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Number of Courses of Induction Therapy Independently Predicts Outcome after Allogeneic Transplantation for AML in First Morphological Remission

Roland B. Walter[1,2,3], **Brenda M. Sandmaier**[1,4], **Barry E. Storer**[1], **Colin D. Godwin**[5], **Sarah A. Buckley**[5], **John M. Pagel**[1,4], **Mohamed L. Sorror**[1,4], **H. Joachim Deeg**[1,4], **Rainer Storb**[1,4], and **Frederick R. Appelbaum**[1,4]

[1]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[2]Department of Medicine, Division of Hematology, University of Washington, Seattle, WA, USA

[3]Department of Epidemiology, University of Washington, Seattle, WA, USA

[4]Department of Medicine, Division of Medical Oncology, University of Washington, Seattle, WA, USA

[5]Department of Medicine, Residency Program, University of Washington, Seattle, WA, USA

Abstract

Whether the number of chemotherapy cycles required to obtain a first morphological remission affects prognosis of patients with acute myeloid leukemia (AML) remains controversial. To clarify how achievement of early remission might influence outcome of allogeneic hematopoietic cell transplantation (HCT), we studied 220 consecutive adults with AML in first morphological remission who were transplanted following myeloablative or nonmyeloablative conditioning to investigate how the number of standard- or high-dose induction courses required to achieve remission influenced post-HCT outcome. Three-year estimates of overall survival were 65% (56-73%), 56% (43-67%), and 23% (6-46%) for patients requiring 1 course, 2 courses, or >2 courses of induction therapy; corresponding relapse estimates were 24% (17-31%), 43% (31-55), and 58% (30-78%), respectively. After covariate adjustment (MRD status, conditioning, age, cytogenetic disease risk, type of consolidation chemotherapy, pre-HCT karyotype, and pre-HCT peripheral blood count recovery), the hazard ratios for 2 or >2 induction courses *vs*. 1 induction

Address for correspondence: Roland B. Walter, MD PhD; Clinical Research Division, Fred Hutchinson Cancer Research Center; 1100 Fairview Ave N, D2-190; Seattle, WA 98109-1024, USA Phone: +1-206-667-3599; FAX: +1-206-667-6519; rwalter@fhcrc.org.

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were 1.16 (0.73-1.85, *P*=0.53) and 2.63 (1.24-5.57, *P*=0.011) for overall mortality, and 2.10 (1.27-3.48, *P*=0.004) and 3.32 (1.42-7.78, *P*=0.006), respectively, for relapse. These findings indicate that the number of induction courses required to achieve morphological remission in AML adds prognostic information for post-HCT outcome that is independent of other prognostic factors.

INTRODUCTION

For many patients with acute myeloid leukemia (AML) in first remission, allogeneic hematopoietic cell transplantation (HCT) is an effective consolidation therapy. Still, even in the absence of morphologically detectable disease at the time of transplantation, relapse remains a major cause of treatment failure,[1,2] although it is widely appreciated that the risk of disease recurrence varies considerably among patients. Hence, there has been interest in understanding pre-transplant factors that could serve as predictors of adverse post-HCT outcome to inform patients accurately about likely treatment outcomes and to develop risk-stratified transplant regimens.

Recent attention has focused on the role of pre-transplant minimal residual disease (MRD) as indicator of increased risk of relapse following allogeneic HCT for patients with AML in morphological remission.[3-6] However, other predictive factors have been recognized, including cytogenetic risk, white blood cell count at diagnosis, time of blast clearance, and the number of induction courses required to enter remission.[7-13] The prognostic impact of early remission achievement (i.e. after the first cycle of chemotherapy), however, has not been fully clarified. Specifically, in a large study conducted by the United Kingdom Medical Research Council in the non-transplant setting, response after course 1 was strongly predictive of outcome.[14] On the other hand, an analysis of 6 trials conducted by the Eastern Cooperative Oncology Group indicated that the outcome after induction therapy was not worse for patients if residual leukemia was present 10 to 14 days after the start of the first course of therapy if a second, similar cycle of treatment was given and patients subsequently achieved a remission.[15] Nonetheless, achievement of an early first remission is recommended in a recent Working Party consensus statement of the European LeukemiaNet as one of the factors for AML risk assessment in the decision-making process regarding allogeneic HCT. With this, a better understanding on how early remission achievement might influence outcome of transplantation is imperative. To address this, we investigated to what degree, if any, the number of cycles of induction therapy required to achieve morphological remission was associated with post-transplant outcome after adjustment for other predictive factors including pre-HCT MRD in 220 consecutive patients who underwent allogeneic HCT for AML in first morphological remission at our institution.

