical siblings; however, outcomes after MUD appear to be associated with higher non-relapse mortality (NRM).[16] Little is known of the use of other alternative donors, such as haploidentical or cord blood in patients with MM.[17-19] We performed a registry-based study to evaluate risk factors and outcomes of patients undergoing umbilical cord blood transplantation (UCBT) with the aim of analyzing the role of this stem cell source in patients with plasma cell disorders.

Methods

Study design, inclusion criteria and data collection

This is a retrospective observational registry-based study using Eurocord/EBMT data.

Patients over 18 years of age and diagnosed with MM or plasma cell leukemia (PCL) receiving single or double UCBT (dUCBT) between 2001 and 2013 were included. Exclusion criteria were: previous alloSCT, primary amyloidosis without MM, manipulated cord blood, intra-bone injection of cord blood cells or cord blood transplants associated with another stem cell source.

All patients gave informed consent for research. The study was conducted in accordance with the Declaration of Helsinki. The Internal Review Board of Eurocord-EBMT approved the study.

End points and definitions

The primary end point was progression-free survival (PFS) defined as time from UCBT to progression, relapse or death from any cause, whichever occurred first. Secondary end points were neutrophil and platelet recovery, acute and chronic graft-*versus*-host disease (GvHD), NRM, relapse incidence (RI) and overall survival (OS). OS was defined as time from transplant to death from any cause. Neutrophil (PMN) engraftment was defined as the first of three consecutive days with an absolute neutrophil count of $0.5x10^9$/L or over, without evidence of autologous reconstitution. Platelet (PLT) engraftment was defined as the first date at which an unsupported platelet count of $20x10^9$/L or over for seven consecutive days was achieved. MAC regimen was defined as a regimen containing total body irradiation (TBI) with a dose of more than 6 Gy or a dose of more than 8 mg/kg oral or more than 6.4 mg/kg intravenous busulfan or chemotherapy combination containing more than 10 mg/kg thiotepa. Response to treatment was defined according to standard criteria.[20] Chemo-refractory myeloma was defined as progression or non-response within 60 days of last therapy. GvHD was evaluated based on standard criteria.[21,22] For dUCBT, human leukocyte antigen (HLA) degree of matching was defined considering the UCB unit with the higher number of disparities with the recipient. High-risk cytogenetic abnormalities included at least one of the following: del17p, t(4;14) or t(14;16) performed by fluorescence *in situ* hybridization (FISH) or conventional metaphase cytogenetics, according to the policy of each center.

Statistical analysis

The probabilities of PFS and OS were estimated using the Kaplan-Meier method and compared with the log rank test. In the case of no event, observations were censored at the time of last follow up. Cumulative incidence (CI) was calculated in a competing risk setting. Death without an event was treated as a competing risk to calculate probabilities of neutrophil and platelet engraftment, acute and chronic GvHD. Death without progression or relapse was considered as competing risk for RI and relapse was the competing event for NRM. $P<0.05$ was considered statistically significant. All variables found to have $P<0.10$ in the univariate analysis were included in a Cox model for PFS and OS, or in a Fine and Gray proportional hazard regression model for engraftment, GvHD, NRM and relapse. Analysis was performed with SPSS 19 and SPLUS software.

Results

Patients' and transplant characteristics are summarized in Tables 1 and 2. A total of 95 patients with a median follow up of 41.3 (range 3.7-96) months met the inclusion criteria for the study. Median age at UCBT was 53.3 years (range 24.1-69.6) and median body weight was 70 kg (range 48-110). Median time from diagnosis to UCBT was 41.6 months (range 4.6-235.6). Diagnosis was MM for 85 (90%) and PCL for 10 (10%) patients. The immunoglobulin (Ig) subtype was IgG in 39 (46%), IgA in 23 (27%) and IgD in one case. Light chain myeloma accounted for 24% of patients, non-secretory for 2%, and the isotype was unknown in 9 patients. Twelve patients (17%) had chemo-refractory disease. Nearly all patients (96%) received at least one ASCT before UCBT: 26 (30%) received a planned tandem auto-auto and 18 (20%) a tandem procedure which included the current UCBT transplantation. The remaining 45 patients received one or more ASCT, but not as part of a planned tandem procedure. Only 4 patients did not receive a previous ASCT: 3 of them had PCL and received UCBT as first-line therapy in a median time of 5.5 months (range 4-6) from diagnosis; one had MM and received a UCBT after relapse at five years from diagnosis. Cytogenetic analysis was performed and available in 45 patients and was abnormal in 32 of them. The most frequent alteration was del13q (n=17). High-risk abnormalities [del17p or t(4;14)] were present in

Table 1. Patients' characteristics.

