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Reduced Intensity Conditioned Allograft Yields Favorable Survival for Older Adults with B-cell Acute Lymphoblastic Leukemia

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Abstract

Older adults with B-cell acute lymphoblastic leukemia (B-ALL) have poor survival. We examined the effectiveness of reduced intensity conditioning (RIC) hematopoietic cell transplant (HCT) in adults with B-ALL age 55 years and older and explored prognostic factors associated with long-term outcomes.

Methods—Using CIBMTR registry data, we evaluated 273 patients (median age 61, range 55-72) with B-ALL with disease status in CR1 (71%), >CR2 (17%) and Primary Induction Failure (PIF)/Relapse (11%), who underwent RIC HCT between 2001-2012 using mostly unrelated donor (59%) or HLA-matched sibling (32%). Among patients with available cytogenetic data, the Philadelphia chromosome (Ph+) was present in 50%.

Results—The 3-year cumulative incidences of non-relapse mortality (NRM) and relapse were 25% (95% confidence intervals (CI): 20-31%) and 47% (95% CI: 41-53%), respectively. Three-year overall survival (OS) was 38% (95% CI: 33-44%). Relapse remained the leading cause of death accounting for 49% of all deaths. In univariate analysis, 3 year risk of NRM was significantly higher with reduced Karnofsky performance status (KPS <90: 34% (95% CI: 25-43%) vs KPS ≥90 (18%; 95% CI: 12-24%, p=0.006). Mortality was increased in older adults (66+ vs. 55-60: Relative Risk (RR) 1.51 (95% CI: 1.00-2.29, p=0.05) and those with advanced

disease (RR 2.13; 95% CI: 1.36-3.34, p=0.001). Survival of patients in CR1 yields 45% (95% CI: 38-52%) at 3 years and no relapse occurred after 2 years.

Conclusions—We report promising OS and acceptable NRM using RIC HCT in older patients with B-ALL. Disease status in CR1 and good performance status are associated with improved outcomes.

Keywords

Acute Lymphoblastic Leukemia (ALL); Older adults; Reduced Intensity Conditioning (RIC); Hematopoietic Cell Transplant (HCT)

INTRODUCTION

Older adults with acute lymphoblastic leukemia (ALL) are the largest ALL subset in which treatment advances have failed to improve outcomes.(1-3) ALL incidence is bimodal(4), it is estimated that 19% of patients diagnosed with ALL are over 55 years of age and this number will likely increase as the general population ages.(5) A recent population-based study of Surveillance, Epidemiology and End Results (SEER) data found that older adults (60 years and older) with B-ALL have 5 year survival rates of only 10% without improvements in the last 30 years.(2) Furthermore, few prospective trials enrolled patients 60 years or older and while remission rates range from 30-70%, the reported median survival varied from 9-14 months.(1, 3) Poorer outcomes among older adults can be partially explained by biological characteristics of ALL and their increased susceptibility to organ-toxicity and infections. Adverse disease characteristics such as the presence of the Philadelphia chromosome (Ph+) t(9;22) increase with age where high risk cytogenetics are reported in half of adults 40 years and older.(3, 4, 6)

Recent advances in older adult B-cell ALL therapy have integrated intensive chemotherapy protocols with tyrosine kinase inhibitors (TKI) for Ph+ ALL. The inclusion of TKI therapy has led to high overall response rates allowing for more patients to proceed to allogeneic donor hematopoietic cell transplantation (HCT).(7-13) Allogeneic HCT has demonstrated Graft vs. Tumor effect and long term survival post HCT.(7, 14, 15) However, older age increases transplant-related mortality (TRM) among patients who receive myeloablative (MA) preparative regimens followed by HCT, mitigating a survival advantage.(16) Data from the CIBMTR indicate that 40% of adult transplants for hematologic malignancy now use reduced-intensity conditioning (RIC) regimens.(17) RIC HCT regimens allow for immune-mediated graft-versus-leukemia responses with potentially less toxicity, permitting allografts in older adults and in patients with reduced fitness or organ compromise. Criteria for decision making and recommendations regarding RIC HCT are unclear in older patients with ALL.(18) The contribution of chronologic age, treatment tolerance, comorbidities, ALL biology, and transplant procedure variables need to be studied to inform future treatment strategies. Using Center for International Blood and Marrow Transplant Research (CIBMTR) data, we examined the transplant outcomes of patients 55 years or older who underwent RIC HCT for ALL and identified prognostic factors affecting non-relapse mortality, relapse, and overall survival.

