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# Effect of Conditioning Regimen Intensity on Acute Myeloid Leukemia Outcomes after Umbilical Cord Blood Transplantation

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Reduced-intensity conditioning (RIC) umbilical cord blood (UCB) transplantation is increasingly used in hematopoietic stem cell transplantation (HCT) for older and medically unfit patients. Data on the efficacy of HCT after RIC relative to myeloablative conditioning (MAC) are limited. We compared the outcomes of acute myeloid leukemia (AML) patients >18 yrs who received UCB grafts after either RIC or MAC. One hundred nineteen adult patients with AML in complete remission (CR) underwent an UCB transplant after RIC (n =74, 62%) or MAC (n = 45, 38%) between January 2001 and December 2009. Conditioning was either reduced intensity and consisted of cyclophosphamide 50 mg/kg, fludarabine 200 mg/m$^2$, and total-body irradiation (TBI) 200 cGy or myelablative and consisted for cyclophosphamide 120 mg/kg, fludarabine 75 mg/m$^2$, and TBI 1200-1320 cGy. All patients received cyclosporine (day $-3$ to day $+180$) and mycophenolate mofetil (day $-3$ to day $+45$) post-HCT immunosuppression and hematopoietic growth factor. Use of RIC was reserved for patients >45 years (n = 66, 89%) or preexisting severe comorbidities (n = 8, 11%). The 2 groups were similar except for preceding myelodysplastic syndrome (RIC = 28% versus MAC = 4%, $P$ <.01) and age that was dictated by the treatment protocols (median, RIC = 55 years versus MAC = 33years; $P$ <.01). The incidence of neutrophil recovery at day $+42$ was higher with RIC (94% versus MAC = 82%, $P$ <.1), whereas platelet recovery at the sixth month was similar (RIC = 68% versus MAC = 67%, $P$ =.30). Incidence of grade II-IV acute graft-versus-host disease (aGVHD) (RIC = 47% versus MAC = 67%, $P$ <.01) was decreased with similar incidence of chronic GVHD (cGVHD) (RIC = 30% versus MAC = 34%, $P$ =.43). Median follow-up for survivors was 3.8 and 4.5 years for RIC and MAC, respectively ($P$ =.4). Using RIC, 3-year leukemia-free survival (LFS) was decreased (31% versus MAC = 55%, $P$ =.02) and 3-year relapse incidence was increased (43% versus MAC = 9%, $P$ <.01). Two-year transplant-related mortality (TRM) was similar (RIC = 19% versus MAC = 27%; $P$ = .55). In multivariate analysis, RIC recipients and those in CR2 with CR1 duration <1 year had higher risk of relapse and poorer LFS with no independent predictors of TRM. UCB with RIC extends the use of allogeneic HCT for older and frail patients without excessive TRM with greater benefit for patients in CR1 and CR2 with longer CR1.

## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) with myeloablative conditioning (MAC) is a po-tentially curative treatment for patients with acute myelogenous leukemia (AML) [1,2]. However, MAC is associated with significant regimen-related toxicity (RRT) and risk of transplant-related mortality (TRM). The introduction of reduced-intensity conditioning (RIC) has extended allogeneic transplantation to older and less medically fit patients by reducing RRT [3,4]. RIC relies largely on graft-versus leukemia (GVL) effect of the immunocompetent cells in the graft, rather than the high-dose chemotherapy for the antitumor effect [1,5-7].

Unrelated umbilical cord blood (UCB) has emerged as an alternative source for HCT and may be particularly valuable patients who have a narrow time window of opportunity to proceed to transplanta-tion [8]. Recent studies have demonstrated similar leukemia-free survival (LFS) after UCB and unrelated

donor (URD) transplantation after MAC in patients with acute leukemia [9-13]. Our group has reported high rates of engraftment, low TRM, and promising event-free survival (EFS) for hematologic malignancies with UCB even after RIC HCT [14].

Although there are limited data comparing the outcomes after RIC and MAC [15-18], none include UCB recipients. Thus, we retrospectively studied the outcomes in adults with AML patients in complete remission (CR) who underwent UCB transplantation after MAC or RIC regimens.

