

ORIGINAL ARTICLE

Comparable non-relapse mortality and survival after HLA-identical sibling blood stem cell transplantation with reduced or conventional-intensity preparative regimens for high-risk myelodysplasia or acute myeloid leukemia in first remission

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We prospectively compared two strategies of allogeneic PBSCT from HLA-identical siblings in adults with poor-risk AML or myelodysplastic syndrome with >5% marrow blasts in an early disease status (AML or refractory anemia with excess blasts (RAEB type 2) in first remission after chemotherapy or untreated RAEB type 1). Based only on age, all consecutive patients were offered one of two specific transplant protocols. Patients ≤50 years old received conventional high-dose conditioning with cyclophosphamide-TBI and use of CD34+-selected PBSCT (CTCD34+ group), while patients aged >50 years received a reduced-intensity conditioning (RIC) with fludarabine and oral busulphan (FB-RIC). Seventy-five patients entered the study (35 in the CTCD34+ and 39 in the FB-RIC group). The median follow-up was >4 years in both groups. The 4-year non-relapse mortality (NRM) was 19 and 20%, respectively ($P=0.8$). Relapse and survival were also equivalent in both groups. These results suggest that in this setting, the expected high NRM in elderly patients can be reduced with an RIC regimen.

Bone Marrow Transplantation (2008) 41, 33–38;
doi:10.1038/sj.bmt.1705879; published online 5 November 2007
Keywords: conditioning regimens; allogeneic transplantation; AML; myelodysplastic syndromes

Introduction

Conventional high-dose TBI-containing conditioning regimens for allogeneic hematopoietic SCT (alloHSCT) have a high non-relapse mortality (NRM) in adults with high-risk myelodysplastic syndromes (MDS) and AML above the age of 45–50 years.^{1–3} In an effort to reduce NRM, several

groups have developed reduced-intensity conditioning (RIC) regimens,^{4–11} which lead to engraftment of donor lymphoid and hematopoietic stem cells without the non-hematologic toxicities of traditional myeloablative transplants.^{4–13} However, experience with RIC alloHSCT in AML and high-risk MDS is limited. We have reported previously that RIC followed by allogeneic PBSCT after a homogeneous RIC regimen produces high rates of engraftment with tolerable toxicity and acceptable outcomes in a heterogeneous group of patients with myeloid malignancies.^{12,13} On the basis of these data, we started a prospective trial in which adult patients with poor-risk AML and MDS in an early disease status and with an HLA-identical sibling were assigned to receive a conventional or an RIC regimen based solely on patient age. The outcomes of both conditioning strategies, with a specific emphasis on NRM, were compared in the 74 adults who received the assigned conditioning strategy, as well as in all patients with an HLA-identical sibling on the basis of intention to treat (ITT).¹⁴

Patients and methods

Patient selection

Between 1998 and December 2005, all consecutive adult patients with ‘poor-prognosis’ AML or MDS in an ‘early disease’ status and with an HLA-identical sibling were programmed to receive an allogeneic PBSCT within this study. Early disease status was defined as AML or refractory anemia with excess blast (RAEB) type 2 (blasts in BM at diagnosis $\geq 10\%$) in CR-1 after chemotherapy¹⁵ and untreated RAEB type 1.

‘Poor-prognosis’ AML and RAEB type 2 were defined as one or more of the following: (1) poor-risk cytogenetics;¹⁴ (2) CR-1 was obtained only after two cycles of intensive induction therapy; and/or (3) presence of flt-3 internal tandem duplication or MLL rearrangement in molecular analysis.¹⁶ Poor-prognosis RAEB type 1 was defined by an international prognostic score intermediate-2 or high.¹⁷

During the study period, 40 consecutive patients 50 years of age or younger were assigned to receive the conventional

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Received 25 January 2007; revised 10 July 2007; accepted 29 August 2007; published online 5 November 2007

high-dose conditioning regimen, while 47 patients above the age of 50 were assigned to receive the RIC regimen. However, five (13%) and eight (17%) patients from each transplant group, respectively, did not reach the assigned therapy because of disease progression ($n = 10$) or death during intensification chemotherapy ($n = 3$). Thus, the number of patients who received the assigned therapy was 35 and 39, respectively. Patients gave written informed consent for inclusion in the protocols, which were approved

by all local ethical review boards and the Spanish Drug Agency. The characteristics and outcomes of the 74 study subjects are shown in Table 1.