PATIENTS AND METHODS

Data Source

The CIBMTR® includes data from a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on allogeneic and autologous HCT. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits and patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on site audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

The CIBMTR collects data at two levels: Transplant Essential Data (TED) level and Comprehensive Report Form (CRF) level. The TED-level data is an internationally accepted standard data set that contains a limited number of key variables for all consecutive transplant recipients. Details on CRF and TED level data collection have been previously published and are described in detail elsewhere.(19) TED and CRF level data are collected pre-transplant, 100 days and six months post-transplant, annually until year 6 post-transplant and biannually thereafter until death. Details of fungal infections, time to achievement of first complete remission (CR1), and cytogenetics were available for a nested cohort of 119 subjects with CRF reports.

Eligibility Criteria

We included all adults with B-cell ALL who were ≥55 years of age undergoing RIC HCT between 2001-2012 who had complete 100-day research form data. Patients at all disease stages CR1, CR2, and with advanced leukemia (defined as ≥CR3, primary induction failure (PIF), or relapsed disease) were included. Patients with T-cell ALL were excluded due to limited numbers (n=12). Two hundred and seventy-three cases met the selection criteria from 95 centers in 16 countries. RIC HCT regimens were defined in this protocol as containing busulfan ≤8mg/kg (orally) or ≤6.4mg/kg (intravenously), melphalan <150mg/m^2, or low-dose total-body irradiation (fractionated TBI <8Gy or unfractionated TBI <5Gy).(20) All graft types were included. Donors were classified as HLA-matched sibling, HLA-matched unrelated donor (MUD), umbilical cord blood (UCB), or Other (HLA-mismatched unrelated and partially matched related).(21)

Outcomes

The primary outcome evaluated was overall survival (OS) which included death from any cause as an event. Secondary outcomes were non-relapse mortality (NRM) defined as death without evidence of leukemia recurrence and leukemia free survival (LFS) defined as the time from HCT to treatment failure (death or relapse). Leukemia relapse was defined as morphologic marrow or clinical extramedullary relapse after HCT. Acute graft versus host disease (aGVHD) was diagnosed and graded based on consensus criteria, and chronic GVHD (cGVHD) was diagnosed based on clinical criteria.(22, 23)

Statistical Methods

We describe the outcomes and important prognostic factors in adults ≥55 years with B-cell ALL utilizing retrospectively detailed information from the CIBMTR. Patient and transplant-related variables were compared using Chi-square test for categorical variables and Mann-Whitney test for continuous variables. Kaplan-Meier curves were used to estimate the probability of OS and LFS. Cumulative incidence was used to estimate the probability of NRM, GVHD, and relapse. For GVHD and relapse, NRM was treated as a competing risk. Conversely, for NRM, relapse was treated as a competing risk. For LFS and OS patients were censored at the time of last follow-up. SAS statistical software version 9.3 (SAS Institute, Cary, North Carolina 2015) was used for all analyses. A univariate Cox regression analysis was carried out; despite having 300 cases, only 119 cases had complete information on cytogenetics and other covariates of importance precluding a multivariate analysis.

RESULTS

Patients, Disease, and Transplant Characteristics

We examined data on 273 patients from 95 reporting centers **(Table 1)**. The median age was 61 years (range 55-72), and 56% had excellent performance status (KPS 90-100%). Most (n=195; 71%) patients were in CR1 and 45% of patients were <6 months from diagnosis. HCT conditioning most commonly utilized alkylating-based RIC (62% vs. 34% low dose TBI), peripheral blood stem cells (85%) T-replete grafts (69%). MUD were more common (n=104; 38%) than HLA-matched sibling donors (n=92; 34%) or UCB grafts (n=21; 8%). 'Other' grafts included partially matched unrelated donors (URD) (n=27), mismatched URD (n=2), matching unknown URD (n=18), and other related (includes haplo-identical) (n=9). In a nested cohort of 119 patients with detailed disease and patient characteristics, 50% had Ph+ chromosome, and 40% achieved CR1 within ≤8 weeks. Extramedullary disease at diagnosis (12%) and pre-transplant fungal infections (8%) were infrequent.