## PATIENTS AND METHODS

### Patients

Patients ≥18 years with AML in first (CR1) or second (CR2) morphologic complete remission, defined by the presence of <5% blasts in the bone marrow, transplanted with unrelated UCB between January 2001 and December 2009, were included in this study. This time period was chosen so that recipients of a RIC and MAC regimens were offered uniform supportive care. Patients with a prior diagnosis of myelodysplastic syndrome (MDS) and myeloproliferative disorders (MPD) were included only if they had progressed to AML, were treated, and achieved a CR. Treatment protocols and retrospective analysis were approved by the institutional review board (IRB) of the University of Minnesota and registered at www.clinicaltrials.gov under numbers NCT00305682, NCT00365287, NCT00290641, and NCT0030984. All patients provided written informed consent in accordance with the Declaration of Helsinki. UCB unit selection has been detailed elsewhere [14,19]. In 86% the graft consisted of 2 UCB units to achieve a combine cell dose ≥2.5 × $10^7$/kg. All UCB units were thawed according to the methods of Rubinstein et al. [20].

### Treatment Plan and Supportive Care

Seventy-four patients received an RIC regimen consisting of fludarabine (40 mg/m² intravenously daily for 5 days) and 200 cGy total-body irradiation (TBI) with cyclophosphamide (50 mg/kg intravenously for 1 day) [14]. Twenty-two of 74 RIC (30%) patients received equine antithymocyte globulin (ATG, ATGAM; Pharmacia, Kalamazoo, MI) 15 mg/kg every 12 hours for 3 days as part of the conditioning regimen for patients considered at high risk for graft rejection [14]. Forty-five patients received a MAC regimen consisting of cyclophosphamide (60 mg/kg intravenously daily for 2 days), 1320 cGy TBI given divided in 8 fractions and fludarabine (25 mg/m² daily for 3 days) [19]. ATG was not given to MAC patients. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (days –3 to at least +100) and mycophenolate mofetil (days –3 to at least +30).

Granulocyte-colony stimulating factor (G-CSF) (5 μg/kg per day) was administered to all patients from day +1 until an absolute neutrophil count (ANC) of 2.5 × $10^9$/L or higher was achieved for 2 consecutive days. All patients received fluconazole or voriconazole for prophylaxis of fungal infections for 100 days and trimethoprim-sulfamethoxazole for prophylaxis of *Pneumocystis jiroveci* after engraftment for 12 months after transplantation and extended spectrum fluoroquinolones for prophylaxis of Gram-positive organisms during treatment of GVHD. Viral prophylaxis included acyclovir if seropositive for herpes simplex or cytomegalovirus (CMV) before transplantation. CMV surveillance was performed weekly with ganciclovir treatment at the time of positive antigenemia or polymerase chain reaction (PCR) testing. Chimerism was determined by quantitative PCR of informative polymorphic variable number tandem repeat (VNTR) or short tandem repeat (STR) regions in the recipient and donor as described [19].

### Endpoints and Definitions

The primary study endpoint was LFS defined as survival without disease relapse. Patients were censored at the time of death, relapse, or last follow-up. Other study endpoints included cumulative incidences of relapse, TRM, neutrophil recovery, platelet recovery, acute and chronic GVHD (aGVHD, cGVHD). Relapse was defined as disease recurrence at any site. TRM was defined as death because of causes other than leukemia relapse. Time to neutrophil engraftment was measured from the date of transplantation to the date of recovery (defined as the first of 3 consecutive days of ANC ≥5 × $10^9$/L), with exclusion for early death (ie, death before day 21 without neutrophil recovery). Patients who had no engraftment by day 42 were treated as graft failures. Time to platelet engraftment was defined as a count higher than $50 × 10^9$/L for the first of 7 days without platelet transfusion support. For double UCB recipients, the cell doses (nucleated cells, CD34$^+$ and CD3$^+$) were reported as the combined dose of the UCB donor units, and HLA and ABO matching were defined by the worst matched of the 2 units. Comorbidities were scored according to the Hematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI) [21]. Diagnostic cytogenetics were classified by Southwest Oncology Group (SWOG) [22] or by presence of monosomal karyotype [23].