	Value
Follow up, median (range)	41.3 mo (3.7-96)
Age at UCBT , median (range)	53.3 yrs (24-69.6)
Diagnosis	
MM	85 (90%)
PCL	10 (10%)
Sex	
Male	51 (54%)
Female	44 (46%)
Subtype	
IgG	39 (46%)
IgA	23 (27%)
IgD	1 (1%)
Lambda or kappa light chain	21 (24%)
Non secretory	2 (2%)
Missing n=9	
ISS stage	
I	26 (38%)
II	17 (26%)
III	24 (36%)
Missing n=28	
Recipient CMV status	
Negative	44 (47%)
Positive	50 (53%)
Missing n=1	
Cytogenetic abnormalities	
High-risk alterations [del17p, t(4;14)]	11 (14%)
Other alterations	21 (27%)
Normal	13 (17%)
Not performed	33 (42%)
Missing n=17	
Chemosensitivity	
Chemo-refractory disease	12 (17%)
Chemosensitive disease	61 (83%)
Missing=22	
Extramedullary disease	
Yes	13 (18%)
No	55 (82%)
Missing=27	
Previous autotransplant	
0	4 (4%)
1	46 (50%)
2	38 (41%)
3	5 (5%)
Missing n=2	
Previous tandem auto-auto transplantation	
Yes	26 (29%)
No	63 (71%)
Missing=6	
Disease status at UCBT	
1st CR	10 (11%)
2nd CR	10 (11%)
VGPR	20(22%)
PR	37 (41%)
SD	4 (4%)
PD	10 (11%)
Missing n=4	
Exposed to new drugs before transplant	
Yes	82 (92%)
No	7 (8%)
Missing n=6	

MM: multiple myeloma; PCL: plasma cell leukemia; Kg: kilogram; CMV: cytomegalovirus; ISS: international scoring system; CR: complete remission; VGPR: very good partial remission; PR: partial remission; SD: stable disease; PD: progressive disease; mo: months; yrs: years; UCBT: umbilical cord blood transplantation.

Table 2. Transplant characteristics.

	Value
Type of UCBT	
sUCBT	36 (38%)
dUCBT	59 (62%)
Planned tandem auto-UCBT	
Yes	18 (20%)
No	71 (80%)
Missing n=6	
HLA mismatches	
0-1 mismatch	28 (32%)
2 or more mismatches	61 (68%)
Missing n=6	
Infused TNCX10^7/Kg, median (range)	3.3 (0.8-7.8)
Infused CD34X10^5/Kg, median (range)	1.25 (0.1-4.5)
Transplant year, median (range)	2009 (2001-2013)
Time from diagnosis to transplant, median (range)	41.6 mo (4.6-235.6)
Conditioning	
MAC	
Bu-based	9 (10%)
TBI-based	7 (7%)
Other	1 (1%)
RIC	
Cy+Flu+TBI	60 (64%)
Others	17 (18%)
Missing n=1	
GvHD prophylaxis	
CsA+MMF	74 (80%)
Others	19 (20%)
Missing n=2	
ATG use	
Yes	22 (24%)
No	68 (76%)
Missing n=5	

*UCBT: umbilical cord blood transplantation; TNC: total nucleated cell at collection; Kg: kilogram; HLA: human leukocyte antigen; MAC: myeloablative conditioning regimen; RIC: reduced conditioning regimen; TBI: total body irradiation; Cy: cyclophosphamide; Flu: fludarabine; Bu: busulfan; GvHD: graft-*versus*-host-disease; CsA: cyclosporine; MMF: mycophenolate mofetil; ATG: anti-thymocyte globulin; mo: months.*

11 patients. Ten patients were in first complete remission (CR) at UCBT, 10 in second CR, 20 in very good partial response (VGPR), 37 in partial response (PR), 14 in stable or progressive disease, and data were missing for the remaining 4 patients. Eighty-two patients received proteasome inhibitors or immunomodulatory drugs before UCBT. Among 43 patients with available information on HCTI-CI, 21 were reported as HCTI-CI 0, 4 HCTI-CI 1, 13 HCTI-CI 2 and 5 HCTI-CI 3.

Fifty-nine patients (62%) received a dUCBT. The majority of patients were conditioned with an RIC regimen (n=77, 82%). The most common conditioning regimen was cyclophosphamide+fludarabine+TBI (2-6 Gy) (64%) and antithymocyte globulin (ATG) was given to 24% of the patients. Cyclosporine A (CSA)+mycophenolate mofetil (MMF) was the most frequent GvHD prophylaxis (80%).

