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Title

Busulfan based myeloablative conditioning regimens for haploidentical transplantation in high risk acute leukemias and myelodysplastic syndromes.

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Running title: Myeloablative haplo-transplant for leukemias and MDS

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ABSTRACT

Background:

High-risk acute leukemia (AL) and myelodysplastic syndrome (MDS) remain a therapeutic challenge. Unmanipulated haploidentical related donor transplantation based on a myeloablative conditioning regimen (HAPLO-MAC) and post-transplant cyclophosphamide (PT-Cy) as prophylaxis against graft *vs* host disease (GvHD) is now a promising rescue strategy that could become universally available.

Objective:

To evaluate the results of HAPLO-MAC with PT-Cy in patients with AL and MDS reported to the Haploidentical Transplantation Subcommittee of the Spanish Group for Hematopoietic Transplantation (GETH).

Patients and methods:

We report our multicenter experience using an IV busulfan–based HAPLO-MAC regimen and PT-Cy for treatment of 65 adults with-high risk AL and MDS.

Results:

Engraftment was recorded in 64 patients (98.5%), with a median time to neutrophil and platelet recovery of 16 and 27 days, respectively. The cumulative incidence of grade II-IV acute GvHD and chronic GvHD was 28.6% and 27.5%, respectively. After a median follow-up of 31 months for survivors, the cumulative incidence of non-relapse mortality and relapse at 2 years was 18.8% and 25%, respectively. Estimated 30-month event-free survival and overall survival were 56% and 54.5%.

Conclusion:

HAPLO-MAC comprising an IV busulfan–based conditioning regimen enabled long-term disease control with acceptable toxicity in high-risk AL and MDS.

KEYWORDS:

Haploidentical transplantation; acute leukemia; myelodysplastic syndromes; myeloablative conditioning; post-transplant cyclophosphamide.

INTRODUCTION

High-risk acute leukemia (AL) and myelodysplastic syndrome (MDS) remain incurable for most patients without allogeneic hematopoietic stem cell transplantation (Allo-HSCT)[1-3]. Only 25-30% of this population have an HLA-identical sibling. A matched unrelated donor (MUD) or umbilical cord blood donor (UCB) suitable for transplantation was found in almost 80% of

patients without a sibling donor; however, MUD and UCB are not always available on time[4]. Allo-HSCT can cure approximately 10-70% of patients after 1-2 induction cycles for AL[1,2,5] or in patients with no previous treatment for high-risk MDS[3]. Success rates depend mostly on the characteristics of the disease and the remission status, which is in turn based on the revised disease risk index (rDRI)[6,7] and age and comorbidities[8]. Moreover, Allo-HSCT with an HLA-identical related or unrelated donor can rescue a larger number of relapsed/refractory cases through myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) regimens[2,3]. However, results remain modest with these approaches owing to a high relapse rate despite the graft *vs* leukemia effect[1-3].

RIC-based transplants using HLA-haploidentical related donors (HAPLO-RIC) with post-transplant high-dose cyclophosphamide (PT-Cy) as prophylaxis for graft *vs* host disease (GvHD) have shown promising results in the treatment of advanced hematologic neoplasms such as AL and MDS[9]. Findings are similar to those for RIC transplants from siblings or unrelated donors[10,11]. Furthermore, this strategy has made it possible for almost any patient with AL or MDS to undergo Allo-HSCT. A recent retrospective comparison between this strategy and MUD transplantation yielded similar results in terms of survival in registry cohorts[10,11] and selected experienced centers[12-15]. Nevertheless, relapse remains problematic[10-15], particularly when conventional RIC transplant approaches in AML[16], mainly in high-risk patients and those with advanced disease.

We attempted to reduce the relapse rate by modifying the original Baltimore RIC regimen[9], that is, we replaced 200cGy total body irradiation with myeloablative doses of IV busulfan. We report the results of a multicenter study performed in Spain with IV busulfan–based HAPLO-MAC in the treatment of AL and MDS patients for whom an HLA-identical related or unrelated donor is not available.