### Statistical Considerations

Patient and transplant characteristics by conditioning intensity were compared using the chi-square test for categoric data and the Wilcoxon rank-sum test for continuous data. LFS was calculated using the Kaplan-Meier method [24]. Univariate comparisons

of all end points were completed by log-rank test [25]. Cumulative incidence was used to estimate the endpoints of hematopietic recovery, relapse, TRM, and aGVHD and cGVHD [26]. A Cox proportional hazards model [27] or the Fine & Gray method [28] for competing hazards was used for multivariate regression of LFS and incidences of relapse and TRM, respectively. Variables included in the models were the number of donor UCB units (1 versus 2), maximum HLA disparity, ABO compatibility, CMV serostatus, disease status at transplantation (CR1 versus CR2 with CR1 duration <1 year (CR2w/CR1<1y) versus CR2 with CR1 duration ≥1 year (CR2w/CR1≥1y), diagnostic cytogenetics by SWOG (favorable, intermediate, and unfavorable), HCT-CI, and conditioning regimen. All factors were tested for the proportional hazards assumption. The conditioning regimen and disease status were included in each model. Age was not included in the models as it was highly correlated with the assigned intensity of the conditioning regimen. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

## RESULTS

### Patient and Grafts Characteristics

Patient characteristics of the 119 eligible patients are shown in Table 1. The 2 groups were similar for patient and graft characteristics except for age, as age >45 years (n = 66) were only eligible for RIC. Median age at transplantation was 55 years for RIC and 33 years for MAC group (*P* < .01). Forty-eight of 74 RIC patients (65%) and 25 of 45 MAC (56%) were in CR1 (*P* = .31) and the remaining patients were in CR2 at UCB transplantation. Twenty-five of 46 patients in CR2 (54%) had CR1 duration <1 year, and this was similarly distributed in both groups (*P* = .9). Detailed results of diagnostic cytogenetic data were available in 115 patients. Thirty RIC (41%) and 17 MAC (38%) patients (*P* = .14) had unfavorable risk karyotype [22]. However, RIC patients had a higher frequency of monosomal karyotype (MK, 11% versus 2%, *P* = .06), which has been shown to carry a poor prognosis [23,29]. The HCT-CI scores at the time of transplantation were similar for the 2 groups with 37 RIC (50%) and 17 MAC (40%) patients having a score ≥3 (*P* = .13). Total nucleated (TNC), $CD34^+$ and $CD3^+$ cell doses were similar for the 2 treatment groups. The majority of patients received a transplant of 2 partially HLA-matched UCB units. Donor-recipient HLA disparity was similar between groups.

### LFS

Point estimates of clinical outcomes are summarized in Table 2. The probability of LFS at 3 years after RIC was 31% (95% confidence interval [CI], 21%-43%) and after MAC 55 %(95% CI, 41%-70%) (Figure 1A). Forty-eight of 74 patients (65%) with RIC and 19 of 45 (42%) patients with MAC relapsed or died with a median time of 0.7 years in the RIC group. The median LFS was not reached after MAC. Considering all patients, the LFS for patients in CR1 was 43% (95% CI, 31%-54%), in CR2w/CR1<1y was 26% (95% CI, 10%-45%) and in CR2w/CR1≥1y was 54% (95% CI, 30%-73%). When the analysis was limited to recipients of MAC the LFS for patients transplanted in CR1 was 52% (95% CI, 31%-69%), in CR2w/CR1<1y was 61% (95% CI, 27%-84%), and in CR2w/CR1≥1y was 65% (95% CI, 25%-87%) (Figure 1B). In contrast, LFS after RIC was 38% (95% CI, 24%-52%) in CR1, 7% (95% CI, 1%-28%) in CR2w/CR1<1y, and 47% (95% CI, 18%-72%) in CR2w/CR1≥1y (Figure 1C). In multivariate analysis, both the intensity of conditioning and disease status at the time of transplantation were independent predictors of LFS (Table 3). Recipients of RIC had a 2.3-fold higher risk of relapse or death compared to MAC recipients. The median follow-up of survivors for RIC was 3.8 years and for MAC 4.5 years (*P* = .4). The most frequent causes of death after RIC (n = 44) were relapse 61%, infection 22%, and GVHD 5%, whereas after MAC (n = 19) were relapse 32%, infection 36%, and GVHD 11%.

