Hematologic Recovery Following Pre-Transplant Chemotherapy Does Not Influence Survival after Allogeneic Hematopoietic Cell Transplantation in Acute Myeloid Leukemia Patients

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Abstract

Pre-transplant remission status in patients with acute myeloid leukemia (AML) is one of the most important factors determining their outcomes after allogeneic hematopoietic cell transplantation (allo-HCT). Most patients are in complete remission with full hematologic recovery (CR) prior to undergoing allo-HCT. However, some patients achieve CR without recovery of platelet count (CRp) or a morphologic leukemia-free state (MLFS), defined as meeting all CR criteria without recovery of both neutrophil and platelet counts. Currently, there is a paucity of data regarding transplant outcomes in AML patients achieving MLFS after chemotherapy. To address this question, we evaluated transplant outcomes in 270 AML patients who received 6/6 HLA-matched sibling or 10/10 HLA-matched unrelated donor transplantation at a single institution between 2006 and 2013. Of our 270 patients, 206 were in complete remission (CR), 45 were in complete remission with incomplete platelet count recovery (CRp), and 19 were in MLFS prior to allo-HCT. Patients in CR, CRp, or MLFS had similar 3-year overall survival (49%, 46%, and 47%, respectively; P = 0.88) and 3-year event-free survival (45%, 36%, and 40%, respectively; P = 0.53). However, the cumulative incidence of non-relapse mortality (NRM) was significantly higher in patients in MLFS compared to those in CR (58% vs. 22%, P =0.0004), while the cumulative

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incidence of relapse in patients in MLFS was significantly lower compared to those in CR (11% vs. 36%, P = 0.03). Our results suggest that survival outcomes in AML patients are not influenced by degree of hematologic recovery prior to allo-HCT.

Keywords

AML; transplantation; hematologic recovery; pre-transplantation remission status; morphologic leukemia-free state; complete remission

INTRODUCTION

Despite the advancements of biomedical knowledge and treatment of acute myeloid leukemia (AML), patients with AML continue to have poor survival outcomes with 5-year overall survival (OS) still close to only 25%. The prognosis is worse for patients older than 60 years, whose 5-year OS is only 5–10%[1]. With new knowledge on molecular and genomic abnormalities such as mutations in the *FLT3, TP53, IDH1/2, TET2,* and *MLL* genes, we also know that these AML-specific factors affect overall prognosis[2–12]. In addition to age and genetic mutations, remission status following chemotherapy is also important in determining prognosis. Achievement of complete remission (CR) following induction treatment has been shown to correlate with improved survival in AML patients[13]. Part of the definition of CR requires hematologic recovery including a platelet count greater than 100,000/uL and absolute neutrophil count greater than 1000/uL[14]. In contrast, studies have shown that complete remission with incomplete hematologic recovery (CRi) is associated with reduced overall survival and increased risk of relapse[13,15–19]. However, most of these studies focused predominantly on patients who did not receive allogeneic hematopoietic cell transplantation (allo-HCT). Furthermore, there is currently a paucity of data on outcomes in AML patients who achieve morphologic leukemia-free state (MLFS), defined as meeting all CR criteria except for hematologic recovery (platelet count < 100,000/uL and absolute neutrophil count < 1000/uL)[14,20]. It is currently a common practice to wait for complete hematologic recovery before proceeding with allo-HCT in most AML patients. However, this approach potentially increases the risk of infectious and non-infectious (bleeding, transfusion-related adverse events, etc.) complications, which could potentially make these patients ineligible for transplant and consequently jeopardize their chances of long-term survival. To address the question of whether achieving MLFS adversely affects survival and relapse in AML patients who undergo allo-HCT, we retrospectively analyzed the post-transplant outcomes of AML patients based on the extent of hematologic recovery following pre-transplant chemotherapy.

METHODS

Study population

The study included a total of 503 consecutive AML patients who underwent their first allo-HCT at Washington University Medical Center in St. Louis between 2006 and 2013. This study was approved by the Institutional Review Board of Washington University School of Medicine, St. Louis.