PATIENTS and METHODS

Patient and donor selection

We retrospectively reviewed 65 adult patients (Table 1) with AL or MDS who underwent HAPLO-MAC and for whom results were sent to the Haploidentical Transplantation Subcommittee of the Spanish Group for Hematopoietic Transplantation (GETH). The study comprised 14 centers and included patients who received their transplant between February 2012 and December 2015. The institutional review board of each participating center approved the study, and all patients gave their written informed consent (Declaration of Helsinki). Patients aged 16-65 years were included. Disease status at transplant was defined based on morphologic criteria. The definitions were as follows: (i) complete remission (CR) was defined as less than 5% blasts in bone marrow and with complete peripheral blood recovery; (ii) CR MRD+ was defined as less than 5% blasts but the presence of any detectable minimal residual disease (MRD) by either flow cytometry or molecular markers. MRD markers were stablished in every center according to local policies based on ongoing European Leukemia Network recommendations; (iii) not in remission (No CR) was defined as more than 5% blasts in bone marrow or incomplete peripheral blood recovery.

Patients were stratified according to the revised Disease Risk Index (rDRI) following the updated criteria of Armand et al[7] and according to the comorbidity-age index following the criteria of Sorror et al[8].

Donors were selected from first-degree relatives (siblings, parents, or children) and matched with the recipient at 5/10 to 8/10 HLA antigens. In addition, a positive HLA crossmatch was avoided in the host *vs* graft direction, as was having donor-specific antibodies according to pre-transplantation panel reactive antibody testing. If several donors were available, younger males and ABO matched donors were preferable.

Conditioning regimen and GvHD prophylaxis

The conditioning regimens were modifications of that reported by Luznik et al[9], in which IV busulfan replaced 200 cGy of total body irradiation (TBI). With the aim of reducing the probability of relapse, and as the choice of the attending physician based on comorbidities, our regimens consisted of fludarabine 40 mg/m^2/day for 4 consecutive days from –6 to –3, and IV busulfan 3.2 mg/kg/day on either days –6 to –4 (BUX3) or days –6 to –3 (BUX4). Prophylaxis against GvHD comprised high-dose cyclophosphamide (50 mg/kg/day) administered at days +3 and +4 supported with hyperhydration and mesna, followed by a calcineurin inhibitor (either cyclosporine A or tacrolimus, depending on the center) and mycophenolate mofetil from day +5. In the absence of acute GvHD, mycophenolate mofetil was discontinued at day +35. Calcineurin inhibitors were maintained until day +90 and tapered thereafter. Earlier tapering was allowed for patients with active disease at the time of transplantation. Bone marrow or unmanipulated peripheral blood stem cells (PBSCs) were used as the graft source at the physician's discretion or according to local preference. Acute and chronic GVHD were assessed and graded based on published criteria[17,18].

Supportive care

Supportive care was provided based on local practice guidelines. Anticonvulsant prophylaxis was mainly with oral phenytoin. Standard antimicrobial prophylaxis included levofloxacin and acyclovir from day –7; antifungal prophylaxis comprised micafungin until oral tolerance and then posaconazole. Prophylaxis of *Pneumocystis* infection with cotrimoxazole was given from day –7 until day –1 and resumed after day +30 for 12 months after transplantation. Filgrastim 5 μg/kg was started on day +5 and continued until neutrophil engraftment. Quantitative PCR-based monitoring of cytomegalovirus (CMV) was performed twice weekly

starting on day +1 until day +100 or later if prolonged immunosuppression was needed because of active GvHD.

Chimerism analysis

Quantitative chimerism analysis was performed using peripheral blood and bone marrow samples and informative microsatellite DNA polymorphisms, as described elsewhere[19]. The analysis started on day +15 and every 15 days thereafter until full donor chimerism was achieved. Full donor chimerism was defined as the absence of recipient-specific allelic patterns detectable by short tandem repeat PCR with a sensitivity of 1%.