The median number of total nucleated cells (TNC) was 4.24x10^7/kg (range 2.2-7.8) at cryopreservation, and 3.3x10^7/kg (range 0.8-7.8) at infusion. The median number of cryopreserved and infused CD34$^+$ cells was 1.78x10^5/kg (range 0.5-6.6) and 1.25x10^5/kg (range 0.1-4.5),

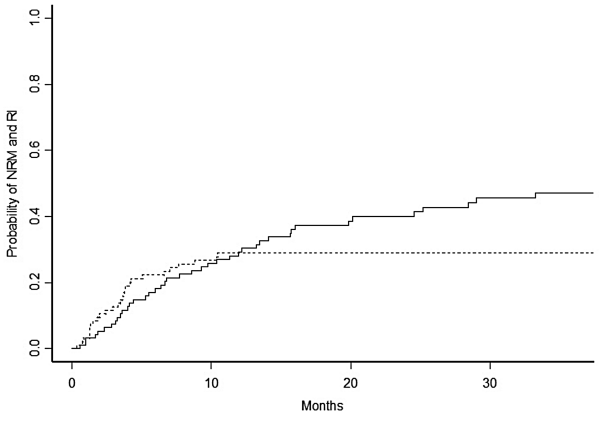

Figure 1. 3-year non-relapse mortality and relapse incidence. Solid line represents relapse incidence; dashed line represents non-relapse mortality incidence.

respectively. The majority of patients (68%) received a graft with 2 HLA mismatches. Among 63 patients with available information on maintenance therapy, 3 were treated with lenalidomide after UCBT.

Summaries of the univariate and multivariate analyses for major outcomes are shown in Tables 3 and 4, respectively.

Engraftment and GvHD

The CI of 60-day PMN and 180-day PLT engraftment were 97%±3% and 72%±5%, respectively. The median time of PMN and PLT engraftment were 20 (range 7-53) and 33 (range 8-98) days, respectively. Seven patients failed to achieve PMN engraftment; of these, 4 died within a median time of 21 months after UCBT. Three patients who experienced graft failure were alive at last follow up, 2 after an autologous rescue.

The CI of 100-day acute GvHD (aGvHD) grade II-IV and grade III-IV were 41%±5% and 16%±4%, respectively. aGvHD was lower in patients who received ATG (18% *vs.* 48%; *P*=0.02) and in those who did not receive TBI (15% *vs.* 49%; *P*<0.001). The use of ATG was associated with significant lower incidence of aGvHD in multivariate analysis (HR 0.25, 95%CI: 0.08-0.80; *P*=0.020).

The CI of chronic GvHD (cGvHD) at two years was 22%±4%, with a median time of onset of 188 days. Among the 23 patients who experienced cGvHD, 11 were alive at last follow up and 9 were disease free. Extensive cGvHD was observed in 5 patients (5 of 23). Patients who underwent dUCBT had a higher incidence of cGvHD than those receiving sUCBT in univariate analysis (30% *vs.* 9%; *P*=0.015).

Non-relapse mortality and relapse incidence

The CI of NRM at three years was 29%±5% (Figure 1). Overall, 63 patients died: 30 of relapse and 33 of transplant-related causes (infections, n=16; GvHD, n=5; other causes, n=12). In univariate analysis, ATG use (52% *vs.* 22%; *P*=0.004), MAC conditioning (54% *vs.* 23%; *P*=0.01) and TBI (51% *vs.* 22%; *P*=0.005) were associated with higher incidence of NRM. The use of ATG was independently associated with higher NRM in the multivariate analysis (HR 3.35, 95%CI: 1.44-7.81; *P*=0.005).

The CI of relapse at three years was 47%±5% (Figure 1). The RI was higher in chemo-refractory MM (75% *vs.* 45%; *P*=0.05). Moreover, in multivariate analysis patients with high cytogenetic risk had higher RI (HR 3.83, 95%CI: 1.26-11.61; *P*=0.018).

Overall survival and progression-free survival

The median follow up for survivors was 41 months (range 3.7-96). The 3-year probability of PFS and OS was 24%±5% and 40%±5%, respectively (Figures 2 and 3). In univariate analysis, RIC regimen and CsA+MMF as GvHD prophylaxis were associated with improved OS (43% *vs.* 30%, *P*=0.05, and 45% *vs.* 14%, *P*<0.001, respectively). Conversely, the use of ATG was associated with a decreased survival (10% *vs.* 46%; *P*<0.001). The effect of ATG use retained significance in multivariate analysis, with decreased OS (HR 4.03, 95%CI: 2.13-7.64; *P*<0.001) and PFS (HR=2.73, 95%CI: 1.48-5.05; *P*=0.001). Moreover, in multivariate analysis patients with high-risk cytogenetic had poorer OS (HR 2.99, 95%CI: 1.31-6.83; *P*=0.009) and PFS (HR 2.88, 95%CI: 1.26-6.57; *P*=0.012).