Patient, donor, and transplant characteristics were collected and retrospectively entered into the Washington University School of Medicine, Blood and Marrow transplant database. Of the 503 patients, data from 270 patients was analyzed based on the following eligibility criteria: (1) 6/6 match at HLA loci A, B, and DRB1 by low-resolution genotyping[21] in related donor transplantation or 10/10 match at HLA loci A, B, C, DRB1, and DQB1 by high-resolution genotyping[22] in unrelated donor transplantation; (2) use of unmodified stem cells/non-manipulated grafts; and (3) no evidence of active disease (bone marrow blasts < 5%) based on last bone marrow biopsy prior to transplant.

The type of conditioning regimen was classified based on consensus definition of conditioning regimen intensity[23]. Reduced intensity and non-myeloablative regimens were grouped together under the reduced intensity conditioning (RIC) cohort.

The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score was calculated for all patients and categorized into 3 risk groups: low risk defined as score of 0, intermediate risk defined as score of 1–2, and high risk defined as score of 3 or greater[24].

Definitions

Based on hematologic recovery prior to initiating pre-transplant conditioning, patients were classified into 3 cohorts: (1) complete remission (CR); (2) complete remission with incomplete platelet count recovery (CRp); and (3) morphologic leukemia-free state (MLFS). CR was defined as follows: (1) bone marrow blasts less than 5%; (2) absolute neutrophil count greater than 1000/uL; (3) platelet count greater than 100,000/uL; (4) absence of blasts with Auer rods; (5) absence of extramedullary disease; and (6) independence of red cell transfusions, according to response criteria from the International Working Group[14]. CR was not further classified into cytogenetic CR or molecular CR. CRp was defined as meeting all CR criteria except for platelet count less than 100,000/uL. MLFS was defined as meeting all CR criteria except for a combination of absolute neutrophil count less than 1000/uL and platelet count less than 100,000/uL. The pre-transplant bone marrow was also evaluated for the persistence of cytogenetic (i.e., translocations, chromosomal deletions) and molecular (i.e., *FLT3, NPM1*, *CEBPA* mutations) abnormalities present at the time of original diagnosis.

Acute graft-versus-host disease (aGVHD) was diagnosed based on signs and symptoms and graded according to accepted criteria[25]. Chronic GVHD (cGVHD) was graded using National Institutes of Health consensus criteria[26].

Etiology of AML was classified into (1) de novo AML or (2) secondary AML, defined as occurring from treatment (radiation, alkylating agents, topoisomerase inhibitors) and bone marrow disorders such as myeloproliferative neoplasm (MPN) or myelodysplastic syndrome (MDS)[14,27]. AML was classified into good, intermediate, and poor prognostic cohorts based on the European LeukemiaNet classification scheme for cytogenetic and molecular genetic data[20].

Post-Transplantation Disease Monitoring

Engraftment of the donor cells was determined by PCR assay for short tandem repeats (STRs) or fluorescence in situ hybridization (FISH) from bone marrow samples and/or peripheral blood mononuclear cells[28]. Complete donor engraftment was defined as the presence of less than 5% of recipient cells at 30 days after transplant. Mixed chimerism was defined as presence of greater than 5% but 95% of recipient cells. Patients underwent bone marrow biopsies after allo-HCT at 30 days, 100 days, and then every 6 months or earlier if peripheral blood counts showed abnormal findings concerning for relapse. Disease in remission after transplant was defined as absence of excess blasts on bone marrow biopsy 30 days after transplant. Extramedullary disease or relapse was defined by presence of blasts in tissue biopsy or cerebrospinal fluid.