Definitions, study endpoints, and statistical methods

Myeloid engraftment was defined as an absolute neutrophil count of 0.5×10^9/L or greater for 3 consecutive days. Platelet engraftment was defined as a platelet count of 20×10^9/L or higher maintained without transfusion for 3 consecutive days. A patient's graft was considered to have failed if the patient survived for more than 30 days after transplantation without achieving myeloid engraftment. Graft rejection was defined as graft failure with recovery of recipient hematopoiesis, as determined by chimerism analysis.

The primary endpoints were non-relapse mortality (NRM), disease relapse or progression, event-free survival (EFS), and overall survival (OS). NRM was defined as death from any cause without previous disease relapse or progression. OS was defined as the time from transplant to death from any cause, and surviving patients were censored at the last follow-up visit. EFS was defined as the time from transplant to relapse, disease progression, or death from any cause, whichever occurred first. We examined a composite end point of GVHD-free/relapse-free survival (GRFS) in which events include grade 3-4 acute GVHD,

systemic therapy-requiring chronic GVHD, relapse, or death, as originally defined by Holtan et al[20]. Follow-up was updated in March 2017.

Statistical analysis

Quantitative variables were expressed as median and either range or interquartile range (IQR). Qualitative variables were expressed as frequency and percentage. EFS and OS were estimated using the Kaplan-Meier method and included the 95% confidence interval (95% CI). Cumulative incidence curves were constructed and competing-risk regression was performed as an alternative to Cox regression for survival data in the presence of competing events[21]. Death and any other event that prevented the appearance of the event under study were considered competing events.

Death before onset of the event was considered a competing event in the estimation of the cumulative incidence of engraftment, full donor chimerism, and acute GvHD. For the cumulative incidence of chronic GvHD, death and relapse were considered competing events. NRM and relapse were considered competing events for each other.

Except for cumulative incidence, all the calculations were made using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp, Armonk, New York, USA). The cumulative incidence calculations were made using R (CRAN project).

RESULTS

Clinical characteristics of patients and donors

The clinical characteristics of patients and donors before transplantation are shown in Table 1.

The study population comprised mainly AL patients (AML 72%, acute lymphocytic leukemia 12%), with a median age of 42 years, who were in morphologic CR at the time of HAPLO-MAC (85%) but with persistent MRD+ (37%) and high or very high rDRI (65%). The MAC regimen used comprised IV busulfan for 3 days (BUX3) in 25 patients (38%) and 4 days (BUX4) in 40 patients (62%). Most patients (82%) had a low age-adjusted hematopoietic cell transplant (HCT) comorbidity index, although 12 cases (18%) had a score ≥3. The graft source consisted of PBSCs in 56 cases (86%) and bone marrow progenitors in 9 cases (14%). When the characteristics of patients who received BUX3 were compared with those of patients who received BUX4, those in the BUX3 group were older (median 47 *vs* 34 years; p=0.04), and the donor relationship tended to be different (more child donors in BUX3 and more siblings in BUX4; p=0.07).

Engraftment and chimerism

The cumulative incidence of neutrophil and platelet engraftment was 97% (95% CI, 92-100%) at 30 days and 86% (95% CI, 77-95%) at 3 months, respectively. Median time to neutrophil and platelet recovery was 16 days (range: 13-39) and 27 days (range: 11-131), respectively.

No graft failure was observed, but 1 patient died of septic shock on day +15 before engraftment. Full donor chimerism on peripheral blood and T cells was observed in all the patients analyzed at a median of 30 days (range, 14-100).

Toxicity and infection

The main toxicities observed were WHO grade 1-2 mucositis (86%), neutropenic fever (76%), and reactivation of CMV infection (58%). Hemorrhagic cystitis was observed in 19 patients (29%), although most cases were grade II and only 6 (9%) were grade III-IV. No

Epstein-Barr–related disease was observed. Only 1 case of severe VOD was recorded (1.5%), although this resolved successfully with defibrotide and supportive treatment.