### Relapse

The incidence of relapse at 3 years after RIC was 43% (95% CI, 31%-55%) and after MAC was 9% (95% CI, 5%-18%; *P* < .01) (Figure 2A). The overall incidence of relapse for patients in CR1 was 30% (95% CI, 19%-41%), in CR2 w/CR1<1y was 48% (95% CI, 27%-69%) and in CR2 w/CR1≥1y was 21% (95% CI, 3%-39%) (*P* = .08). In recipients of MAC the relapse incidence in CR1 was 12% (95% CI, 0%-24%), in CR2w/CR1<1y was 19% (95% CI, 0%-42%), and in CR2w/CR1≥1y was 13% (95% CI, 0%-33%) (Figure 2B). In contrast, patients with RIC had relapse incidence of 40% (95% CI, 25%-55%) in CR1, 71% (95% CI, 21%-99%) in CR2w/CR1<1y, and 27% (95% CI, 2%-52%) in CR2w/CR1≥1y (Figure 2C). Median time to relapse was 1.8 years in RIC and not reached in the MAC group. In multivariate analysis, after adjusting for disease status at transplantation, RIC had a 4.7-fold higher risk of relapse compared to MAC recipients (Table 3).

### TRM

TRM at 2 years was similar in the 2 groups (19% [95% CI, 10%-28%] in RIC versus 27% [95% CI, 14%-40%] in MAC, *P* = .5). Neither receiving a TNC cell dose above or below the median (21% [95% CI, 11%-31%] versus 23% [95% CI,

**Table 1. Demographics of UCB Recipients with AML Treated with RIC or MAC HCT**

| Patient Characteristics | RIC<br>n (%) | MAC<br>n (%) | P-value |
|---|---|---|---|
| Number of patients | 74 | 45 | NA |
| Year of transplant | | | |
| 2001-2004 | 24 (32%) | 11 (24%) | .35 |
| 2005-2009 | 50 (68%) | 34 (76%) | |
| Age | | | |
| ≤45 | 8 (11%) | 45 (100%) | <.01 |
| Median | 55 | 33 | |
| (range) | (25-69) | (19-43) | |
| Preceding MDS or MPD | 21 (28%) | 2 (4%) | <.01 |
| Disease status | | | |
| CR1 | 48 (65%) | 25 (56%) | .31 |
| CR2w/CR1<1y | 14 (19%) | 11 (24%) | |
| CR2w/CR1>=1y | 12 (16%) | 9 (20%) | |
| Cytogenetics | | | |
| Favorable | 3 (4%) | 7 (16%) | .14 |
| Intermediate | 31 (42%) | 14 (31%) | |
| Unfavorable | 30 (41%) | 17 (38%) | |
| Unknown significance | 5 (7%) | 3 (7%) | |
| Median time from diagnosis to transplant for CR1 patients days (range) | 128 (46-2861) | 114 (67-230) | .84 |
| HCT-CI | | | |
| 0 | 18 (25%) | 7 (16%) | .13 |
| 1-2 | 18 (25%) | 20 (44%) | |
| ≥3 | 37 (50%) | 17 (40%) | |
| CMV seropositive recipient | 43 (58%) | 26 (58%) | .97 |
| TNC ($\times 10^7$)/kg* | 3.3 | 3.9 | .32 |
| Median (range) | (0.2-6.3) | (1.7-5.9) | |
| CD34$^+$ ($\times 10^5$)/kg* | 4.9 | 4.9 | .34 |
| Median (range) | (1.3-12.9) | (1.1-1.9) | |
| CD3$^+$ ($\times 10^6$)/kg* | 1.3 | 1.3 | .96 |
| Median (range) | (0.4-2.6) | (0.3-3.0) | |
| HLA-matching† | | | |
| 4/6 | 38 (51%) | 28 (62%) | .47 |
| 5/6 | 25 (34%) | 13 (29%) | |
| 6/6 | 11 (15%) | 4 (9%) | |
| ABO compatibility† | | | |
| Matched | 16 (22%) | 8 (18%) | .68 |
| Minor mismatch | 31(42%) | 17 (38%) | |
| Major mismatch | 27 (36%) | 20 (44%) | |
| Number of units | | | |
| 1 | 11 (15%) | 5 (11%) | .56 |
| 2 | 63 (85%) | 40 (89%) | |
| Median follow-up of survivors years (range) | 3.8 (0.6-8.5) | 4.5 (0.7-8.5) | .40 |