Study Endpoints and Statistical Analysis

The study end points included 3-year overall survival (OS); 3-year event-free survival (EFS); and cumulative incidences of relapse, non-relapse mortality (NRM), aGVHD, and cGHVD. OS was defined as the time from transplant to death from any cause or last follow-up. Those patients alive were censored at the last follow-up. EFS was defined as the time from transplant to relapse or death without relapse, whichever occurred first, while those patients alive and free of disease were censored at the last follow-up[14]. The distributions of demographic and clinical characteristics across the 3 cohorts (CR, CRp, and MLFS) were compared using Chi-square test, Kruskall-Wallis rank-sum test, or one-way ANOVA as appropriate. Survival curves by remission status were estimated using the Kaplan-Meier product-limit method, and the differences in OS or EFS at 3 years were compared using Klein's pseudo-value approach[29]. To assess whether remission status was an independent predictor of OS and EFS, propensity-score matching was used to adjust for potential confounding effects of patient characteristics[30]. The propensity scores for achieving complete remission were estimated using multivariate logistic regression, including age, donor-patient sex mismatch, disease etiology, disease status at transplant, disease classification by cytogenetics, conditioning regimen, transplant type, and anti-thymocyte globulin (ATG) regimen. A 3:1 matching (e.g., identifying 3 matched patients from CR cohort for every patients in MLFS cohort) was used for comparing CR versus MLFS cohorts, while a 1:1 matching was used for CR versus CRp cohorts. The cumulative incidences of NRM and relapse were calculated using Gray's sub-distribution method to account for the presence of competing risks[31]. All analyses were two-sided, and significance was set at a *P*-value of 0.05. Statistical analyses were performed using statistical packages cmprsk (http://biowww.dfci.harvard.edu/~gray) for competing risk analysis and SAS 9.3 (SAS Institutes, Cary, NC) for all other analyses.

RESULTS

Patient Characteristics

The distribution of patients among these cohorts was as follows: 206 in CR, 45 in CRp, and 19 in MLFS. Patient, disease, and transplant characteristics of these cohorts are summarized in Table 1. In our entire patient cohort, the median age was 54 years old (range, 17 to 74 years old). There was no significant difference in median age or time between last

chemotherapy and transplant among the 3 individual cohorts. Likewise, there was no significant difference in distribution by gender, disease prognosis, disease etiology, and type of transplant. There were five significant differences between the cohorts. First, there were more female donor/male recipient transplants in the MLFS cohort than in the CR and CRp cohorts (P = 0.007). Second, there was a lower percentage of patients in the CRp cohort who underwent a myeloablative conditioning regimen than in the CR and MLFS cohorts (P = 0.024). Third, there was a higher percentage of patients in the CRp cohort with a high HCT-CI score (3 or greater) than in the CR and MLFS cohorts (P = 0.024). Fourth, there was a higher percentage of patients in the MLFS cohort with pre-transplant bone marrow cellularity of 10% or less than in the CR or CRp cohorts (P < 0.001). However, the range of bone marrow cellularity was wide in all cohorts, with a max cellularity of 80% in the MLFS cohort, 90% in the CR cohort, and 70% in the CRp cohort (data not shown). Fifth, there was a higher percentage of patients in the MLFS cohort who had persistent cytogenetic and/or molecular abnormalities in the pre-transplant bone marrow (P < 0.001).

The types of chemotherapy regimens immediately prior to transplant were relatively similar in distribution for the 3 cohorts, except that high-dose cytarabine was less commonly used in the MLFS cohort than in the CR and CRp cohorts, while CLAG- or FLAG-based regimens were less commonly used in the CR cohort than in the MLFS and CRp cohorts. These results are summarized in Table 2.

3-year Overall Survival and Event-Free Survival

Median follow-up for the CR, CRp, and MLFS cohorts were 524, 410, and 290 days, respectively. The upper panel of Figure 1 described the differences in OS using data from all patients, and the 3-year OS for the CR, CRp, and MLFS cohorts were 49%, 46%, and 47%, respectively (p=0.88). After adjusting for the effects of other demographic and clinical characteristics using propensity-score matching, we did not find any significant difference in 3- year OS between the MLFS and CR cohorts (P = 0.73). Similarly, we did not find any significant difference between the CRp and CR cohorts (P = 0.62).