Severe procedure-related events resulted in 12 deaths. Six patients (9%) died before day +100 after HAPLO-MAC as a result of the following: septic shock (2 patients), and 1 case each of disseminated aspergillosis, multi-organ failure, refractory grade IV acute GvHD, and acute GvHD complicated by pulmonary infection and CMV reactivation on days +15, +21, +67, +77, +66, and +87 respectively. The causes of death within the first year post-HAPLO-MAC were grade IV acute GvHD, overlapping GvHD complicated by sepsis of unknown origin, acute GvHD complicated by respiratory infection and CMV reactivation, BK virus hemorrhagic cystitis, sudden death, and progression of pre-existing breast cancer.

GVHD

Twenty-two patients developed acute grade II-IV GvHD at a median of 40 days (range, 19-117 days). The cumulative incidence at day +100 was 28.6% (95%CI, 19-43%) for grade II to IV acute GvHD and 6.3% (95%CI, 2.5-16.5%) for acute GvHD grade III-IV (Figure 1).

Chronic GvHD was recorded in 21 of the 49 evaluable patients (limited in 14 cases [28%] and extensive in 7 cases [14%]). The cumulative incidence of chronic GvHD at 2 years was 27.5% (95%CI, 18-41%); that of extensive chronic GvHD was 9.5% (95%CI, 4.5-21%) (Figure 2).

NRM, relapse, EFS, and OS

The median follow-up for survivors was 31 months (range, 5-60 months), and the cumulative incidence of NRM at 2 years was 18.8% (95%CI, 11-31.5%; Figure 3).

Relapse or progression was diagnosed in 15 patients, of whom 14 died (10 from relapse and 4 from infectious complications) and 1 patient achieved an ongoing CR after donor

lymphocyte infusions. The cumulative incidence of relapse at 2 years was 25.5% (95%CI, 16.5-39%), with a median time to relapse or progression of 7 months (range, 1.7-14 months; Figure 3). Out of 35 patients with CR MRD+ or not in CR at HAPLO-MAC, 20 were in CR at day +100 and remained in CR at the last follow-up visit.

The projected 30-month OS and EFS were 54.5% (95%CI, 41-68%) and 56% (95%CI, 43-68%), respectively, and the 30-month GFRS was 47% (95%CI, 45-60%) (Figure 4). In the univariate analysis, the only statistical trend was observed for rDRI status before HAPLO-MAC (p=0.22) as a predictive factor for relapse when very-high-risk patients were compared with others, yielding lower EFS in this population (Figure 5). No statistically significant differences were observed for EFS or OS between patients in CR without MRD and those who were MRD+ or between those with and without acute or chronic GvHD. Cumulative incidence of relapse at 24 months in patients in CR without MRD was 17% (8-39) *vs* 33% (20-54) in CR/MRD+ or non CR patients (p=0.14).

No significant differences were observed in terms of NRM, relapse, EFS, or OS when the BUX3 and BUX4 conditioning regimens were compared with each other (data not shown). The incidence of relapse did not differ between patients who developed acute or chronic GvHD (data not shown). No significant differences were found for any endpoint when mothers as donors were compared with other donors or when bone marrow was compared with PBSCs as the graft source (data not shown).

DISCUSSION

Allogeneic transplantation is the preferred option for high-risk AL and MDS[1,2,3]. HAPLO-HSCT with PT-Cy is the new standard of care when MSD or MUD is not available[22]. Therefore, it is increasingly used worldwide[23], mostly in high-risk neoplasms such as AL and MDS[24,25].

We studied the role of IV busulfan–based HAPLO-MAC with PT-Cy as prophylaxis against GvHD and investigated toxicity and disease control in patients with AL and MDS managed under real-world conditions (ie, not in a clinical trial).

Our strategy was original not only because we included myeloablative doses of IV busulfan in the conditioning regimen, but because we also limited the duration of post-transplant immunosuppressive therapy in an attempt to reduce the high relapse rate observed in these high-risk patients. Of note, IV busulfan made it easier to program conditioning than TBI. In addition, its radiomimetic properties[26,27] enabled it to enhance anti-tumoral activity in radiosensitive neoplasms such as AL. Moreover, this approach may even play a role in reducing the incidence of graft failure previously reported with the HAPLO-RIC strategy[9].