Conditioning regimens and supportive care

A homogeneous transplant protocol was used in each study (or age) group. Young patients (those with 50 years of age or younger) were conditioned with cyclophosphamide plus

Table 1 Patient characteristics and transplant outcomes (% in parentheses)

	CTCD34+ group	FB-RIC group	P
Patients assigned to a study group ^a	40	47	
Patient and transplant characteristics (patients who reached the assigned transplant group) ^b	35 (88%) ^b	39 (83%) ^b	
Age, median (range)	42 (19–50)	59 (51–69)	NT
Patient male-donor female	7 (20)	11 (28)	NS
<i>Underlying disease</i>			
Acute myelogenous leukemia	33 (94)	22 (56)	<0.01
Refractory anemia with excess blasts (types 1 and 2)	2 (6)	17 (44)	
Median BM blasts at transplantation ^c (range)	1 (<0.1–5%)	1 (0.5–6%)	NS
Poor-risk cytogenetics ^d	15 (43)	28 (72)	0.03
High hematopoietic cell transplantation-comorbidity index (≥ 3) ^e	9 (26)	18 (46)	0.002
Do or Re CMV seropositive	32 (91)	36 (92)	NS
<i>Major post transplant outcomes</i>			
Median days to neutrophil count $>0.5 \times 10^9/l$ (range)	13 (10–28)	15 (9–21)	NS
Median days of early inpatient care (range) ^f	20 (14–30)	9 (0–18)	<0.02
<i>CDC in UF nucleated cells from PB (subset CDC in T cells/granulocytes)^g</i>			
Day +30	90 (20/90)	80 (20/80)	NS
Day +90	100 (40/100)	95 (60/95)	
Days +180 to +360	100 (55/100)	100 (100/100)	
Developed grade II–IV aGVHD (% CumInc, 95% CI) ^h	6 (18%, 6–30)	8 (21%, 14–28)	NS
Developed cGVHD (% CumInc, 95% CI) ^h	12 (32%, 15–49)	20 (71%, 56–86)	<0.01
% CumInc extensive cGVHD	20%	46%	0.04
Final m-sGVHD (% CumInc, 95% CI) ^h	13 (32%, 21–43)	23 (51%, 39–62)	0.056
Relapse at 4 years (% CumInc, 95% CI)	21 (6–42)	21 (7–41)	0.8
Disease-free survival at 4 years (% probability, 95% CI)	60 (41–79)	59 (42–78)	0.9
Disease-free survival as ITT (% probability, 95% CI) ⁱ	50 (31–69)	43 (30–66)	0.7
Overall survival at 4 years (% probability, 95% CI)	59 (39–77)	60 (41–79)	0.9
Overall survival as ITT (% probability, 95% CI) ⁱ	52 (32–70)	49 (29–67)	0.8
4-year mortality post transplant	15 (43)	15 (38)	
GVHD \pm infections	7	7	
Other causes of non-relapse mortality	1	—	
Disease relapse	7	8	
Median months follow-up in survivors (range)	52 (12–91)	50 (13–85)	NS

Abbreviations: aGVHD = acute GVHD; CDC = complete donor chimerism; cGVHD = chronic GVHD; CI = confidence interval; CTCD34+ = high-dose myeloablative conditioning with cyclophosphamide (120 mg/kg) plus TBI (13.5 Gy) and CD34+ -positive cell selection;^{15,18} CumInc = cumulative incidence; DFS = disease-free survival; Do = Donor; ECOG = Eastern Cooperative Oncology Group; FB-RIC = oral busulfan (10 mg/kg) and fludarabine (150 mg/m²) reduced-intensity conditioning;^{12,13} IPSS = international prognostic scoring system;¹⁹ ITT = intention to treat; m-sGVHD = moderate-to-severe GVHD; MDS = myelodysplastic syndrome; NT = not tested; Re = recipient; UF = unfractionated.