The lower panel of Figure 1 described the differences in EFS using data from all patients, and the 3-year EFS for the CR, CRp, and MLFS cohorts were 45%, 36%, and 40%, respectively (p=0.53). After propensity-score matching, we did not find any significant difference in EFS between the MLFS and CR cohorts (P = 0.84). Similarly, we did not find any significant difference between the CRp and CR cohorts (P = 0.40).

NRM, Relapse and GVHD

The cumulative incidence of relapse in the MLFS cohort was 11%, significantly lower than 36% (P = 0.03) for those in CR and 47% (P = 0.004) for those in CRp (Fig. 2). However, the cumulative incidence of NRM in the MLFS cohort was 58%, significantly higher than 22% (P = 0.0004) for those in CR and 16% (P = 0.002) for those in CRp (Fig. 2). Within the MLFS cohort, 8/13 (62%) patients who received myeloablative conditioning experienced NRM compared to 3/6 (50%) patients who received reduced intensity conditioning (P > 0.99). The causes of death included infection, sepsis, recurrence or progression of leukemia, graft failure, and acute and chronic GVHD. There was a higher percentage of patients in the

MLFS cohort who died from causes other than GVHD, infection, sepsis, graft failure, and relapse or progression of leukemia. Those deaths included 2 from multiple organ failure, 1 from accidental death, 1 from sinusoidal obstruction syndrome, 1 from cardiac arrest, and 1 from unknown cause. Two of these deaths (1 cardiac arrest, 1 sinusoidal obstruction syndrome) occurred before remission and engraftment were documented. The results are summarized in Table 3.

The cumulative incidence of grade 2–4 aGVHD in the CR, CRp, and MLFS cohorts were 38%, 38%, and 42%, respectively (P = 0.93). Likewise, the cumulative incidence of cGVHD in patients in the CR, CRp, and MLFS cohorts were 34%, 38%, and 16%, respectively (P = 0.22).

DISCUSSION

Our results suggest that AML patients in CRp or MLFS prior to allo-HCT have similar overall and event-free survival compared to patients in CR, suggesting that hematologic recovery following pre-transplant chemotherapy does not significantly influence survival outcomes. Previous studies have shown that incomplete hematologic recovery (CRi) is associated with reduced overall survival and increased risk of relapse[13,15_19]. However, these studies did not include outcomes in AML patients with MLFS in which neither absolute neutrophil count nor platelet count has recovered. Our results seem to suggest that allo-HCT overcomes the negative impact that poor hematologic recovery might have on survival in AML patients. In fact, a study by Sievers et al. showed similar overall survival in gemtuzumab-treated patients who received allo-HCT, whether or not they were in CR or CRp[32]. It is not clear why there was a higher incidence of NRM in our MLFS cohort. One possibility is the type of conditioning regimen prior to allo-HCT as there seems to be a higher rate of NRM in patients who received myeloablative conditioning compared to those who received non-myeloablative or reduced intensity conditioning, though this did not reach statistical significance possibly due to the small cohort size. There was also a higher percentage of female donor-to-male recipient (FM) transplants in our MLFS cohort which could have also contributed to high NRM in this cohort consistent with a recent published study[33]. Furthermore, differences in HCT-CI or performance status were unlikely to have contributed to higher NRM in MLFS patients as we did not find any significant differences in these measures among the three cohorts. Similarly, there is no obvious explanation for the lower relapse rates seen in this cohort, though it is possible that use of myeloablative conditioning regimens and female donor-to-male recipient transplants also contributed to lower relapse rates in these patients.