UCB indicates umbilical cord blood; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; HCT, hematopoietic stem cell transplantation; NA, not applicable; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; CR1, first complete remission; CR2w/CR1<1y, second complete remission with CR1 duration <1 year; CR2w/CR1>=1y, second complete remission with CR1 duration ≥1 year; HCT-CI, hematopoietic stem cell comorbidity index; CMV, cytomegalovirus; TNC, total nucleated cell dose; HLA, human leukocyte antigen.
*For double UCB recipients, the nucleated CD34$^+$ and CD3$^+$ cell doses reported are the combined dose of the UCB donor units.
†For double UCB recipients, HLA and ABO matching was defined by the worst matched of the 2 units.

**Table 2. Summary of Point Estimates of Study Endpoints**

| Outcome | Reduced-Intensity Conditioning<br>(95% CI) | Myeloablative Conditioning<br>(95% CI) | P-Value |
|---|---|---|---|
| Hematopoietic recovery | | | |
| Neutrophil recovery at 42 days | 94% (89%-99%) | 82% (71%-93%) | <.01 |
| Platelet recovery at sixth month | 68% (51%-85%) | 67% (50%-84%) | .30 |
| Sustained donor engraftment | 86% (78%-94%) | 82% (71%-93%) | .57 |
| Grade II-IV acute GVHD | 47% (35%-59%) | 67% (51%-82%) | <.01 |
| Grade III-IV acute GVHD | 16% (8%-24%) | 31% (18%-44%) | .05 |
| Chronic GVHD | 30% (19%-41%) | 34% (19%-49%) | .43 |
| 2-year TRM | 19% (10-28) | 27% (14-40) | .55 |
| Relapse at 3 years | 43% (31%-55%) | 9% (5%-18%) | <.01 |
| Leukemia-free survival at 3 years | 31% (21%-43%) | 55% (41%-70%) | .02 |

CI indicates confidence interval; GVHD, graft-versus-host disease; TRM, transplant-related mortality.
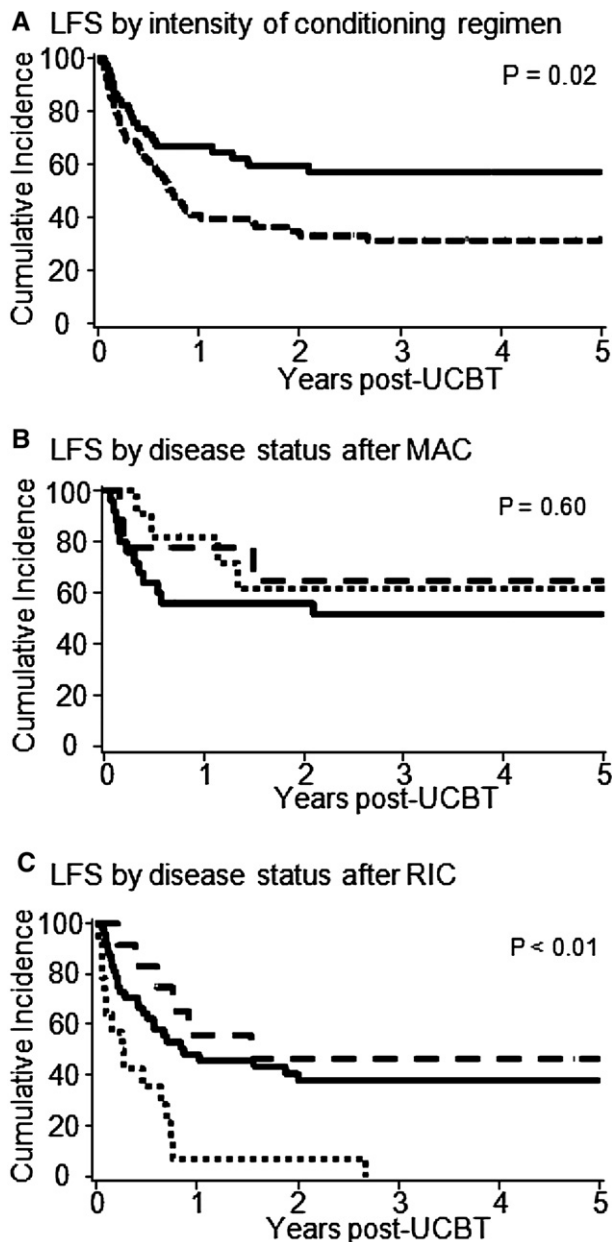
**Figure 1.** Leukemia-free survival of AML patients in first and second complete remission (CR1-2) who underwent umbilical cord blood hematopoietic stem cell transplantation (A) after myeloablative conditioning (MAC) (——) versus reduced-intensity conditioning (RIC) (– – –); (B) for patients receiving MAC or (C) RIC according to disease status at the time of transplantation categorized as CR1 (——), CR2 with CR1 ≥ 1 year (– – –) and CR2 with CR1 <1 year (■ ■ ■ ■ ■).