^aRefers to all patients who had an HLA-identical sibling and were assigned to receive one of the two transplant strategies according to their age (i.e., intention-to-treat analysis).

^bThe % in parentheses refers to patients with a compatible sibling donor who actually received the assigned allogeneic HSCT. All other % shown in brackets in the table refer to patients who were actually transplanted.

^cThe % of BM blasts was analyzed by multiparameter flow cytometry.¹⁶

^dCytogenetics were classified using the EORTC/GIMEMA criteria.¹⁴

^eThe HCT-comorbidity index was calculated as described by Sorror *et al.*²⁰

^fDays required of in-patient supportive care in the early post transplantation period (\leq day +30).

^gData on CDC in peripheral blood nucleated cells refers to the finding of 100% donor cells in unfractionated (UF) nucleated cells in patients who were alive and without disease progression at each given time point shown, and without prior donor lymphocyte infusions. In brackets, the CDC in fractionated T lymphocytes and granulocytes from the same PB samples are shown.

^hRefers to GVHD that occurred spontaneously, i.e., without prior donor lymphocyte infusions.

ⁱIn the ITT analysis, DFS and OS were calculated for all patients with a donor ($n = 87$ patients) and in an early disease status from the moment an HLA-identical sibling was identified. At last follow-up, 2/5 patients in CTCD34+ group (age ≤ 50 years) and 2/8 patients in the FB-RIC group (> 50 years) who did not receive the assigned alloHSCT strategy per protocol were alive and disease-free.

TBI, and PBSC underwent CD34+ -positive cell selection^{15,18} (CTCD34+ transplant group), while the RIC regimen used in elderly patients (more than 50 years of age) consisted of fludarabine plus busulphan^{12,13} (10 mg/kg) (FB-RIC transplant group). GVHD prophylaxis consisted of cyclosporine A alone or in combination with short-course methotrexate in each group, respectively.

Statistical analysis

The biological features of unselected groups of young and elderly patients with AML and high-risk MDS are expected to differ, especially since all consecutive patients were included. These biological differences have an impact on the risk of relapse and disease-free survival (DFS), which may not be apparent in small patient subgroups, and a detailed statistical risk factor analysis for these outcomes would be unreliable. NRM, however, is strongly linked to age. Consequently, the current analysis focuses on NRM in each transplant group as well as in the entire cohort.

Non-relapse mortality and disease relapse were calculated using cumulative incidence estimates. Univariate Cox regression was used for univariate analyses, and variables with a $P \leq 0.1$ were included in multivariate Cox regression analyses, while the probabilities of DFS and overall

survival (OS) were estimated using Kaplan–Meier product-limit estimates. Variables analyzed for their impact on outcomes included the hematopoietic cell transplant (HCT)-comorbidity index, cytogenetics risk group, disease type (AML and RAEB type 2 or RAEB type 1), acute GVHD 2–4, chronic GVHD, patient age, CD34+ cell dose infused, sex mismatch, origin of AML-MDS (*de novo* vs therapy-related AML-MDS vs secondary AML) and patient’s CMV serostatus.

All outcomes were measured from the date of transplantation, except for the ITT analysis, which was done from the date that a patient who fulfilled the criteria for an alloHSCT was found to have an HLA-identical sibling donor.^{19,21}

Results

All patients had initial donor-derived hematological recovery. The number of days with neutrophils below $0.5 \times 10^9/l$ and platelets below $20 \times 10^9/l$ were shorter in the FB-RIC with respect to the CTCD34+ group (15 vs 8 days for neutrophils and 14 vs 4 days for platelets, respectively; $P < 0.05$ for both comparisons). Using DNA-based chimer-