In our study, 86% of patients received PBSCs as their graft source. The comparison of bone marrow with PBSCs had no relevant effect on any of the major endpoints analyzed (EFS, OS, NRM, and acute/chronic GvHD). We previously found that PBSCs are a safe graft source in HAPLO-RIC for treatment of Hodgkin's lymphoma[28].

Our HAPLO-MAC conditioning regimen differed from that of the HAPLO-RIC[9] used by the Baltimore group in that instead of the 200 cGy TBI usually administered, we included IV busulfan $\times 3$ or $\times 4$ days in order to reduce the high relapse rate in patients with advanced disease. After a median follow up of 31 months for surviving patients, the cumulative incidence of relapse was 25% at 2 years, the 30-month estimated EFS was 56%, the estimated OS was 54.5% and the estimated GRFS was 47%. These results are very similar to those reported by other groups using other myeloablative conditioning regimens[29-32]. Additionally, the sub-analysis comparing patients receiving BUX3 with those receiving BUX4 revealed no significant advantages in any of the endpoints analyzed, although a possible selection bias cannot be ruled out considering the older age in the BUX3 group and the slightly different donors selected. Nevertheless, the 2-year NRM we observed was 18.8%, that is, slightly higher than reported elsewhere[11-13], probably because of the fact that patients

had advanced disease, the multicenter design of our study, and the higher incidence of GvHD that we recorded.

Our HAPLO-MAC procedure was well tolerated in our cohort of intensively treated patients, of whom 52% had persistent disease, remission status before HAPLO-MAC had no effect on NRM, with no significant differences in toxicity between patients in CR and patients not in CR or between those with an HCT comorbidity index of 2 or lower *vs* higher than 2. Conversely, we found that remission status was not the main determinant for relapse and did not generate differences in terms of EFS, probably because of the small sample size. Surprisingly, rDRI did not split our cases according to their risk categories. It remains unclear whether this observation was a consequence of the uniformly high-risk composition of our series or whether it was due to the relatively small number of patients reported. Only by including more patients with a longer follow-up period we will be able to elucidate this issue.

Our conditioning regimen resulted in no graft failure, in contrast with previously reported rates of 4-13% using the PT-Cy HAPLO-RIC strategy[9,14,25,29].

The cumulative incidence of grade II-IV acute GvHD in our study was 28.6%, including grade III-IV in 6.3%. In addition chronic GvHD was observed in 27.5% of individuals. These figures are slightly higher than those reported elsewhere[9,13,14], probably owing to the use of PBSC grafts and early tapering of immunosuppressive therapy. However, mortality attributable to acute or chronic GvHD was under 5% (3 out of 63 at risk) and that way, our serie shows a promising 30-month GRFS of 47%, so close to half of our patients remain alive, in remission and free of severe GvHD after a median follow-up of more than 30 months.

Finally, our results are almost identical to those of previous series on myeloablative conditioning in AL[14,15,30-32], and to those of other alternative donor approaches such as cord blood transplants[25,33]. Our findings confirm the feasibility and safety of PT-Cy HAPLO-MAC in advanced AL and MDS in a real-world, multicenter setting where patients were managed

under conditions of daily clinical practice. Our study is limited by its retrospective design and small sample size. Consequently, our data should be interpreted with caution until data from prospective trials with larger samples and longer follow-up periods are available.

In conclusion, our results for HAPLO-MAC strategies in advanced AL and MDS are similar to those reported elsewhere. Our regimen differed in that we used an IV busulfan–based conditioning regimen and mainly PBSC grafts.

Relapse is still the main problem for recipients, particularly those with persistent disease before HAPLO-MAC. Innovative ways to improve these results are urgently needed. Treatment could be improved by means of more appropriate donor selection, administration during earlier phases of the disease, optimal administration during CR after the use of new options such as tyrosine-kinase inhibitors, or post-transplant strategies such as adoptive immunotherapy with donor lymphocyte infusions to prevent or treat relapses.