12%-34%], $P = .75$) nor a CD34$^+$ cell dose above or below the median (22% [95% CI <12%-32%] versus 22% [95% CI, 14%-30%], $P = .79$) affected the incidence of TRM. The incidence of TRM for patients with HCT-CI score of 0, 1-2, or ≥3 was 17% (95% CI, 2%-32%), 16% (95% CI, 4%-28%), and 29% (95% CI, 14%-41%), respectively ($P = .31$). TRM was also not significantly influenced by whether patients were transplanted in CR1 (22%, 95% CI, 12%-32%), CR2 w/CR1<1yr (20%, 95% CI, 4%-36%) or CR2 w/CR1≥1yr (24%, 95% CI, 6%-42%)

($P = .99$). No variables were independent predictors of TRM in the multivariate model.

### Hematopoietic Recovery

The incidence of neutrophil recovery at day 42 after RIC was 94% (95% CI, 89%-99%) at a median of 10 days (range: 5-39 days) and after MAC was 82% (95% CI 71%-93%) at a median of 23 days (range: 13-38 days) ($P < .01$). In contrast, the proportion with full chimerism at day 21 among evaluable patients (n = 105) after RIC was 20% (95% CI, 10%-30%) and after MAC was 60% (95% CI, 45%-75%) ($P < .01$); the difference was no longer present at day 100 among evaluable patients (n = 85). The cumulative incidence of platelet recovery ≥50,000/μL after RIC was 68% (95% CI, 51%-85%) at a median time of 55 days (range: 0-181 days) and after MAC was 67% (95% CI, 50%-84%) at a median of 77 days (range: 42-177 days) ($P = .30$).

### GVHD

The incidences of grade II-IV aGVHD after RIC was 47% (95% CI, 35%-59%) and after MAC was 67% (95% CI, 51%-82%) ($P < .01$). Similarly, the incidence of grade III-IV aGVHD was lower after RIC compared to MAC (Table 2). However, subgroup analysis evaluating risk of grade II-IV aGVHD in recipients of ATG versus no-ATG after RIC showed lower incidence with ATG (27% [95% CI, 9%-45%] versus 56% [95% CI, 41%-71%], $P = .04$). The 2-year incidence of cGVHD was similar in RIC and MAC recipients (30 [95% CI, 19%-41%] versus 34% [95% CI, 19%-49%], $P = .43$).

### DISCUSSION

We studied the effect of the intensity of the conditioning regimen on the outcome of allogeneic transplantation for patients with AML in CR1-2. The main observations of our study were that (1) there was a lower risk of relapse and superior LFS after MAC, with similar TRM regardless of the intensity of the conditioning regimen, (2) lower risk of aGVHD after RIC, and (3) similar rates of sustained donor engraftment.

Although single center and registry data both support the use RIC in patients with AML [15-18,30-33], to date there has been no randomized clinical trial that has evaluated the impact of RIC compared to MAC in outcomes for AML or other hematologic malignancies. Our study is unique as it is focused on recipients of UCB grafts with all patients receiving a uniform conditioning regimen (within their respective groups) and supportive care. Using matched related donors (MRD), European Group for Blood and Marrow Transplantation Group