Discussion

We conducted a registry-based study with the objective of defining the role of UCBT in patients with plasma cell disorders. AlloSCT is not a standard treatment for patients with MM, and transplantation with alternative stem cell sources, such as UCBT, is even less common. The results of the current study suggest that UCBT is a feasible alternative for MM patients, and that high-risk cytogenetics and the use of ATG are independently associated with worse survival.

In the recent guidelines from the American Society for Blood and Marrow Transplantation on the indications for ASCT and alloSCT, the former was considered "standard of care" for MM patients in initial response or in sensitive relapse, and is considered "standard of care with clinical evidence" in refractory MM and PCL. On the other hand, alloSCT is still considered "developmental" for MM in initial response, but for patients in other disease stages or PCL, it is accepted as "standard of care with clinical evidence".[23] These recommendations do not take into account other factors such as age, comorbidities, donor source, and HLA incompatibilities. Overall, results of alloSCT are poor because of the high transplant-related mortality and high risk of relapse. The EBMT reported 3-year OS and PFS of 41% and 21%, respectively, in 229 MM patients who received RIC alloSCT from related and unrelated donors.[24] To date, only a few studies on the use of UCBT in MM have been published, and they were mostly isolated cases.[17,18] Recently, a more comprehensive survey was reported by the Japanese registry[19] in 86 patients with MM, showing 6-year OS and PFS of 15.2% and 13%, respectively. However, it has been shown in several publications that results are not always similar for Japanese and Western populations.[25] Moreover, our study differs from the previous publication because it includes both single and double UCBT and uses a different classification for high-risk cytogenetics.

In our series, in which 82% of patients received RIC regimen, OS and PFS were 40% and 24% at three years,

Table 3. Univariate analysis of main transplant outcomes.

		aGvHD		cGvHD		NRM		Relapse		OS		PFS	
	n	(%)	*P*	(%)	*P*	(%)	*P*	(%)	*P*	(%)	*P*	(%)	*P*
All patients	95	41		22		29		47		40		24	
Sex	95												
Male	51	42%	0.82	16%	0.22	36%	0.07	42%	0.24	36%	0.20	22%	0.32
Female	44	40%		29%		21%		53%		43%		26%	
Cytogenetics	45												
High risk	11	18%	0.09	0%	0.06	45%	0.21	36%	0.43	18%	0.07	17%	0.27
Not high risk	34	44%		25%		27%		49%		47%		18%	
Type of graft	95												
Single	36	31%	0.12	9%	0.01	28%	0.94	45%	0.9	39%	0.49	27%	0.80
Double	59	37%		30%		29%		49%		40%		21%	
Number of HLA disparities	89												
0-1HLA disparities	28	43%	0.96	14%	0.20	33%	0.66	50%	0.98	40%	0.96	17%	0.52
2 HLA disparities	61	43%		26%		26%		49%		37%		24%	
Conditioning regimen	94												
RIC	77	45%	0.06	24%	0.41	23%	0.01	52%	0.14	43%	0.05	25%	0.20
MAC	17	20%		14%		54%		20%		30%		27%	
Use of TBI	94												
No	21	15%	<0.001	19%	0.50	22%	<0.001	32%	0.15	25%	<0.001	17%	0.10
Yes	73	49%		24%		51%		52%		44%		25%	
GvHD prophylaxis	90												
CsA MMF	71	46%	0.11	25%	0.19	24%	<0.001	47%	0.73	45%	<0.001	28%	<0.001
Others	19	26%		10%		53%		39%		14%		8%	
Use of ATG before day 0	91												
No	69	48%	0.02	23%	0.31	22%	<0.001	49%	0.57	46%	<0.001	28%	<0.001
Yes	22	18%		11%		52%		39%		10%		0%	
TNCx10^7/kg	93												
≤3.3	48	38%	0.60	17%	0.18	34%	0.45	46%	0.66	33%	0.27	20%	0.42
>3.3	45	43%		28%		25%		47%		47%		28%	

*aGvHD: acute graft-*versus*-host-disease; cGvHD: chronic graft-*versus*-host-disease; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; HLA: human leukocyte antigen; MAC: myeloablative conditioning regimen; RIC: reduced conditioning regimen; TBI: total body irradiation; ATG: anti-thymocyte globulin; TNC: total nucleated cell infused.*

respectively. Although the number of previous therapy lines is not available, 90% of patients were transplanted beyond CR1, indicating that UCBT was not the first-line therapy for these patients. Our results are comparable to those observed in MM patients undergoing RIC-alloSCT with other stem cell sources, not only for PFS and OS, but also NRM (29%).[24]