Conflicts of interest

The authors declare that they have no conflicts of interest regarding the contents of this paper.

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Table 1:

Table 1. Patient and donor characteristics.

	TOTAL	BUX3	BUX4	
Number of patients:	65	25 (38%)	40 (62%)	
Males	43 (66%)	17 (68%)	26 (65%)	p=0.80
Age (years, range):	42 (16-67)	47 (16-67)	34 (15-59)	p=0.04
Primary disease:				p=0.22
AML	47 (72%)	17 (68%)	30 (75%)	
ALL	8 (12%)	2 (8%)	6 (15%)	
MDS-CMML	5 (8%)	4 (16%)	1 (2.5%)	
Other	5 (8%)	2 (8%)	3 (7.5%)	
Previous AUTO-HSCT:	6 (9%)	2 (8%)	4 (10%)	p=0.25
Previous ALLO-HSCT:	3 (5%)	3 (12%)		p=0.10
Disease status at HAPLO-MAC:				p=0.13
Morphologic CR	55 (85%)	22 (88%)	33 (82%)	
CR MRD positive	24 (37%)	13 (52%)	11 (28%)	
No CR	10 (15%)	3 (12%)	7 (17%)	
Revised Disease Risk Index:				p=0.64
Low	2 (3%)		2 (5%)	
Intermediate	21 (32%)	9 (36%)	12 (30%)	
High	27 (42%)	11 (44%)	16 (40%)	
Very high	15 (23%)	5 (20%)	10 (25%)	
Age-HCT Comorbidity Index (median; range):	1 (0-6)	2 (0-5)	1 (0-6)	p=0.68
0-2	53 (82%)	21 (84%)	32 (80%)	
>3	12 (18%)	4 (16%)	8 (20%)	
Donor:				p=0.07
Sibling	28 (43%)	8 (32%)	20 (50%)	

Mother	14 (21%)	5 (20%)	9 (23%)	
Father	8 (12%)	2 (8%)	6 (15%)	
Child	15 (23%)	10 (40%)	5 (12%)	
Donor-recipient sex mismatch:	32 (49%)	11 (44%)	21 (53%)	p=0.50
Female donor to male recipient:	20 (31%)	7 (28%)	13 (33%)	p=0.50
CMV serologic status (patient/donor):				p=0.81
NEG/NEG	2 (3%)	1 (4%)	1 (2.5%)	
NEG/POS	8 (12%)	3 (12%)	5 (12%)	
POS/NEG	8 (12%)	2 (8%)	6 (15%)	
POS/POS	45 (69%)	19 (76%)	26 (65%)	
Unknown/Indeterminate	2 (3%)		2 (5%)	
Graft source:				p=0.25
BM	9 (14%)	5 (20%)	4 (10%)	
PB	56 (86%)	20 (80%)	36 (90%)	

Legend: AUTO-HSCT=autologous hematopoietic stem cell transplantation; ALLO-HSCT=allogeneic hematopoietic stem cell transplantation; CR=complete remission; MRD=minimal residual disease; CMV=cytomegalovirus; NEG=negative; POS=positive; BM=bone marrow; PB=peripheral blood; BUX3=conditioning regimen including 3-days IV busulfan; BUX4=conditioning regimen including 4-days IV busulfan; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; MDS-CMML, myelodysplastic syndrome-chronic myelomonocytic leukemia; HAPLO-MAC, haploidentical-myeloablative conditioning; HSCT, hematopoietic cell transplant.

FIGURE LEGENDS

Figure 1: Cumulative incidence of acute GvHD.

Figure 2: Cumulative incidence of chronic GvHD.

Figure 3: Cumulative incidence of NRM and relapse.

Figure 4: OS, EFS and GFRS in 65 patients with high risk AL and MDS.