Comparing three age groups (55-60 vs 61-65 vs 66+ years), disease status at HCT was similar (75% vs 66% vs 76% in CR1), but patients 66 years of age and older had worse KPS (<90%), more comorbidities, and were more likely to receive a MUD compared to younger patients **(Table 1)**. Low-dose TBI /fludarabine conditioning regimen was common across age categories, whereas 66+ patients more often received busulfan/fludarabine. In a nested cohort of 119 patients with available cytogenetic data, Ph+ was more common in the 55-60 age group (n=31, 53%) and 80% Ph+ patients were in CR1 (n=47) compared to Ph− population. Yet other patient, disease, and transplant characteristics were similar among Ph+ and Ph− populations **(Supplementary Table A)**.

Relapse and Non-Relapse Mortality

The cumulative incidences of relapse at 3 years was 47% (95% CI: 41% to 53%) and NRM was 25% (95% CI: 21% to 32%) (Supplementary Figure 1). Patients >66 years old had higher NRM (40%; 95%CI: 26% to 56%), while NRM was similar between patients 55-60 and 61-65 years old (23%; 22%; p=0.07; **Table 2**). KPS <90% led to a higher cumulative incidence of NRM; (34% (95% CI: 25% to 43%) vs. KPS ≥90%: 18% (95% CI: 12% to 24%); p=0.006). Relapse was more common in *in-vivo* T-cell depleted transplants 60%

(95% CI: 49% to 70%); p=0.004. Three-year relapse rate tended to be lower among patients in CR1, but this did not reach statistical significance: CR1 43% (95% CI: 36% to 50%), >CR2 57% (95% CI: 43% to 71%), advanced disease 56% (95%CI 37% to 73%) (p=0.13). Type of conditioning (alkylator vs. low-dose TBI), donor source, GVHD prophylaxis, and year of HCT were not significantly associated with relapse or NRM (**Table 2**). In a nested cohort of 119 patients, we determined that history of prior fungal infection was associated with a 3-fold higher NRM (yes 67% (95% CI: 35% to 92%) vs. none 20% [95% CI: 13% to 28%], p=0.004}. Presence of Ph+ chromosome and delayed time to CR1 (>8 weeks) were not associated with relapse or NRM.

Leukemia Free Survival and Overall Survival

LFS and OS at 3 years were 28% (95% CI: 23 to 34) and 38% (95% CI: 33 to 44), respectively (Supplementary Figure 2). Patients in CR1 at HCT had improved OS compared to higher overall mortality of patients in CR2 (RR 1.95 95% CI: 1.36 to 2.80; p=<0.001) or with advanced disease (RR 2.13 95% CI: 1.36 to 3.34; p=0.001) **(Figure 1A)**. A univariate Cox regression model demonstrated that RIC HCT yielded similar survival rates among patients aged 55-60 and 61-65 years (RR 1.27; 95% CI: 0.92 to 1.75; p=0.15), but increased mortality in the 45 patients aged 66 years or above (RR 1.51; 95% CI: 1.00 to 2.29; p=0.05) **(Figure 1B)**. LFS was significantly inferior in patients who were in CR2 (RR 1.75 95% CI: 1.21 to 2.54; p=0.003) or who had advanced disease (RR 1.99 95% CI: 1.33 to 2.99; p<0.001) at HCT; yet, age and KPS were not associated with LFS. Survival was not impacted by the conditioning regimen type, year of HCT, donor type, CMV matching, or type of GVHD prophylaxis **(Table 3)**. In the nested cohort, history of fungal infections, as well as disease risk factors such as presence of Ph+ or time to CR1 were not associated with survival. The cumulative incidences of grade II-IV aGVHD, grade III-IV aGVHD, and cGVHD were similar in each of the three age groups **(Supplementary Table B)**. The main cause of death across all age categories was disease relapse followed by infections and GVHD **(Supplementary Table C)**.

RIC HCT in CR1

The subset of 195 RIC HCT recipients who were transplanted in CR1 with median age 61 years (range 55-72) had 3-year survival rates of 45% (95% CI: 38% to 52%). A univariate Cox regression model demonstrated that NRM in patients 55-60 and 61-65 years old was significantly lower (19%; 21%) compare to 41% (95% CI: 25% to 58%) in patients older than 66 years (p=0.05) yielding better survival among patients aged 55-60 compared to >66 years old (overall mortality HR 1.69; 95% CI: 1.04 to 2.76; p=0.04). Relapse was more common in *in-vivo* T-cell depleted transplants 56% (95% CI: 42% to 69%); p=0.004 **(Supplementary Table D)**.