There are possible explanations why some patients have poor hematologic recovery after chemotherapy. These include the number of pre-existing comorbidities, type of chemotherapy used, and the persistence of cytogenetic and/or molecular abnormalities on the pre-transplant bone marrow. Our CR cohort had the lowest percentage of patients with an HCT-CI score of 3 or greater. There was also a significant difference in the distribution of types of chemotherapy regimens used in our three cohorts. Some chemotherapy regimens might be more myelosuppressive than others. In fact, Martin et al. showed that the addition of gemtuzumab ozogamicin to FLAG-I chemotherapy was associated with more

thrombocytopenia with a CRp rate of 27% compared to 13% in patients who underwent FLAG-I by itself[17]. Furthermore, failure to recover counts might be a harbinger of residual leukemia as suggested by a higher percentage of patients in our MLFS cohort with persistent cytogenetic and/or molecular abnormalities. Recently, several studies have shown the negative impact of minimal residual disease (MRD) on post-transplant outcomes in AML patients[34–36]. We did not assess the pre-transplant MRD status in any of the patient cohorts, which could have potentially influenced our results.

In summary, our results suggest that in AML patients undergoing allo-HCT, degree of hematologic recovery after pre-transplant chemotherapy has no significant effect on survival outcomes. Thus, it might not be necessary to wait for a prolonged period of time for complete hematologic recovery prior to transplant, thereby mitigating the potential risk of infectious and non-infectious complications which are relatively common in patients with prolonged cytopenias. Furthermore, MLFS in AML patients could indicate persistence of cytogenetic and/or molecular abnormalities. Lower relapse rates observed in our MLFS cohort are encouraging, however the higher incidence of NRM (> 50%) suggests that allo-HCT might best be reserved for MLFS patients who still have good performance status and low co-morbidity scores.

Acknowledgments

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- Allogeneic hematopoietic cell transplantation provides acceptable long-term survival in AML patients with CR, CRp and MLFS.

- There is a higher persistence of cytogenetic and molecular abnormalities in AML patient with MLFS.

- MLFS in AML patients is associated with high NRM and therefore transplant conditioning regimens should be carefully chosen in these patients.

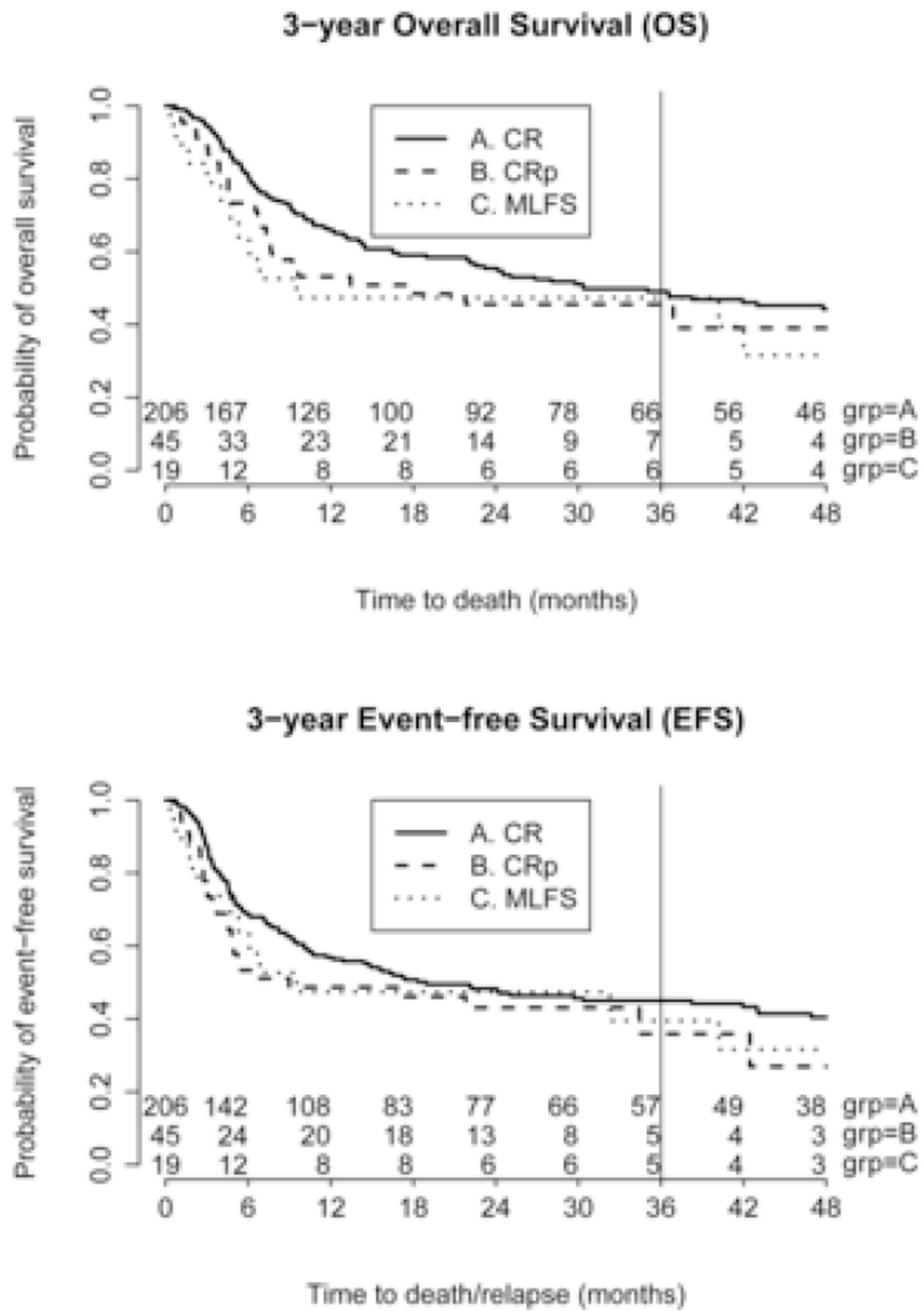## 3-year Overall Survival (OS)