We observed a detrimental impact of adverse karyotype in PFS and OS in multivariate analysis. Other authors have previously shown the negative impact of high-risk abnormalities, such as t(4;14), t(14;16), t(14;20) and del17p, on survival outcomes in patients with newly diagnosed MM.[26,27] Similar findings were demonstrated in patients receiving front-line ASCT, in which high-risk cytogenetics was associated with worse outcomes[28] and unsustained CR at one year.[29] The prognostic impact of adverse cytogenetics on alloSCT outcome in MM is not well established. Schilling *et al.* showed that alloSCT can be beneficial for patients with t(4;14), but not for those with del17p.[30] On the contrary, Roos-Weil *et al.* demonstrated that the increased risk associated with either of these mutations could be overcome with alloSCT.[31] More recently, the benefit of alloSCT for patients with MM harboring both t(4;14) and del17p was confirmed in a prospective tandem auto/RIC-alloSCT protocol.[32]

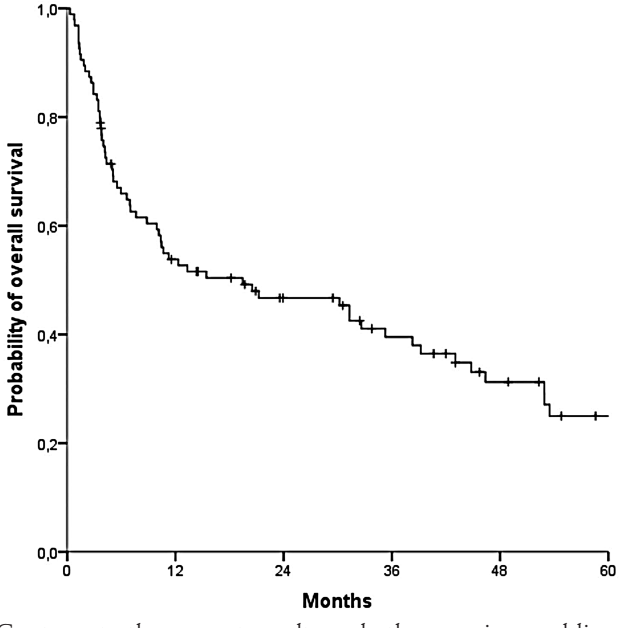

Figure 2. 3-year overall survival.

Contrary to the current results and other previous publica-

Table 4. Multivariate analysis.

	HR	95% CI	P
PFS			
ATG use *vs.* no ATG	2.73	1.48-5.05	0.001
High-risk cytogenetics *vs.* no high risk	2.88	1.26-6.57	0.012
Number of mismatch (0-1 *vs.* 2 or more)	1.07	0.58-1.97	0.83
Single *vs.* double UCBT	1.06	0.86-1.32	0.59
Median year of UCBT (≤2009 *vs.*>2009)	1.41	0.79-2.5	0.24
CR1/CR2/VGPR *vs.* PR/SD/PD	1.64	0.96-2.83	0.72
Median infused TNCx10^7/kg (≤3.3 *vs.* >3.3)	0.99	0.59-1.68	0.98
OS			
ATG use *vs.* no ATG	4.03	2.13-7.64	<0.001
High-risk cytogenetics vs no high risk	2.99	1.31-6.83	0.009
Number of mismatch (0-1 *vs.* 2 or more)	1.33	0.70-2.51	0.38
Single *vs.* double UCBT	1.08	0.85-1.36	0.55
Median year of UCBT (≤2009 *vs.* >2009)	1.54	0.82-2.88	0.18
CR1/CR2/VGPR *vs.* PR/SD/PD	1.31	0.73-2.34	0.38
Median infused TNCx10^7/kg (≤3.3 *vs.* >3.3)	1.02	0.57-1.81	0.95
RI			
High-risk cytogenetics *vs.* no high risk	3.83	1.26-11.61	0.018
Number of mismatch (0-1 *vs.* 2 or more)	0.86	0.39-1.93	0.72
Single *vs.* double UCBT	0.98	0.75-1.29	0.88
Median year of UCBT (≤2009 *vs.* >2009)	0.88	0.39-2.03	0.77
CR1/CR2/VGPR *vs.* PR/SD/PD	1.76	0.85-3.63	0.13
Median infused TNCx10^7/kg (≤3.3 *vs.* >3.3)	1.13	0.58-2.20	0.72
ATG use *vs.* no ATG	2.01	0.67-6.05	0.21
NRM			
ATG use *vs.* no ATG	3.35	1.44-7.81	0.005
High-risk cytogenetics *vs.* no high risk	2.06	0.55-7.6	0.28
Number of mismatch (0-1 *vs.* 2 or more)	1.68	0.64-4.39	0.30
Single *vs.* double UCBT	1.24	0.87-1.75	0.24
Median year of UCBT (≤2009 *vs.* >2009)	2.47	1.03-5.95	0.04
CR1/CR2/VGPR *vs.* PR/SD/PD	1.46	0.63-3.40	0.38
Median infused TNCx10^7/kg (≤3.3 *vs.* >3.3)	0.75	0.31-1.80	0.52
Acute GvHD			
ATG use *vs.* no ATG	0.24	0.08-0.80	0.020
High-risk cytogenetics *vs.* no high risk	0.51	0.12-2.23	0.37
Number of mismatch (0-1 *vs.* 2 or more)	0.77	0.35-1.70	0.51
Single *vs.* double UCBT	1.00	0.75-1.32	0.98
Median year of UCBT (≤2009 *vs.* >2009)	1.31	0.63-2.72	0.46
CR1/CR2/VGPR *vs.* PR/SD/PD	1.08	0.49-2.38	0.86
Median infused TNCx10^7/kg (≤3.3 *vs.* >3.3)	1.24	0.62-2.48	0.54