Table 2 Summary of the results of risk factor analyses for non-relapse mortality

	Overall analysis ^a			CTCD34+ group ^a		FB-RIC group ^a	
	4-year CumInc	HR (95% CI)	Multivariate P	4-year CumInc	Univariate P	4-year CumInc	Univariate P
<i>Patients who received the alloHSCT (95% CI)</i>							
CTCD34+ conventional conditioning (n = 35)	19 (9–37)						
FB-RIC (n = 39)	20 (11–37)	0.8	NA	—	—	—	—
<i>Patient age^b</i>							
Below the median age in each group	16	NA		12	<0.01	17	0.7
Above the median age in each group	22		—	31		20	
<i>Sex mismatch</i>							
Female Do/male Re	54	8.3 (2–34)	<0.01	40	<0.01	38	0.01
Other combinations	4			8		5	
<i>HCT-comorbidity index^c</i>							
0	6			3		6	
1–2	14	9.8 (1.01–39)	0.05	19	0.01	10	0.04
≥3	49			65		45	
<i>CD34+ cell dose/kg infused^b</i>							
Below the median in each group	20	NA		16	0.9	33	<0.01
Above the median in each group	18		—	20		7	
<i>Acute GVHD 2–4^d</i>							
Yes	35	NA	0.2	36		28	0.3
No	10			10	0.09	12	

Abbreviations: CI = confidence interval; CTCD34+ = high-dose myeloablative conditioning with cyclophosphamide (120 mg/kg) plus TBI (13.5 Gy) and CD34+ -positive cell selection;^{15,18} CumInc = cumulative incidence; Do = Donor; FB-RIC = oral busulphan (10 mg/kg) and fludarabine (150 mg/m²) reduced-intensity conditioning;^{12,13} HCT = hematopoietic cell transplantation; HR = hazard ratio; NA = not applicable; the hazard ratio was not calculated since the variable had no impact in univariate or multivariate analysis; Re = recipient.

^aMultivariate analysis was done in the whole patient population, while only univariate analyses were done separately in each transplant group, due to the small sample sizes.

^bPatient age and dose of CD34+ cells/kg infused were divided in two categories: above and below the median value in each group analyzed (53 years old (y.o.) in all 72 patients, 42 y.o. in the CTCD34+ group and 59 y.o. in the FB-RIC group).

^cThe HCT-comorbidity index was calculated as described by Sorror et al.²⁰ The P-values and hazard ratios refer to the comparison of an index of 0–2 vs ≥3.

^dAnalyzed as a time-dependent covariate.

ism testing in peripheral blood,²² the proportion of patients who had complete donor chimerism in T cells on days +90, +180 and +360 was higher in the FB-RIC group (Table 1).

The day +100 cumulative incidence of acute GVHD (grades 2–4) was 18% (95% confidence interval (CI), 6–30%) for CTCD34+ and 21% (95% CI, 14–28%) for FB-RIC groups ($P=0.8$). The cumulative incidence of chronic GVHD (cGVHD) at 4 years was 32 and 71%, respectively ($P<0.01$).

NRM and other post transplant outcomes

The median follow-up for survivors was around 4 years as of 30 March 2007. The transplant group had no impact on any outcome at 4 years post transplant. Table 1 shows in detail the 4-year incidence of relapse, DFS and OS (including the ITT analysis for DFS and OS).

Results of univariate and multivariate analyses of NRM (primary end point of the study) are shown in detail in Table 2. The 4-year incidence of NRM was 20 and 19% in the FB-RIC and CTCD34+ group, respectively ($P=0.8$). Multivariate analysis was done in the whole patient population, while only univariate analyses were done separately in each transplant group due to the small sample sizes. Of note, a high HCT-comorbidity showed a strong deleterious impact in both patient groups (Figure 1).