PATIENTS AND METHODS

Study cohort

Adult AML patients ≥18 years of age were included in this retrospective study if they received induction therapy with “7+3” or high-dose cytarabine-based regimens, provided they met the criteria for morphological remission (i.e. <5% blasts by light microscopy

without extramedullary disease). We included patients with or without complete peripheral blood count recovery and irrespective of the presence of flow cytometric or cytogenetic MRD at the time of HCT, underwent myeloablative or nonmyeloablative allogeneic HCT, and received peripheral blood or bone marrow as stem cell source. Patients were eligible for our analyses regardless of whether the treatment regimen was changed during re-induction therapy. We included all patients meeting these criteria between late April 2006 until April 2012. Analyses of the role of pre-HCT MRD on outcome have been published previously.[16-18] We used the 2008 WHO criteria to define AML[19] and the refined United Kingdom Medical Research Council (MRC) criteria to assign cytogenetic risk.[20] Pretransplantation comorbidities were assessed retrospectively using the HCT-specific comorbidity index (HCT-CI).[21,22] Treatment response criteria were used as proposed by the European LeukemiaNet.[23] Information on typing at the HLA-A, B, C, DR, and DQ locus was collected. Criteria for diagnosis and grading of acute and chronic GVHD have been reported previously.[24,25] Information on post-transplant outcomes was captured via the Long-Term Follow-Up Program through medical records from our outpatient clinic and local clinics that provided primary care for patients. All patients were treated on Institutional Review Board-approved protocols or standard treatment plans and gave consent to their data being used for research in accordance with the Declaration of Helsinki. Follow-up was current as of April 24, 2014.

Multiparameter flow cytometry (MFC) detection of MRD

Ten-color MFC was performed on bone marrow aspirates obtained as routine baseline assessment before HCT as described previously.[16-18] The routine sensitivity of this assay was estimated at 0.1%, although a higher level of sensitivity was possible for a subset of leukemias featuring more frankly aberrant immunophenotypes. When identified, the abnormal population was quantified as a percentage of the total $CD45^+$ white cell events. Any level of residual disease was considered MRD^{pos}.[16-18]

Statistical analysis

Categorical patient characteristics were compared between patients requiring 1, 2, or >2 courses of induction therapy using Fisher's Exact tests, and continuous characteristics were compared with Kruskal Wallis tests. Unadjusted probabilities of overall survival (OS) and relapse-free survival (RFS) were estimated using the Kaplan-Meier method, and probabilities of NRM, relapse, and acute as well as chronic graft-versus-host disease (GVHD) were summarized using cumulative incidence estimates. NRM was defined as death without prior relapse and was considered a competing risk for relapse, while relapse was a competing risk for NRM; death was considered a competing risk for acute and chronic GVHD. All outcomes were treated as time-to-event endpoints. Outcomes between patients requiring 1, 2, or >2 courses of induction therapy were compared using Cox regression. Multivariate models included the following additional factors: presence of MRD by MFC (yes *vs*. no), type of conditioning regimen (nonmyeloablative *vs*. myeloablative), age at the time of HCT, HCT-CI, cytogenetic risk group at time of AML diagnosis (unfavorable *vs*. favorable/intermediate), type of AML at diagnosis (secondary *vs*. de novo), type of consolidation chemotherapy (none *vs*. high-dose cytarabine [HIDAC]-containing *vs*. non-HIDAC containing), karyotype at time of HCT (normalized *vs*. not normalized for patients

presenting with abnormal karyotypes), and peripheral blood counts at the time of HCT (not recovered *vs*. recovered). Missing cytogenetic risk and karyotype were accounted for as separate categories. No adjustments were made for multiple comparisons, and all two-sided *P*-values from the regression models were derived from the Wald test. Statistical analyses were performed using STATA (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics

Our retrospective analyses included 220 patients undergoing first myeloablative (n=151) or nonmyeloablative (n=69) HCT from HLA-matched related or unrelated donors between April 2006 and April 2012 for AML in first morphological remission (i.e. <5% bone marrow blasts). Among these, 136 patients achieved a remission after 1 course of induction therapy, whereas 66 and 16 required 2 or >2 courses, respectively. In 41 of the 66 patients requiring 2 courses of induction chemotherapy, the therapeutic regimen was changed for re-induction, whereas the treatment regimen was changed at least once in all but one patient requiring >2 courses of therapy to achieve morphological remission. The characteristics of the study population, induction and consolidation chemotherapies, donors, and transplants stratified by number of induction courses are summarized in **Table 1**. While generally relatively well balanced across these patient strata, statistically significant differences were noted with regard to gender distribution (P=0.01), post-remission consolidative chemotherapy (P<0.001), remission duration before HCT (P=0.002), and proportion of patients with fully recovered peripheral blood counts at the time of HCT (P=0.009).

Acute and Chronic GVHD

The 120-day cumulative incidences of grade 3 or 4 acute GVHD differed slightly but not statistically significantly between patient strata, with estimates of 9% (5-15%), 17% (9-27%), and 13% (2-35%) for patients requiring 1 course, 2 courses, or >2 courses of induction therapy to achieve remission, respectively (P>0.13). Likewise, the 180-day cumulative incidences of chronic GVHD were not statistically significantly different between these patient cohorts: 49% (41-57%) for those who required 1 course of induction therapy, 53% (40-64%) for those requiring 2 courses, and 50% (25-71%) for those requiring >2 courses, respectively (P>0.07).

Association between Number of Induction Courses and Post-HCT Outcome

There were 95 deaths, 73 relapses, and 36 NRM events contributing to the probability estimates for OS, RFS, relapse, and NRM. The median follow-up after HCT among survivors was 4.0 [1.4-7.7] years, 4.0 [1.4-7.1] years, and 3.7 [1.4-6.3] years for patients requiring 1, 2, or >2 courses of induction therapy, respectively. The 3-year estimates of OS where 65% (56-73%), 56% (43-67%), and 23% (6-46%) for patients requiring 1 course, 2 courses, or >2 courses of induction therapy to achieve remission, respectively (**Figure 1A**). For RFS, the corresponding estimates were 60% (51-68%), 44% (31-56%), and 17% (3-39%) (**Figure 1B**). The 3-year estimate of relapse among patients who required 1 course of induction chemotherapy was 24% (17-31%), whereas for those requiring 2 and >2 courses of induction therapy, this risk was projected to be 43% (31-55) and 58% (30-78%),

respectively (**Figure 1C**). Finally, the 3-year estimates of NRM where 16% (11-23%), 13% (6-23%), and 25% (8-47%) for patients requiring 1, 2, or >2 courses of induction therapy, respectively (**Figure 1D**).

Relationship between Number of Induction Courses and Post-HCT Outcome

Univariate regression models for OS, RFS, relapse, and NRM were fit to assess the relevance of the number of induction courses as prognostic factor, and indicated an association between this pre-treatment covariate and post-HCT outcome. Specifically, as summarized in **Supplemental Table 1**, patients who required 2 induction courses had a shorter RFS (hazard ratio [HR] = 1.51 [95% confidence interval: 1.00-2.28], P=0.05) and increased risk of relapse (HR=1.97 [1.21-3.23], P=0.007) relative to those who required only 1 induction course, whereas OS and NRM were not statistically significantly different (OS: HR=1.20 [0.77-1.88], P=0.42; NRM: HR=0.82 [0.37-1.82], P=0.624). Moreover, requiring >2 induction courses to achieve CR1 was significantly associated with shorter OS (hazard ratio [HR] = 3.18 [95% confidence interval: 1.69-5.96], P<0.001) and RFS (HR=3.36 [1.83-6.17], P<0.001), an increased risk of relapse (HR=3.73 [1.78-7.83], P<0.001), and a trend toward increased NRM (HR=2.83 [0.97-8.25], P=0.06) relative to those requiring only 1 course of induction therapy.