**Table 3. Multivariate Analysis of Outcomes**

| Outcome | Relative Risk | 95% CI | P-Value |
|---|---|---|---|
| Leukemia-free survival | | | |
| Conditioning intensity | | | |
| MAC | 1.0 | | |
| RIC | 2.3 | 1.3-4.0 | <.01 |
| Disease status at HCT | | | |
| CR1 | 1.0 | | |
| CR2w/CR1<1y | 1.9 | 1.0-3.4 | .03 |
| CR2w/CR1≥1y | 0.7 | 0.3-1.4 | .33 |
| Relapse incidence | | | |
| Conditioning intensity | | | |
| MAC | 1.0 | | |
| RIC | 4.7 | 2.0-11.0 | <.01 |
| Disease status at HCT | | | |
| CR1 | 1.0 | | |
| CR2w/CR1<1y | 1.9 | 1.0-3.8 | .06 |
| CR2w/CR1≥1y | 0.5 | 0.2-1.5 | .21 |
| Treatment-related mortality | | | |
| Conditioning Intensity | | | |
| MAC | 1.0 | | |
| RIC | 0.6 | 0.3-1.4 | .24 |
| Disease status at HCT | | | |
| CR1 | 1.0 | | |
| CR2w/CR1<1y | 0.9 | 0.3-2.7 | .86 |
| CR2w/CR1≥1y | 1.1 | 0.4-3.1 | .85 |

CI indicates confidence interval; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; HCT, hematopoietic stem cell transplantation; CR1, first complete remission; CR2w/CR1<1y, second complete remission with CR1 duration <1 year; CR2w/CR1>=1y, second complete remission with CR1 duration ≥1 year.

(EBMT) showed an increased incidence of relapse, but similar LFS after RIC in AML patients older than age 50 [16]. With matched unrelated donor (MUD), although patients >50 years enjoyed similar risks of relapse and LFS using either conditioning intensity, in patients <50 years the relapse risk was increased after RIC although LFS was similar [17]. Recently the Center for International Blood and Marrow Transplantation and Research (CIBMTR) compared the outcomes after RIC versus MAC in patients with AML and MDS patients transplanted with marrow or peripheral blood from an unrelated or related donor. They reported higher relapse incidence after RIC and a marginally better LFS for those treated with MAC [18]. These registry-based studies included some patients with advanced or active leukemia, we included only patients in CR1-2. Notably, in this cohort transplanted with UCB, patients in CR1 and those in CR2 with longer CR1 derived greater benefit after RIC. In subgroup analysis of 24 CR2 patients with short and long CR1 who received RIC, no difference in patient and disease characteristics, including diagnostic cytogenetics, was observed (data not presented).

In this study, the risk of relapse after MAC UCB HCT was relatively low (9% at 3 years), and compared favorably to that of other donor sources [16,17]. Approximately 90% of our patients had 2 partially HLA-matched UCB units, which was reported to have an enhanced GVL effect in acute leukemia patients after transplantation [34]. The use of more mismatched grafts in double UCB setting, KIR-ligand mismatching or in vivo selection of the cord with the greater inherent