In multivariate analysis, only not developing cGVHD (hazard ratio 5.8, 95% CI 1.6–24, $P=0.04$) had an independent impact on relapse (10% incidence in patients with and 38% in patients without cGVHD, $P=0.01$). For OS and DFS, in multivariate analysis, the only variables that showed an impact were not developing cGVHD (hazard ratio 3.6, 95% CI 1.2–20, $P=0.02$ for OS; hazard ratio 5.3, 95% CI 1.2–29, $P=0.02$ for DFS) and a high HCT-comorbidity index ($P=0.05$ for OS and $P=0.06$ for DFS), while a trend was found for male recipient with a female donor ($P=0.06$ for OS and $P=0.08$ for DFS).

Only two variables clearly had an opposite impact on post transplant outcomes in the univariate analyses done separately in each transplant group: (i) patient age (<42 vs ≥ 42 years) had an impact on NRM, OS and DFS only in the CTCD34+ group (Figure 2a); while (ii) the dose of CD34+ cells/kg infused ($\geq 6 \times 10^6$ vs $< 6 \times 10^6$ /kg) had an impact on survival only in the FB-RIC group (Figure 2b).

In keeping with previous observations, all early post transplant extrahematological toxicities were milder in the FB-RIC group, leading to fewer days of hospitalization in the first 30 days after transplant for supportive care, mainly due to gastrointestinal toxicity (median 9 vs 20 days in the FB-RIC and CTCD34+ group, respectively; $P<0.02$). However, the median number of readmissions after day +30 and up to 1 year post transplant was higher in the FB-RIC group (3 (range: 0–6) vs 1 (range: 0–4) readmission, respectively; $P<0.05$), mostly due to severe infections and/or gastrointestinal GVHD (details not shown).

The proportion of surviving patients with a Karnofsky score of $\geq 90\%$ in the CTCD34+ vs the FB-RIC groups was 50 vs 30%, respectively, at 1 year, 75 vs 40% at 2 years and 90 vs 60% at 4 years.