Number of Induction Courses as Independent Prognostic Factor

Next, multivariate models were fitted for OS, RFS, relapse, and NRM to assess the potential role of the number of induction courses to achieve first remission (1 vs. 2 vs. >2) as an independent prognostic factor. We considered the following covariates: MRD status, HCT type, age at HCT, HCT-CI, cytogenetic disease risk at diagnosis, type of AML, type of consolidation chemotherapy before HCT, pre-HCT karyotype, and pre-HCT peripheral blood count recovery as covariates. Final models were built with inclusion of covariates that yielded P-values of <0.1 in univariate analyses (see **Supplemental Table 1**). After adjustment for these factors, the hazard ratios for 2 or >2 induction courses *vs*. 1 induction were 1.16 (0.73-1.85, P=0.53) and 2.63 (1.24-5.57, P=0.011) for overall mortality, 1.66 (1.09-2.54, P=0.018) and 2.84 (1.44-5.60, P=0.003) for failure for RFS, 2.10 (1.27-3.48, P=0.004) and 3.32 (1.42-7.78, P=0.006) for relapse, and 0.86 (0.38-1.99, P=0.73) and 1.79 (0.59-5.45, P=0.31) for NRM, respectively (**Table 2**).

DISCUSSION

It has become increasingly clear that post-treatment data bear important prognostic information that can significantly refine risk stratification in AML. For example, rapid clearance of peripheral blood blasts, determined either by manual differential blood counts or by flow cytometry, is predictive of remission achievement and survival.[26-31] Moreover, the presence of submicroscopic amounts of residual AML, measured at various time points during and after therapy, identifies a subset of patients at particularly high risk of overt disease recurrence and poor outcome.[3-6] This is also true for assessments before allogeneic HCT, a situation where MRD is now well recognized as a strong, independent predictor for adverse post-HCT outcome.[3-6]

Intrinsically, however, post-treatment information entails an assessment of the dynamic response of AML cells to anti-leukemia therapy, which may not be fully captured by single time-point analyses. This notion is illustrated by recent data from the Children's Oncology Group AAML03P1 trial, in which patients who cleared MRD early after initiation of chemotherapy and remained MRD^{neg} at the end of therapy had significantly better outcomes than those who were similarly MRD^{neg} at the end of therapy but had previously documented flow cytometric evidence of residual disease at some point during therapy.[32] Thus, as a snap-shot assessment of the sensitivity of the patient's leukemia cells late in the course of treatment, it is plausible that the knowledge gained from this assessment could be refined by including additional data from earlier time points during the course of therapy to provide more dynamic response information.

The present findings support this assumption, demonstrating that the early response to induction therapy, as estimated by the number of induction courses required to achieve initial remission, is associated with post-transplant outcome independently of the pre-HCT MRD status. These results thus extend previous studies by Keating *et al*.[9] showing that the time to remission maintains its prognostic relevance even after accounting for MRD, arguably one of the most important prognostic factors recognized to date for AML patients undergoing allogeneic HCT. Although the present findings may represent only a crude measure of chemosensitivity, data on the number of induction courses do provide additional prognostic information on expected outcomes beyond what can be gleaned from the MRD status, and, therefore, could be useful to educate patients. The data may also provide a more accurate and, perhaps, better guide to risk-stratified decision-making. Indeed, our study indicates that the constellation of early remission achievement and absence of MRD at the time of transplant can identify a subset of patients with excellent long-term outcome. For example, in our cohort, patients undergoing myeloablative HCT had an estimated 3-year OS of 80% (69-87%) and RFS of 79% (67-86%) if they required only one course of induction therapy to achieve remission and were MRD^{neg} during the pre-HCT assessment.