Figure 5: Event-free survival according to rDRI before HAPLO-MAC

FIGURE 1: Cumulative incidence of acute GvHD

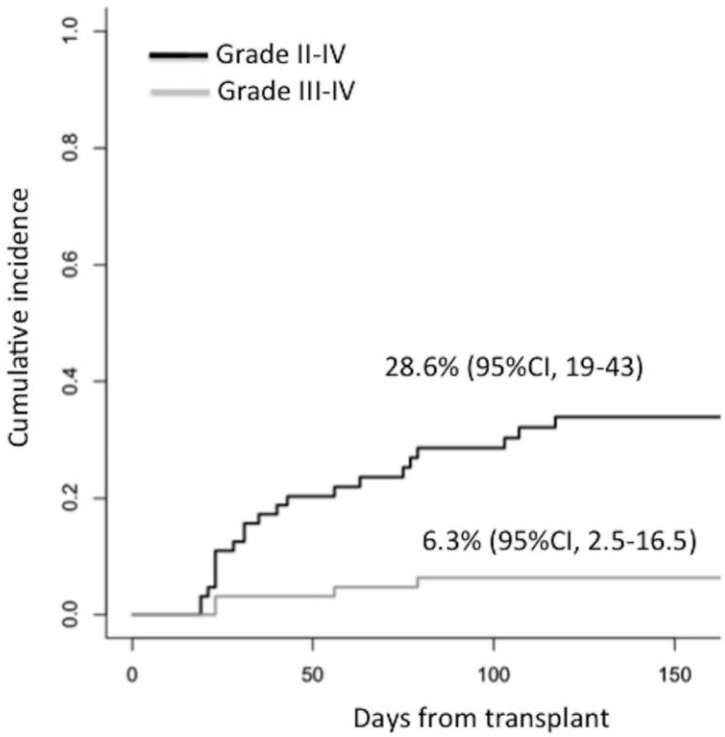

FIGURE 2: Cumulative incidence of chronic GvHD

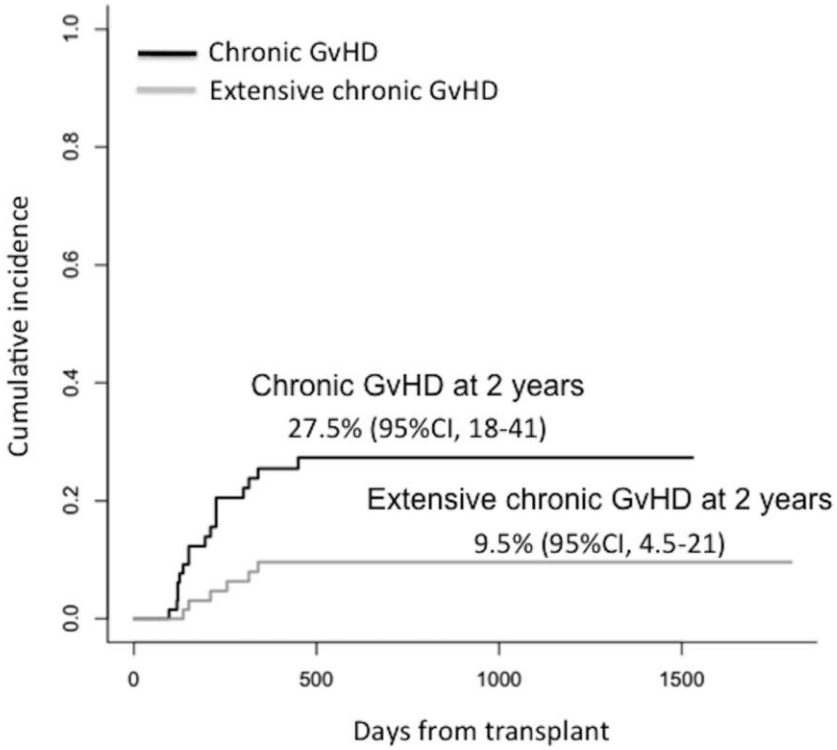