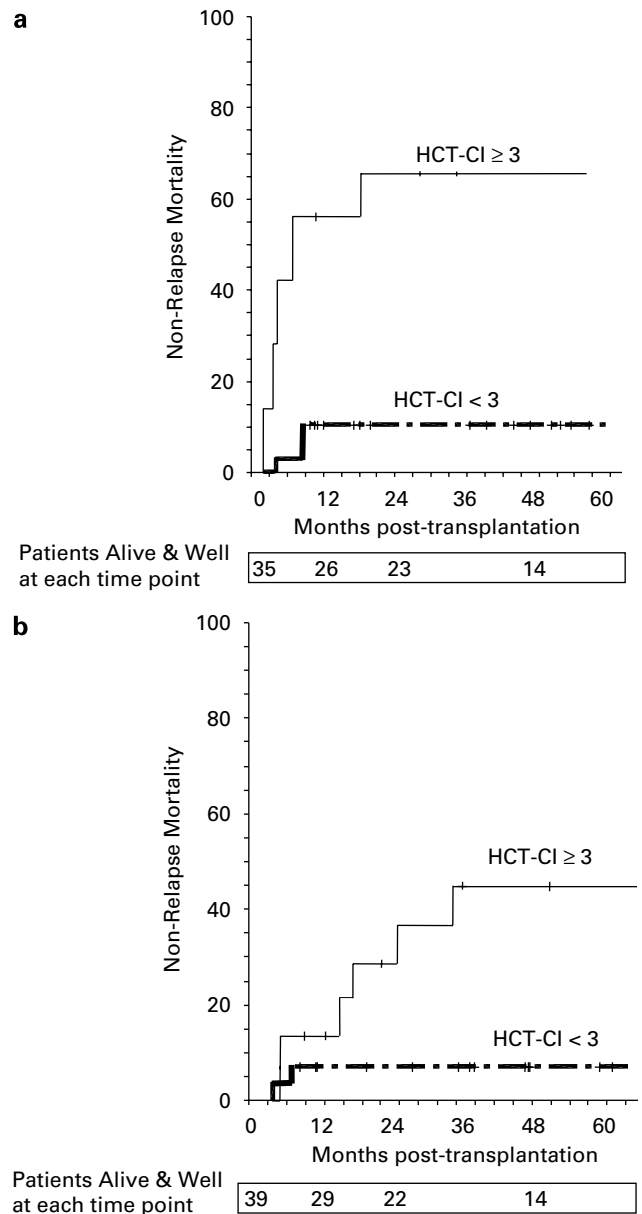


Figure 1 Incidence of non-relapse mortality (NRM) (a) in the CTCD34+ group by the hematopoietic cell transplantation-comorbidity index (HCT-CI); the 4-year NRM in patients with an HCT-CI ≥ 3 and < 3 was 65 and 10%, respectively ($P=0.01$). (b) In the FB-RIC group, the 4-year NRM was 45 and 7%, respectively ($P=0.04$).

Discussion

Elderly age has been considered a major risk factor for failure of a conventional myeloablative alloHSCT, attributed mainly to a high early post transplant conditioning-related NRM. The results obtained from this single-center prospective study suggest that the negative impact of elderly age on the outcome of alloHSCT for patients with early-status AML and MDS can be reduced with an RIC protocol. We believe that the main strength of this study is the prospective 'age-randomized' nature of the trial. In the context of a single-center consecutive patient cohort, 'age randomization' can be a suitable way of comparing two

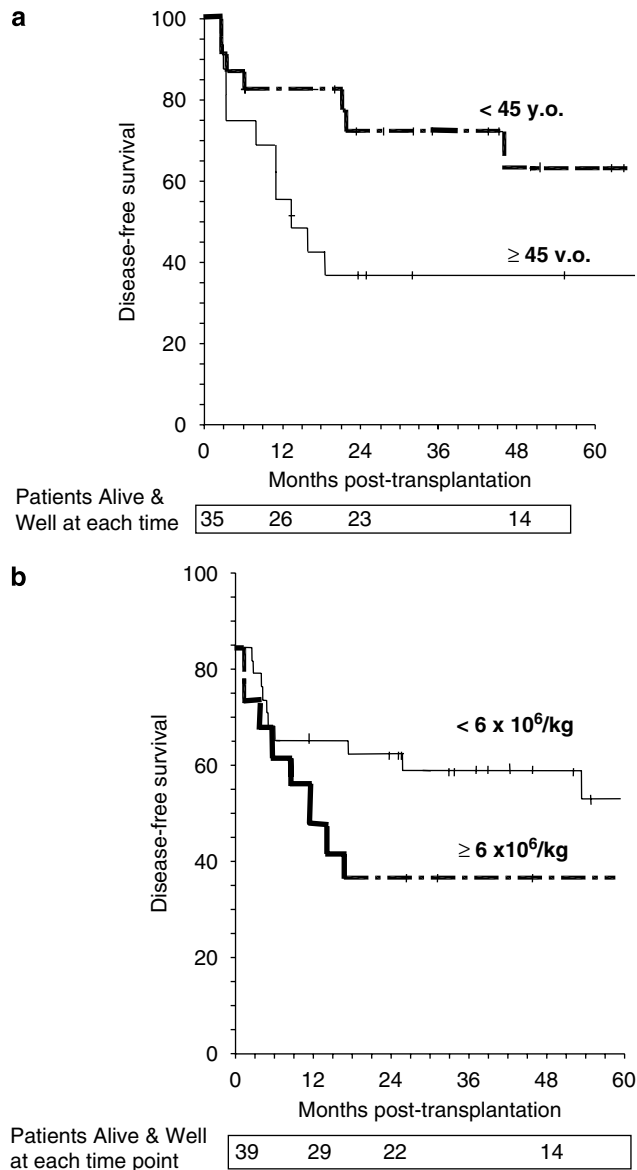


Figure 2 Probability of disease-free survival (DFS) (a) in the CTCD34+ group by patient age; the 4-year DFS in patients ≥ 42 and < 42 years old was 37 (95% confidence interval (CI), 19–55%) and 64% (95% CI, 49–79%), respectively ($P=0.08$). (b) In the FB-RIC group, the 4-year DFS in patients who received a CD34+ cell dose in the graft $\leq 6 \times 10^6$ and $> 6 \times 10^6/\text{kg}$ was 42 (95% CI, 19–65%) and 72% (95% CI, 55–89%), respectively ($P=0.05$).