As one potential limitation of our study, the majority of patients were referred to our institution for transplantation after having received induction and consolidation chemotherapy elsewhere. Thus, although patients generally received an anthracycline and cytarabine, many variations were used, and the decision and timing to initiate a second induction therapy cycle was not standardized. Because many patients were referred from elsewhere, information on molecular testing was not universally available and could thus not be included in our analyses; for example, data on *NPM1* and *FLT3*-ITD status was only available for 51 and 55 patients, respectively. We also did not have MRD information available from time points other than the pre-transplant assessment, as systematic MRD measurements are not generally obtained outside of clinical trials, and such data are, thus, not typically available to the transplant physician. In the future, it is likely that sequential MRD assessments will become an integral part of the routine care of AML patients and may offer an optimized approach to the dynamic response monitoring. At least until then, information on the number of induction courses required to achieve initial remission may offer some value in the risk stratification of AML patients presenting for allogeneic transplantation while in remission.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- We wondered how induction therapy influenced post-transplant outcome in adult AML
- We studied 220 consecutive adults with AML in first remission
- Need for ≥2 induction courses was associated with worse post-HCT outcome
- Impact of induction therapy on post-HCT outcome is independent of other risk factors
- Induction therapy data add prognostic information for AML patients undergoing HCT

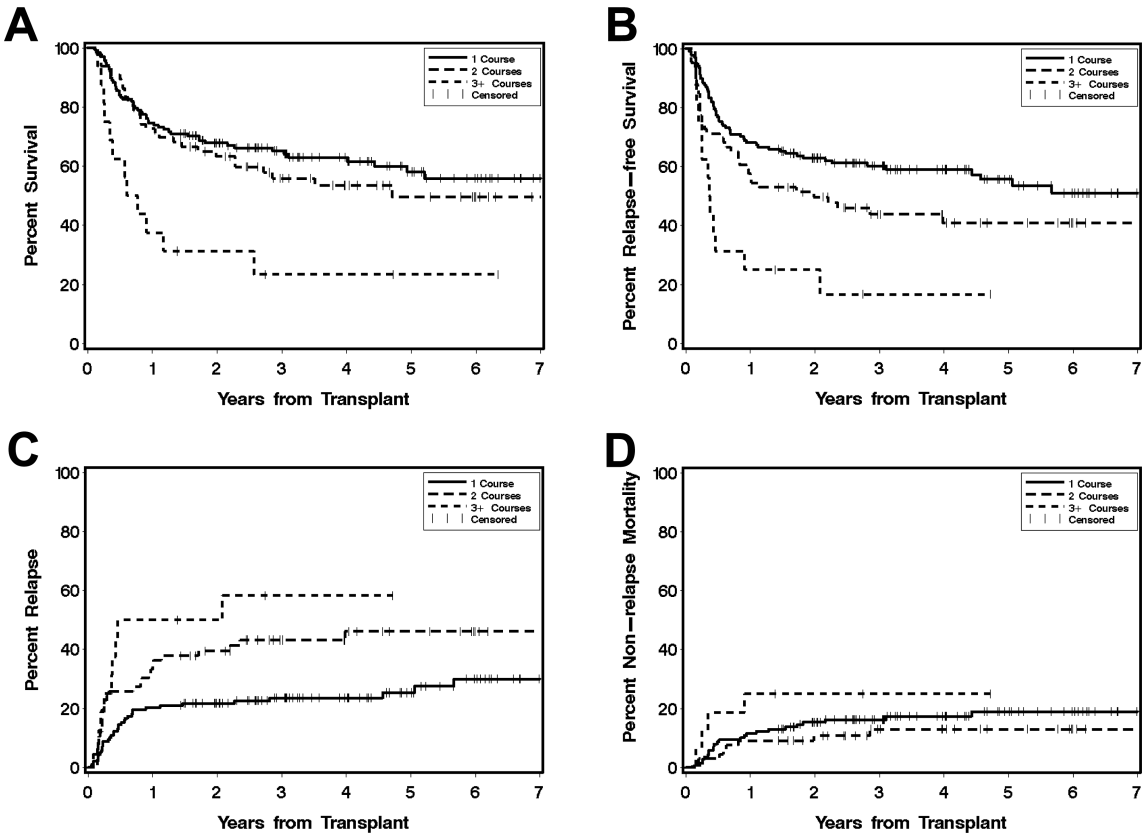

Figure 1. Association between number of induction courses and post-HCT outcome for AML patients in CR1

Estimates of overall survival **(A)**, relapse-free survival **(B)**, cumulative incidence of relapse **(C)**, and cumulative incidence of non-relapse mortality **(D)** following myeloablative allogeneic HCT for AML in complete morphologic remission, shown individually for patients who required 1 course (n=138; black, solid line), 2 courses (n=66; grey, solid line), or >2 courses (n=16; grey, dashed line) of induction therapy to achieve CR1.