immune reactivity after 2 UCB units may be possible explanations for this effect. On the other hand, the risk with RIC (43% at 3 years) was not different from what has been reported previously [7,16-17,35]. Preceding MDS/MPD [36] and monosomal karyotype [23,29], both of which have been shown to be associated with poorer outcomes after HCT, were more frequent in the RIC group and may have contributed to the higher risk of relapse. In this retrospective study we had insufficient molecular data to further define leukemia phenotypes and the risk of relapse. Considering RIC patient were older compared with MAC in our study, it is possible that poor prognosis inherent with older age could not be overcome by the GVL effect of RIC UCB transplantation. On the other hand, with a median follow-up time of 3.8 years, 3 year LFS of 31% represents an improvement when compared with historic data using chemotherapy in older patients [37-39]. Although a larger study is required to clarify the risk factors yielding a higher risk of relapse after RIC, comprehensive molecular and cytogenetic evaluation and risk stratification at diagnosis in order to consider high risk AML patients for allogeneic transplantation in early remission may be warranted. Our institutional defined age cutoff for offering RIC rather than MAC UCB transplantation may need to be revised, in particular for older patients who are in good clinical condition and are likely to tolerate more intensive therapy. Less clinically fit patients who are poor candidates for MAC need to be counseled on the relative risk benefit of RIC UCB early in the course of their disease so that the opportunity to administer
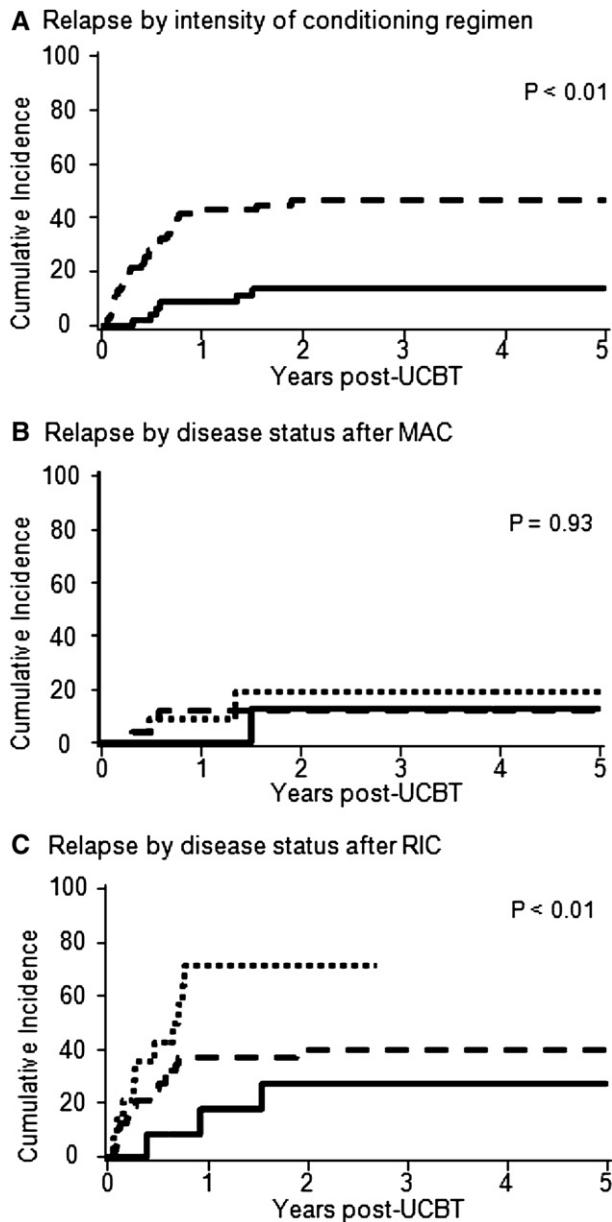
## A  Relapse by intensity of conditioning regimen



## B  Relapse by disease status after MAC



## C  Relapse by disease status after RIC



**Figure 2.** Cumulative incidence of relapse for AML patients in first and second complete remission (CR1-2) who underwent umbilical cord blood (UCB) hematopoietic stem cell transplantation (HCT) (A) after myeloablative conditioning (MAC) (——) versus reduced-intensity conditioning (RIC) (– – –); (B) for patients receiving MAC or (C) RIC according to disease status at the time of transplantation categorized as CR1 (——), CR2 with CR1 ≥1 year (– – –), and CR2 with CR1 <1 year (■ ■ ■ ■ ■).

potentially curative therapy is not missed. Alternative strategies such as higher intensity conditioning and/or posttransplantation antileukemic therapy may be considered for patients with high-risk leukemia who had a short CR1.

We found that the time to neutrophil recovery was shorter after RIC, but notably there was no difference in the incidence of sustained donor engraftment between the 2 groups. We and other have previously shown that UCB has sufficient numbers of immune cells to reproducibly engraft after RIC [14,40-43].

This observation demonstrates that concerns about donor engraftment depending on the intensity of the conditioning regimen should not be a factor limiting an AML patient in remission from proceeding to UCB transplantation.

In contrast to EBMT but similar to CIBMTR analyses [18], we did not observe a significant difference for 2-year TRM between conditioning groups. This result was seen despite the possible bias to select older and less fit patients with comorbidities for RIC. Thus, in our study, we achieved the goal of using RIC to reduce toxicity and TRM for frail patients who would not eligible for HCT otherwise.

In summary, MAC compared to RIC in AML patients resulted similar TRM and superior LFS with decreased risk of relapse in UCB HCT. Disease control was especially poor for patients in CR2 with short C1 duration. Our study highlights the importance of considering older patients with high risk AML for UCB transplantation in CR1 rather than in CR2 after a short lived CR1.

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