transplant strategies, while eliminating potentially unknown selection biases.²¹ In addition, we analyzed survival according to the ITT principle to avoid misleading interpretations and biased treatment effects,¹⁹ since reasonable doubts have arisen as to the true impact of RIC alloHSCT to elderly patients due to the various biases that lead to selection of only very fit older patients.^{23–25} The similar 4-year OS and DFS in this ITT analysis suggest that RIC alloHSCT may be proposed for elderly patients with AML/MDS. Other strengths of this study are the inclusion only of patients with very poor-risk AML/MDS, the relatively long median follow-up of 4 years and the homogeneous

donor type, stem cell source and conditioning regimen used in each cohort.

On the other hand, the main weakness of the current study is the small sample sizes, and, as previously highlighted, the age-dependent differences in the biological characteristics of AML and high-risk MDS. Because of these differences, only the statistical analyses of NRM are shown. In addition, many centers would disagree with the conventional high-dose conditioning chosen for young patients and the RIC strategy chosen for elderly patients; it should be stressed, however, that these strategies showed good outcomes in each age group in our previous single-arm studies, and this prompted us to choose them and keep them homogeneous throughout the study. The trend for increased NRM in the CTCD34+ group in the patients with an age near 50 and the relatively low NRM in the FB-RIC group suggest that our goals may have been met. Interestingly, the higher NRM in patients with a high HCT-comorbidity index in both age groups (Figure 1) is in line with previous observations, confirming that comorbidities, and not simply age alone, may help identify proper candidates for RIC regimens.²⁰

In summary, these single-center results suggest that in this disease setting, the expected high NRM in elderly patients can be reduced with an RIC regimen, leading to equivalent survival when compared to young patients receiving a myeloablative alloPBSCT from an HLA-identical sibling. Our study was not powered to identify the impact of the type of conditioning on other outcomes, and for this purpose, a larger multicenter protocol is ongoing.

Acknowledgements

This study was performed in the setting of the CETLAM cooperative group (Grupo Cooperativo para el Estudio y Tratamiento de las Leucemias Agudas y Mielodisplasias, protocols CET-LAM-99 and CET-LAM-2003), in part with grants C03/010 and 603/008 from the Instituto de Salud Carlos III and two grants from Fundació d'Investigació Sant Pau and Fundació 'La Caixa' (Barcelona, Spain).

Specific contribution(s) of each coauthor: RM: conceived and executed the research reported in the paper, the integrity and data analysis, was involved in patient care and wrote the various versions of the manuscript. In addition, he also had the task of data management and statistical analyses. DV: collaborated in patient care, data management and the statistical analyses. All other co-authors contributed in the conception and execution of the research reported in the paper and in-patient care, and participated in writing or interpreting relevant parts of the manuscript.

References

- Appelbaum FR, Pearce SF. Hematopoietic cell transplantation in first complete remission versus early relapse. *Best Pract Res Clin Haematol* 2006; **19**: 333–339.
- de WT, Oosterveld M, Span B, Muus P, Schattenberg A. Stem cell transplantation for leukemias following myelodysplastic