3-year Event-free Survival (EFS)

Figure 1.
OS and EFS stratified for the 3 cohorts.

Relapse

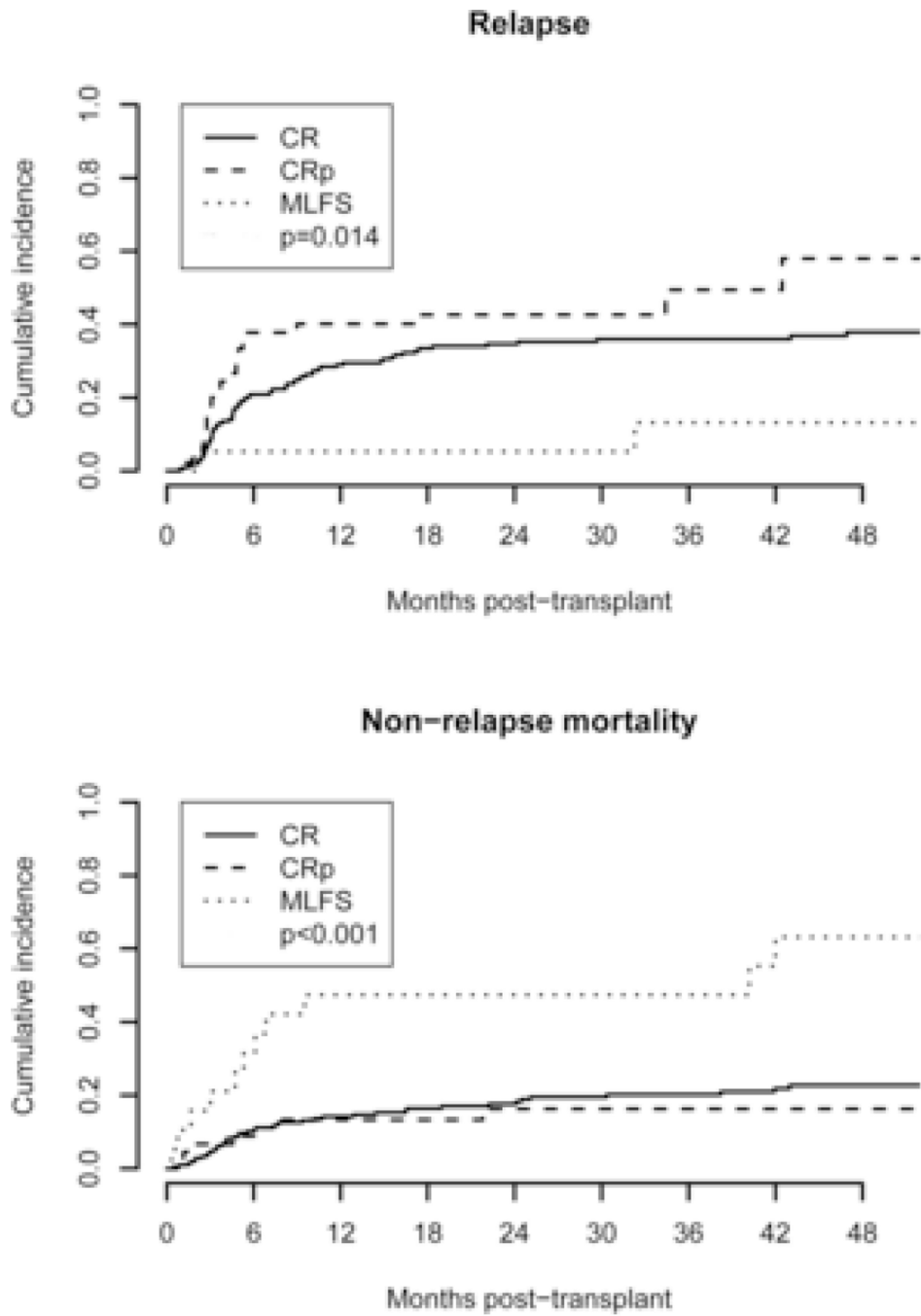**Non-relapse mortality**

Figure 2.
Cumulative incidences of relapse and NRM for the 3 cohorts.

TABLE 1

Patient, Donor, and Transplant Characteristics

	All Patients	Patients in CR	Patients in CRp	Patients in MLFS	P value
Number of patients (%)	270	206 (76%)	45 (17%)	19 (7%)	
Median patient age, yr (range)	54 (17–74)	53 (17–72)	58 (21–74)	57 (24–73)	0.085
Patient sex (%)					0.112
Female	124 (46)	101 (49)	18 (40)	5 (26)	
Male	146 (54)	105 (51)	27 (60)	14 (74)	
Donor sex (%)					0.364
Female	93 (34)	71 (34)	13 (29)	9 (47)	
Male	177 (66)	135 (66)	32 (71)	10 (53)	
Donor-Patient sex (%)					0.007
Female-Male	44 (16)	29 (14)	7 (16)	8 (42)	
Other	226 (84)	177 (86)	38 (84)	11 (58)	
Disease etiology (%)					0.228
De novo	212 (79)	166 (81)	31 (69)	15 (79)	
Secondary	37 (14)	25 (12)	8 (18)	4 (21)	
Therapy related	21 (7)	15 (7)	6 (13)	0 (0)	
Disease classification by cytogenetics (%)					0.392
Favorable	26 (10)	21 (10)	3 (7)	2 (11)	
Intermediate	163 (60)	123 (60)	26 (58)	14 (73)	
Poor	77 (29)	59 (29)	16 (35)	2 (11)	
Unknown	4 (1)	3 (1)	0 (0)	1 (5)	
Time from last chemotherapy to transplant, days (range)	62 (16–366)	61 (16–366)	76 (66–198)	61 (20–273)	0.079
Pre-transplant bone	37 (14)	18 (8.7)	10 (22)	9 (47)	<0.001