DISCUSSION

We report a large recent registry cohort of RIC HCT recipients ≥55 years old with B-cell ALL and a variety of donor sources. We report OS of 38% at 3 years and NRM of 25% for this patient population. Comparing reported outcomes in older adults with ALL undergoing transplant is difficult due to bias in age selection for RIC vs. MAC,(24, 25) differences in

graft sources,(26) overlap in operational definitions for RIC vs. non-myeloablative conditioning,(27-29) and variable disease control at the time of transplant.(24) Therefore we sought to examine several prognostic factors that will aid the clinician in a decision making strategy for older adults with ALL.

One of the main findings of our study is the prognostic impact of disease status at the time of transplant on survival reflecting the recognized unfavorable biology of older adult ALL.[26,27] The decision to proceed with transplant in CR1 is associated with improved survival of 45% at 3 years and long term disease control with few relapses beyond 2 years, which suggests graft-versus-leukemia effect delivered by RIC HCT. In contrast to increasing age, which was not associated with the risk of relapse, patients in CR2 or with advanced disease treated with RIC HCT as a salvage option were twice as likely to experience treatment failure across all age cohorts and disease relapse was by far the leading cause of death after HCT. These data mitigate the concern that HCT in CR1 is risky particularly for highly functional older adults, and is an opportunity for cure as others have reported.(30) Interestingly, nearly half of evaluable patients were Ph+ and HCT outcomes were quite similar in both groups. Lack of data on tyrosine-kinase inhibitors use before and after transplant limits our data interpretation, nevertheless most transplants occurred in era when TKI were largely available. Recent registry study showed that 41% of patients with Ph+ ALL undergoing RIC HCT were MRD negative pre-HCT and about a third received post-HCT TKI(10).

Nearly a quarter of older adults with ALL with intention to proceed to transplant actually undergo transplant, reflecting the heterogeneity in treating older adults with ALL and selection bias of transplant studies.(31) Importantly, we found that aging adults with B-ALL tolerate RIC with acceptable outcomes. Although we identified that aging patients have similar NRM, we also report that NRM is higher with poor performance status by univariate analysis. Notably, the observed association of older age (above 65 years) and impaired KPS limits our conclusions and signifies the need to incorporate validated prognostic tools to assess functional status prior to transplant.(32, 33) One major limitation of our study is that comorbidity data are incomplete for a third of the population and a comprehensive geriatric assessment was not performed routinely at HCT evaluation. A composite score of age and comorbidities can predict NRM and survival in HCT recipients (34) yet the interaction of age, co-existing disease and functional status are complex and dynamic. The transplant decision-making process can benefit from using validated assessment tools to predict the risk of toxicity in older adults with cancer. (32, 35-40) It is important to recognize that chronologic age should not be a deterrent for a bone marrow transplant evaluation. Full intensity conditioning has been reported to have significantly higher NRM among patients above 40 years of age thus considerably limiting the benefit of allografting; nevertheless the age in which RIC HCT should be considered for ALL is not well established.(10, 16, 41) Our data showed acceptable NRM for older ALL patients, and we hypothesize that performance status is the driving force for morbidity and mortality related to RIC transplant. While HCT in older patients with ALL is feasible and yield long-term survival, these outcomes may be improved by more careful patient selection. For example, our data albeit limited by small sample, suggest that prior fungal infection may be associated with mortality risk and could represent an additional concern prior to a planned HCT.

Alternative treatment strategies should be explored for patients in >CR2. The availability of novel and less toxic therapies and better diagnostic methods offers an opportunity to deepen remissions prior to allogeneic transplant. Whether novel therapies currently under development will provide safer, more effective treatment options for older adults with B-ALL is an important area for further study. Increased availability of the alternative donor pool (42, 43) and advances in supportive care continues to extend curative RIC HCT to selected eligible patients of all ages with acceptable organ function and performance status. Our results suggest that type of donor (matched sibling, MUD, umbilical cord blood, or mismatched donors) does not significantly influence transplant outcomes. Although the sample sizes were small, alternative graft sources may be particularly relevant for elderly adults who lack suitable HLA-matched sibling donors and deserve future studies. Consistent with others, we observed that *in vivo* T-cell depleted grafts were associated with more relapse, suggesting a potential approach to minimize relapse, although we are limited by small sample size and univariate analysis to imply deleterious effects on survival. Furthermore, the future transplant decision making process may also be guided by minimal residual disease (MRD) status, where it has been shown that patients with evidence of MRD who undergo transplant have longer relapse free survival, compared to non-transplant approach.(44) MRD may identify incipient relapse and permit either earlier transplant or novel therapies (45, 46) to deepen response while preparing for an allograft. Ultimately, age and conventional cytogenetics in prognostication should be supplemented for advances such as routine use of a comprehensive geriatric assessment,(32) MRD evaluation,(44) molecular analyses and/or genomic profiling.(44, 47)