*HR: hazard ratio; CI: confidence interval; NRM: non-relapse mortality; RI: relapse incidence; OS: overall survival; PFS: progression-free survival; GvHD: graft-*versus*-host disease; UCBT: umbilical cord blood transplantation; CR1/2: first/second complete remission; VGPR: very good partial response; PR: partial remission; SD: stable disease; PD: progressive disease; TNC: total nucleated cells.*

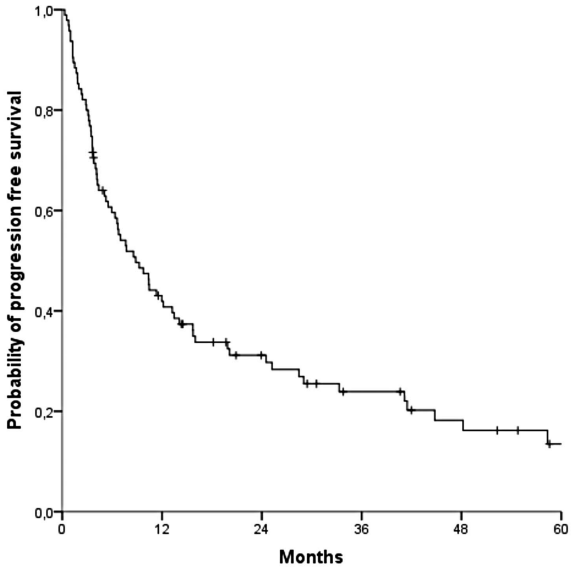

Figure 3. 3-year progression-free survival.

tions,[27] a recent study on UCBT[19] showed no association between high-risk cytogenetic and poor outcomes. A possible explanation for these findings might be the different risk group classification of patients harboring del13q.

In our series, ATG use was associated with lower OS, PFS and aGvHD, and with higher NRM. This was also reported, recently, in a larger series of patients with hematologic malignancies undergoing UCBT after RIC regimen.[33] As described in previous studies, immunosuppression with ATG is associated with a high incidence of infections.[34] In our series, infection was the primary cause of transplant-related deaths among patients who received ATG (n=22). We were unable to identify any significant association between the impact of disease status at UCBT and planned tandem transplantation on MM outcomes, as suggested by the Japanese group.[19] The lack of association of these factors on UCBT outcomes may be related to the low number of patients included in the categories of some specific variables or to actual differences between the populations in the different studies.

In our series, RI was high (47%), but comparable to results reported with other stem cell sources (bone marrow and peripheral blood stem cell) in previous alloSCT for MM studies.

Strategies to prevent relapse after UCBT may include post-transplant consolidation and/or maintenance with immunomodulatory drugs or proteasome inhibitors.[2]

Thalidomide has been investigated as salvage therapy in 31 patients[35] and at low doses with DLI in 18 patients,[36] both after alloSCT. Lenalidomide is already used after ASCT, but its use is still controversial after alloHSCT.[37] However, it may be beneficial, especially for high-risk MM,[38] as it has been demonstrated to improve response rate and to increase T-cell activity.[39] Bortezomib has been used in relapsed MM after RIC alloSCT (n=18) with a certain level of toxicity[40] and in patients not responding to DLI.[41] However, the application of novel agents in the UCBT setting and their potential in intensifying the GvMM effect after transplant ought to be further explored. In fact, there are several ongoing prospective studies (*clinicaltrials.gov identifiers: 02440464, 020308280, 01460420, 01131169, 02447055*) including anti-myeloma drugs as maintenance therapy early after alloSCT that may improve outcomes of MM patients.[42] One study in particular (*clinicaltrials.gov identifier: 02440464*) will investigate the use of a 2nd-generation anti-myeloma drug (ixazomib) in association with immunosuppressive therapy after alloSCT.