	All Patients	Patients in CR	Patients in CRp	Patients in MLFS	P value
marrow cellularity 10% (%)					
Persistent cytogenetic and/or molecular abnormalities on pre-transplant bone marrow (%)	37/244 (15)	24/183 (13)	7/42 (17)	6/19 (32)	<0.001
HCT-CI score (%)					0.024
Low risk	28 (11)	26 (13)	1 (3)	1 (5)	
Intermediate risk	47 (17)	37 (18)	6 (13)	4 (21)	
High risk	195 (72)	143 (69)	38 (84)	14 (74)	
Conditioning regimen (%)					0.024
MA	193 (72)	155 (76)	25 (56)	13 (68)	
RIC	76 (28)	50 (24)	20 (44)	6 (32)	
Unknown	1 (0)	1 (0)	0 (0)	0 (0)	
ATG regimen (%)					0.437
No	206 (76)	160 (78)	31 (69)	15 (79)	
Yes	64 (24)	46 (22)	14 (31)	4 (21)	
Transplant type (%)					0.913
MRD	104 (39)	78 (38)	18 (40)	8 (42)	
MUD	166 (61)	128 (62)	27 (60)	11 (58)	
Stem cell source (%)					0.195
Peripheral blood	254 (94)	191 (93)	45 (100)	18 (95)	
Bone marrow	15 (6)	14 (7)	0 (0)	1 (5)	
Immune prophylaxis (%)					0.801
MTX, MMF, tacrolimus	33 (12)	23 (11)	8 (18)	2 (11)	
MTX, tacrolimus	213 (79)	165 (80)	33 (73)	15 (78)	
Other[1]	24 (9)	18 (9)	4 (9)	2 (11)	
CMV Reactivation (%)					

	All Patients	Patients in CR	Patients in CRp	Patients in MLFS	P value
Yes	134 (50)	97 (47)	24 (53)	13 (68)	0.118
No	136 (50)	109 (53)	21 (47)	6 (32)	

MRD, matched related donor; MUD, matched unrelated donor; MA, myeloablative; RIC, reduced intensity and non-myeloablative; ATG, anti-thymocyte globulin; MTX, methotrexate; MMF, mycophenolate mofetil.

[1] Other includes cyclosporine and sirolimus.

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TABLE 2

Last chemotherapy prior to transplant

	Patients in CR, number (%)	Patients in CRp, number (%)	Patients in MLFS (%)	P value
MEC[1]	27 (13%)	5 (11%)	2 (11%)	<0.001
HiDAC[2]	92 (45%)	16 (36%)	1 (5%)	
CLAG or CLAG-M[3]	4 (2%)	4 (9%)	1 (5%)	
FLAG, FLAG-I, FLAG-IM[4]	11 (5%)	7 (16%)	3 (16%)	
Decitabine	11 (5%)	2 (4%)	2 (11%)	
Other[5]	61 (30%)	11 (24%)	10 (52%)	

[1] MEC = Mitoxantrone, etoposide, cytarabine

[2] HiDAC = High-dose cytarabine

[3] CLAG = Cladribine, cytarabine, filgrastim; CLAG-M = CLAG plus mitoxantrone

[4] FLAG = Fludarabine, cytarabine, filgrastim; FLAG-I = FLAG plus idarubicin; FLAG-IM = FLAG-I plus gemtuzumab ozogamicin

[5] Includes clofarabine, all-trans retinoic acid, sorafenib, plerixafor, 5+2, 7+3, gemtuzumab ozogamicin alone, mitomycin, imatinib, and azacitidine.

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TABLE 3

Cause of Death

Cause of Death	Patients in CR, number (%)	Patients in CRp, number (%)	Patients in MLFS, number (%)	P value
Acute GVHD	13 (12)	0 (0)	3 (24)	0.012
Chronic GVHD	6 (5)	3 (12)	0 (0)	
Infection or sepsis	17 (15)	3 (12)	2 (15)	
Relapse or progression of disease	59 (53)	17 (65)	2 (15)	
Graft failure	1 (1)	1 (4)	0 (0)	
Other[1]	15 (14)	2 (7)	6 (46)	
Total	111	26	13	

[1]Other includes multiple organ failure, sinusoidal obstruction syndrome, cardiac arrest, intracranial hemorrhage, and unknown.