FIGURE 3: Cumulative incidence of Relapse and NRM

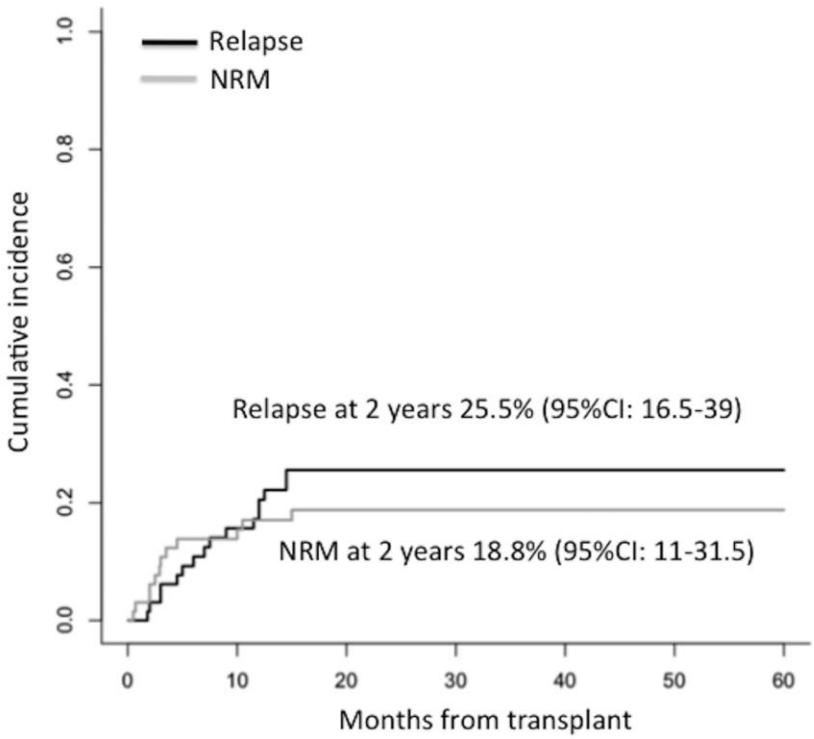

FIGURE 4: OS, EFS and GRFS of 65 patients with high risk AL and MDS

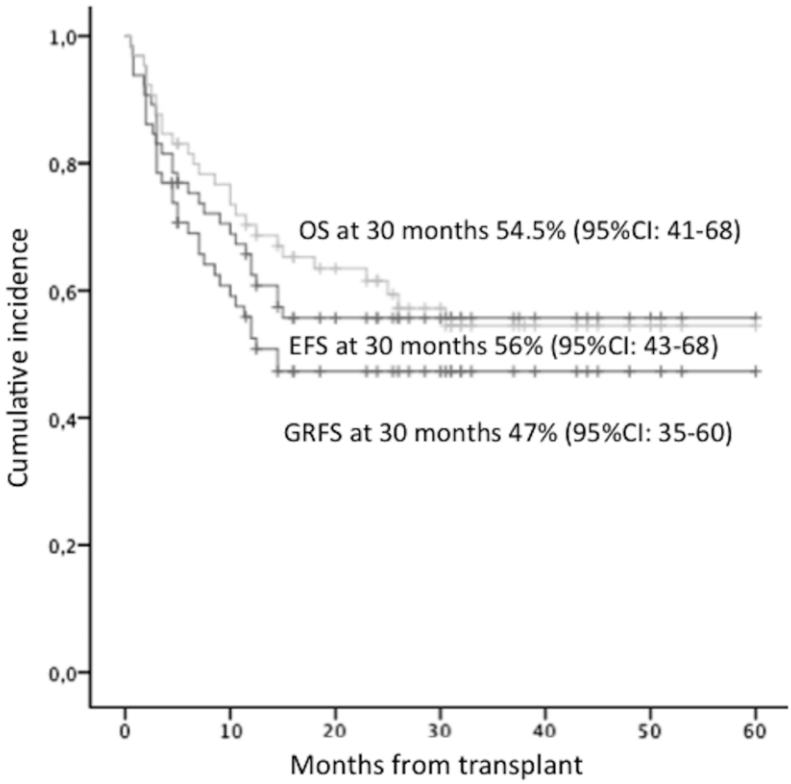

FIGURE 5: EFS according to rDRI