Unfortunately, only 3 patients in this series were reported to have received maintenance therapy, therefore we were unable to evaluate such strategies. Despite some limitations intrinsic to the retrospective nature of our study, we have demonstrated that UCBT is a feasible option for MM patients needing alloSCT.

Furthermore, the clinical applications for UCBT are still evolving. Several methods, such as the combination of cord blood and CD34+ selected haploidentical graft, the addition of mesenchymal stem cells, cord blood intrabone infusion and *ex vivo* expansion techniques are under investigation to improve engraftment.[43-45] However, further studies are needed to determine the potential benefit of these innovative strategies. Also, the use of haploidentical transplantation may deserve to be investigated to determine its applicability in this setting.

The place of alloSCT, including UCBT, is still unclear, but progress may be expected with a better identification of high-risk criteria, and a co-ordinated sequential approach with new drugs and transplant strategies.

Funding

MM was supported by educational grants from the "Association for Training, Education and Research in Hematology, Immunology and Transplantation" (ATERHIT). M Mohty would like to thank Prof. Junia V. Melo (University of Adelaide, Australia, and Imperial College, London) for critical reading of this manuscript.

References

1. Warren JL, Harlan LC, Stevens J, Little RF, Abel GA. Multiple myeloma treatment transformed: a population-based study of changes in initial management approaches in the United States. J Clin Oncol. 2013;31(16):1984-1989.
2. Lonial S, Boise LH, Kaufman J. How I treat high-risk myeloma. Blood. 2015; 126(13):1536-1543.
3. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349(26):2495-2502.
4. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol. 2007;25(17):2434-2441.
5. Morris C, Iacobelli S, Brand R, et al. Benefit and timing of second transplantations in multiple myeloma: clinical findings and methodological limitations in a European Group for Blood and Marrow Transplantation registry study. J Clin Oncol. 2004;22(9):1674-1681.
6. Barlogie B, Attal M, Crowley J, et al. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. J Clin Oncol. 2010;28(7):1209-1214.
7. Barlogie B, Tricot GJ, van Rhee F, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. Br J Haematol. 2006;135(2):158-164.
8. Alici E, Bjorkstrand B, Treschow A, et al. Long-term follow-up of gene-marked CD34+ cells after autologous stem cell transplantation for multiple myeloma. Cancer Gene Ther. 2007;14(3):227-232.
9. Mohty M, Boiron JM, Damaj G, et al. Graft-versus-myeloma effect following antithymocyte globulin-based reduced intensity conditioning allogeneic stem cell transplantation. Bone Marrow Transplant. 2004;34(1):77-84.
10. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. New Engl J Med. 2007;356(11):1110-1120.
11. Moreau P. Death of frontline allo-SCT in myeloma. Blood. 2012;119(26):6178-6179.
12. Lokhorst HM, van der Holt B, Cornelissen JJ, et al. Reduced relapse rate in upfront tandem autologous/reduced intensity allogeneic transplantation in multiple myeloma only results in borderline non-significant prolongation of progression free and not of overall survival. Haematologica. 2015; 100(12):e508-510.
13. Corradini P, Cavo M, Lokhorst H, et al. Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. Blood. 2003;102(5):1927-1929.
14. Rosinol L, Perez-Simon JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood. 2008; 112(9):3591-3593.
15. Gahrton G, Iacobelli S, Bjorkstrand B, 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.
16. Kroger N, Shimoni A, Schilling G, et al. Unrelated stem cell transplantation after reduced intensity conditioning for patients with multiple myeloma relapsing after autologous transplantation. Br J Haematol. 2010;148(2):323-331.
17. Fenk R, Neumann F, Fenk B, et al. Unrelated umbilical cord blood transplantation as salvage treatment for engraftment failure following autologous stem cell transplantation. Leuk Res. 2008;32(7):1157-1159.
18. Kasahara I, Nishio M, Yamamoto S, et al. Cord blood transplantation with a reduced-intensity conditioning regimen for patients with relapsed aggressive multiple myeloma after cytoreduction with bortezomib. Int J Hematol. 2009;90(3):413-415.
19. Kawamura K, Takamatsu H, Ikeda T, et al. Cord Blood Transplantation for Multiple Myeloma: A Study from the Multiple Myeloma Working Group of the Japan Society for Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2015;21(7):1291-1298.
20. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20(9):1467-1473.
21. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-828.
22. Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. Hematol Oncol Clin North Am. 1999;13(5):1091-1112, viii-ix.
23. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015; 21(11):1863-1869.
24. Crawley C, Lalancette M, Szydlo R, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. Blood. 2005;105(11):4532-4539.
25. Tanimoto TE, Yamaguchi T, Tanaka Y, et al. Comparative analysis of clinical outcomes after allogeneic bone marrow transplantation versus peripheral blood stem cell transplantation from a related donor in Japanese patients. Br J Haematol. 2004;125(4):480-493.
26. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood. 2007;109(8):3489-3495.
27. Bergsagel PL, Mateos MV, Gutierrez NC, Rajkumar SV, San Miguel JF. Improving overall survival and overcoming adverse prognosis in the treatment of cytogenetically high-risk multiple myeloma. Blood. 2013;121(6):884-892.
28. Moreau P, Cavo M, Sonneveld P, et al. Combination of international scoring system 3, high lactate dehydrogenase, and t(4;14) and/or del(17p) identifies patients with multiple myeloma (MM) treated with front-line autologous stem-cell transplantation at high risk of early MM progression-related death. J Clin Oncol. 2014;32(20): 2173-2180.
29. Paiva B, Gutierrez NC, Rosinol L, et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood. 2012;119(3):687-691.
30. Schilling G, Hansen T, Shimoni A, et al. Impact of genetic abnormalities on survival after allogeneic hematopoietic stem cell transplantation in multiple myeloma. Leukemia. 2008;22(6):1250-1255.
31. Roos-Weil D, Moreau P, Avet-Loiseau H, et al. Impact of genetic abnormalities after allogeneic stem cell transplantation in multiple myeloma: a report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Haematologica. 2011; 96(10):1504-1511.
32. Kroger N, Badbaran A, Zabelina T, et al. Impact of high-risk cytogenetics and achievement of molecular remission on long-term freedom from disease after autol-