- syndromes or secondary to cytotoxic therapy. *Rev Clin Exp Hematol* 2002; **6**: 72–85.
- 3 Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J *et al*. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. *Blood* 2006; **108**: 836–846.
 - 4 de Lima M, Giralt S. Allogeneic transplantation for the elderly patient with acute myelogenous leukemia or myelodysplastic syndrome. *Semin Hematol* 2006; **43**: 107–117.
 - 5 de Lima M, Anagnostopoulos A, Munsell M, Shahjahan M, Ueno N, Ippoliti C *et al*. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. *Blood* 2004; **104**: 865–872.
 - 6 Niederwieser D, Lange T, Cross M, Basara N, Al-Ali H. Reduced intensity conditioning (RIC) haematopoietic cell transplants in elderly patients with AML. *Best Pract Res Clin Haematol* 2006; **19**: 825–838.
 - 7 Lazarus HM, Rowe JM. Reduced-intensity conditioning for acute myeloid leukemia: is this strategy correct. *Leukemia* 2006; **20**: 1673–1682.
 - 8 Ho AY, Pagliuca A, Kenyon M, Parker JE, Mijovic A, Devereux S *et al*. Reduced-intensity allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab (FBC) conditioning. *Blood* 2004; **104**: 1616–1623.
 - 9 Scott BL, Sandmaier BM, Storer B, Maris MB, Sorrow ML, Maloney DG *et al*. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. *Leukemia* 2006; **20**: 128–135.
 - 10 Shimoni A, Hardan I, Shem-Tov N, Yeshurun M, Yerushalmi R, Avigdor A *et al*. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia* 2006; **20**: 322–328.
 - 11 Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb HJ *et al*. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). *Leukemia* 2005; **19**: 2304–2312.
 - 12 Martino R, Caballero MD, Simon JA, Canals C, Solano C, Urbano-Ispizua A *et al*. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. *Blood* 2002; **100**: 2243–2245.
 - 13 Martino R, Perez-Simon JA, Moreno E, Queralto JM, Caballero D, Mateos M *et al*. Reduced-intensity conditioning allogeneic blood stem cell transplantation with fludarabine and oral busulfan with or without pharmacokinetically targeted busulfan dosing in patients with myeloid leukemia ineligible for conventional conditioning. *Biol Blood Marrow Transplant* 2005; **11**: 437–447.
 - 14 Suci S, Mandelli F, de Witte T, Zittoun R, Gallo E, Labar B *et al*. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMAAML-10 trial. *Blood* 2003; **102**: 1232–1240.
 - 15 Brunet S, Esteve J, Berlanga J, Ribera JM, Bueno J, Marti JM *et al*. Treatment of primary acute myeloid leukemia: results of a prospective multicenter trial including high-dose cytarabine or stem cell transplantation as post-remission strategy. *Haematologica* 2004; **89**: 940–949.
 - 16 Munoz L, Aventin A, Villamor N, Junca J, Acebedo G, Domingo A *et al*. Immunophenotypic findings in acute myeloid leukemia with FLT3 internal tandem duplication. *Haematologica* 2003; **88**: 637–645.
 - 17 Greenberg P, Cox C, LeBeau MM, Fenau P, Morel P, Sanz G *et al*. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997; **89**: 2079–2088.
 - 18 Urbano-Ispizua A, Brunet S, Solano C, Moraleda JM, Rovira M, Zuazu J *et al*. Allogeneic transplantation of CD34+ selected cells from peripheral blood in patients with myeloid malignancies in early phase: a case control comparison with unmodified peripheral blood transplantation. *Bone Marrow Transplant* 2001; **28**: 349–354.
 - 19 Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol* 1992; **21**: 837–841.
 - 20 Sorrow ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG *et al*. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005; **106**: 2912–2919.
 - 21 Gray R, Wheatley K. How to avoid bias when comparing bone marrow transplantation with chemotherapy. *Bone Marrow Transplant* 1991; **7** (suppl 3): 9–12.
 - 22 Valcarcel D, Martino R, Caballero D, Mateos MV, Perez-Simon JA, Canals C *et al*. Chimerism analysis following allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning. *Bone Marrow Transplant* 2003; **31**: 387–392.
 - 23 Mengis C, Aebi S, Tobler A, Dahler W, Fey MF. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. *J Clin Oncol* 2003; **21**: 3933–3939.
 - 24 Estey E, de Lima M, Tibes R, Pierce S, Kantarjian H, Champlin R *et al*. Prospective feasibility analysis of reduced intensity conditioning regimens (RIC) for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood* 2007; **109**: 1395–1400.
 - 25 Deschler B, de Witte T, Mertelsmann R, Lubbert M. Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: problems and approaches. *Haematologica* 2006; **91**: 1513–1522.