TABLE 1

Pre-transplantation demographic and clinical characteristics of study cohort, stratified by number of induction courses before CR achievement

	All (n=220)	1 Induction Course (n=138)	2 Induction Courses (n=66)	>2 Induction Courses (n=16)	*P*-value
Median Age at HCT (range), years	51.9 (18.2-75.0)	51.5 (18.2-75.0)	51.9 (20.2-73.7)	61.1 (18.2-67.3)	0.22
Male Gender	57.3%	50.0%	66.7%	81.3%	0.01
Median WBC at Diagnosis, $\times 10^3/\mu L$	5.0 (0.2-280)	4.2 (0.3-238)	5.7 (0.2-280)	34.9 (0.6-145)	0.31
Cytogenetics					0.40
Favorable	4.6%	6.5%	1.5%	0%	
Intermediate	67.3%	67.4%	65.2%	75.0%	
Adverse	25.0%	22.5%	31.8%	18.8%	
Missing	3.2%	3.6%	1.5%	6.3%	
Secondary AML	37.7%	42.0%	30.3%	31.3%	0.25
Consolidation Therapy					<0.001
No	16.8%	10.9%	16.7%	68.8%	
Yes (HiDAC-containing)	70.9%	74.6%	75.8%	18.8%	
Yes (not HiDAC-containing)	12.3%	14.5%	7.6%	12.5%	
Median CR Duration before HCT (range), days	116 (16-788)	121 (22-788)	120 (26-465)	59 (16-231)	0.0014
Recovered Peripheral Blood Counts before HCT*	84.1%	87.7%	83.3%	56.3%	0.009
Routine Cytogenetics before HCT					0.23
Normalized karyotype	48.2%	50.7%	45.5%	37.5%	
Abnormal karyotype	11.4%	8.0%	18.2%	12.5%	
Missing/non-informative data	40.5%	41.3%	36.4%	50.0%	
HCT Comorbidity Index					0.73
0	15.0%	13.0%	19.7%	12.5%	
1-2	31.8%	30.4%	34.9%	31.3%	
≥3	52.7%	55.8%	45.5%	56.3%	
Missing	0.5%	0.7%	0%	0%	
MRD^{pos} at HCT by MFC	19.6%	16.7%	22.7%	31.3%	0.24
Myeloablative Conditioning	68.6%	67.4%	75.8%	50.0%	0.12

	All (n=220)	1 Induction Course (n=138)	2 Induction Courses (n=66)	>2 Induction Courses (n=16)	*P*-value
Unrelated Donor	61.8%	63.0%	60.6%	56.3%	0.82
Median Donor Age (range), years	40.1 (18.1-76.6)	40.1 (18.1-71.5)	38.6 (18.6-76.6)	43.7 (20.2-71.8)	0.55
HLA-Matching					0.32
Matched/identical	81.4%	82.6%	80.3%	75.0%	
1 locus mismatch	16.8%	16.7%	15.2%	25.0%	
≥2 loci mismatch	1.8%	0.7%	4.6%	--	
Conditioning Regimen					
L-TBI ± Flu or Clo	31.4%	32.6%	24.2%	50.0%	
Bu/Cy ± L-TBI	26.4%	24.6%	33.3%	12.5%	
Bu/Flu	14.1%	15.9%	12.1%	6.3%	
H-TBI/Cy or H-TBI/Tepa/Flu	7.3%	3.6%	10.6%	25.0%	
Treo/Flu ± L-TBI	18.6%	21.7%	15.2%	6.3%	
Flu/Radiolabeled Ab/L-TBI ± Cy	2.3%	1.4%	4.5%	0%	
Source of Stem Cells					0.07
PBSC	81.4%	84.1%	72.7%	93.8	
BM	18.6%	15.9%	27.3%	6.3	
GVHD Prophylaxis					
Calcineurin Inhibitor + Methotrexate	55.5%	54.3%	59.1%	50.0%	
Calcineurin Inhibitor + MMF	32.3%	32.6%	27.3%	50.0%	
Cy ± Calcineurin Inhibitor	9.5%	9.4%	12.1%	0%	
Other	2.7%	3.6%	1.5%	0%	