ogous-allogeneic tandem transplantation in patients with multiple myeloma. Biol Blood Marrow Transplant. 2013; 19(3):398-404.
33. Pascal L, Tucunduva L, Ruggeri A, et al. Impact of ATG-containing reduced-intensity conditioning after single- or double-unit allogeneic cord blood transplantation. Blood. 2015;126(8):1027-1032.
34. Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. Blood. 2007; 110(8):3064-3070.
35. Mohty M, Attal M, Marit G, et al. Thalidomide salvage therapy following allogeneic stem cell transplantation for multiple myeloma: a retrospective study from the Intergroupe Francophone du Myelome (IFM) and the Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC). Bone Marrow Transplant. 2005;35(2):165-169.
36. Kroger N, Shimoni A, Zagrivnaja M, et al. Low-dose thalidomide and donor lymphocyte infusion as adoptive immunotherapy after allogeneic stem cell transplantation in patients with multiple myeloma. Blood. 2004;104(10):3361-3363.
37. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after non-myeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. Blood. 2011;118(9):2413-2419.
38. Alsina M, Becker PS, Zhong X, et al. Lenalidomide maintenance for high-risk multiple myeloma after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2014;20(8): 1183-1189.
39. Wolschke C, Stubig T, Hegenbart U, et al. Postallograft lenalidomide induces strong NK cell-mediated antimyeloma activity and risk for T cell-mediated GvHD: Results from a phase I/II dose-finding study. Exp Hematol. 2013;41(2):134-142 e133.
40. Kroger N, Zabelina T, Ayuk F, et al. Bortezomib after dose-reduced allogeneic stem cell transplantation for multiple myeloma to enhance or maintain remission status. Exp Hematol. 2006;34(6):770-775.
41. van de Donk NW, Kroger N, Hegenbart U, et al. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. Bone Marrow Transplant. 2006;37(12):1135-1141.
42. Dhakal B, Vesole DH, Hari PN. Allogeneic stem cell transplantation for multiple myeloma: is there a future? Bone Marrow Transplant. 2016;51(4):492-500.
43. Frassoni F, Gualandi F, Podesta M, et al. Direct intrabone transplant of unrelated cord-blood cells in acute leukaemia: a phase I/II study. Lancet Oncol. 2008; 9(9):831-839.
44. Delaney C, Heimfeld S, Brashem-Stein C, Voorhies H, Manger RL, Bernstein ID. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nat Med. 2010;16(2):232-236.
45. Kwon M, Bautista G, Balsalobre P, et al. Haplo-cord transplantation using CD34+ cells from a third-party donor to speed engraftment in high-risk patients with hematologic disorders. Biol Blood Marrow Transplant. 2014;20(12):2015-2022.