*ANC ≥1,000/μL and platelets ≥100,000/μL Abbreviations: Ab, antibody; BM, bone marrow; Bu, busulfan; Clo, clofarabine; Cy, cyclophosphamide; Flu, fludarabine; H-TBI, high-dose total body irradiation; HCT, hematopoietic cell transplantation; HiDAC, high-dose cytarabine; L-TBI, low-dose total body irradiation; MFC, multiparameter flow cytometry; MMF, mycophenolate mofetil; PBSC, peripheral blood stem cells; Tepa; thiotepa; Treo, treosulfan

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TABLE 2

Multivariate Cox Regression Models

	Overall Mortality	Failure for RFS	Relapse	NRM
Induction Therapy				
1 Induction course (n=138)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2 Induction courses (n=66)	1.16 (0.73-1.85), *P*=0.532	1.66 (1.09-2.54), *P*=0.018	2.10 (1.27-3.48), *P*=0.004	0.86 (0.38-1.99), *P*=0.731
>2 Induction courses (n=16)	2.63 (1.24-5.57), *P*=0.011	2.84 (1.44-5.60), *P*=0.003	3.32 (1.42-7.78), *P*=0.006	1.79 (0.59-5.45), *P*=0.308
MRD Status				
Negative (n=177)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Positive (n=43)	2.97 (1.77-4.98), *P*<0.001	4.06 (2.43-6.77), *P*<0.001	4.86 (2.71-8.70), *P*<0.001	2.21 (0.88-5.58), *P*=0.092
HCT Type				
Myeloablative (n=151)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Nonmyeloablative (n=69)	1.59 (0.97-2.61), *P*=0.068	1.68 (1.12-2.52), *P*=0.012	1.43 (0.87-2.35), *P*=0.159	1.89 (0.86-4.13), *P*=0.113
Age (per 10 years)	1.01 (0.82-1.23), P=0.960	*Not included*	*Not included*	1.26 (0.89-1.77), *P*=0.188
Cytogenetic Risk Group				
Intermediate/favorable (n=158)	1 (Reference)	1 (Reference)	1 (Reference)	*Not included*
Adverse (n=55)	2.19 (1.23-3.91), *P*=0.008	2.06 (1.20-3.54), *P*=0.009	1.49 (0.87-2.56), *P*=0.150	
Consolidation before HCT				
No (n=37)	1 (Reference)	1 (Reference)	1 (Reference)	*Not included*
Yes, with HiDAC (n=156)	1.22 (0.66-2.26), *P*=0.530	1.35 (0.75-2.43), *P*=0.313	1.26 (0.65-2.46), *P*=0.490	
Yes, without HiDAC (n=27)	1.06 (0.49-2.30), *P*=0.879	1.26 (0.61-2.59), *P*=0.526	0.94 (0.39-2.29), *P*=0.889	
Pre-HCT Karyotype				
Normalized (n=106)	1 (Reference)	1 (Reference)	*Not included*	1 (Reference)
Not normalized (n=25)	1.35 (0.69-2.64), *P*=0.387	1.07 (0.57-2.02), *P*=0.830		2.01 (0.66-6.11), *P*=0.218
Pre-HCT Blood Counts*				
Recovered(n=185)	1 (Reference)	1 (Reference)	*Not included*	1 (Reference)
Not recovered (n=35)	1.32 (0.77-2.27), *P*=0.308	1.52 (0.91-2.53), *P*=0.111		1.63 (0.73-3.60), *P*=0.232

Number of events: deaths=95; relapses=73; deaths without prior relapse=36

Included are covariates that yielded a P-value of <0.1 in univariate analyses.

* Recovered: ANC ≥1,000/μL and platelets ≥100,000/μL; not recovered: ANC <1,000/μL and/or platelets <100,000/μL