In conclusion, our results provide the clinician with data to support decision making regarding the use of RIC HCT in older adults with ALL. While age should not limit access to RIC HCT, functional status should be carefully assessed and enrollment to clinical trials or alternative therapies should be sought for patients not in CR1. Clinical trials prospectively testing RIC in older adult ALL such as United Kingdom ALL XIV (UKALL14) are needed to inform on future directions in this challenging disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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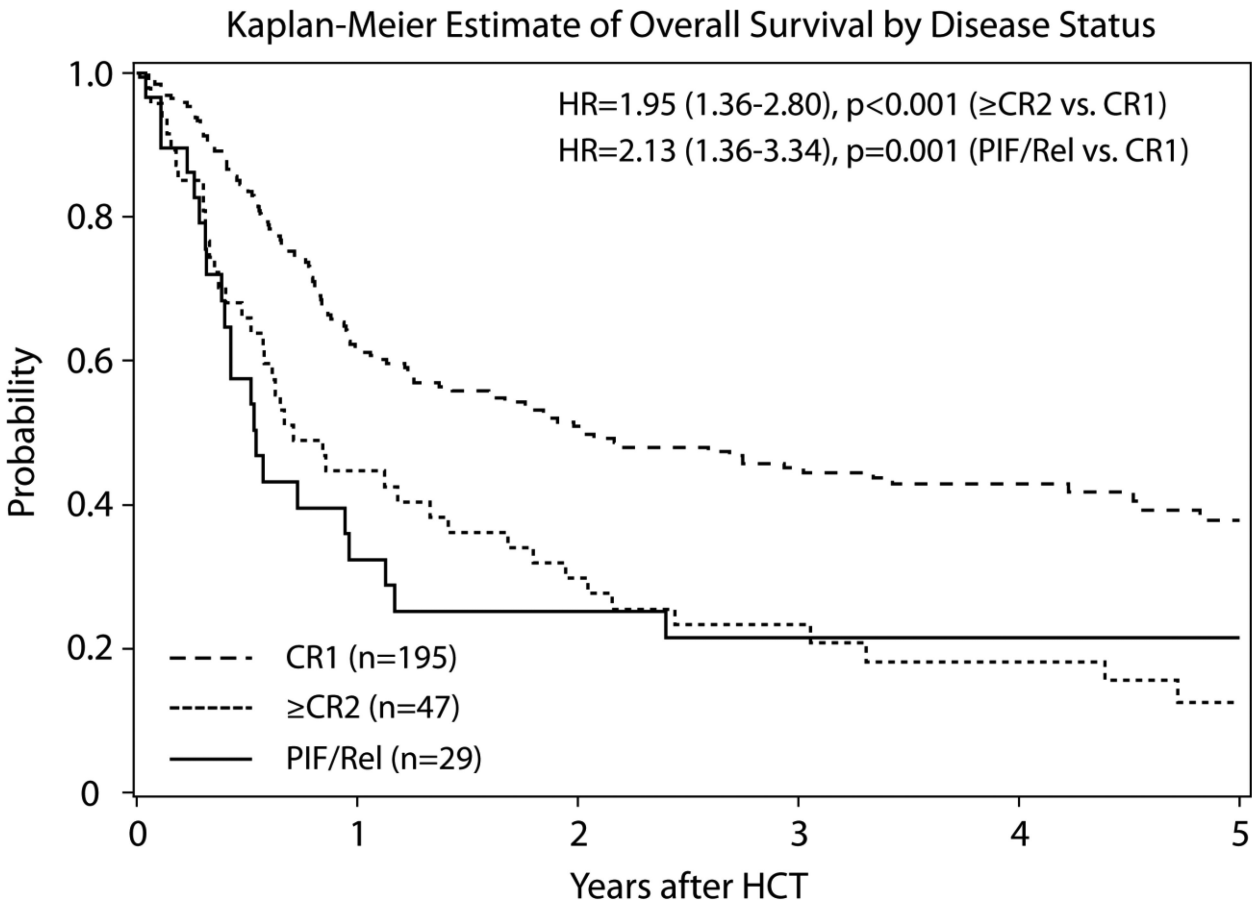

Figure 1A.
Kaplan-Meier estimate of overall survival by disease status

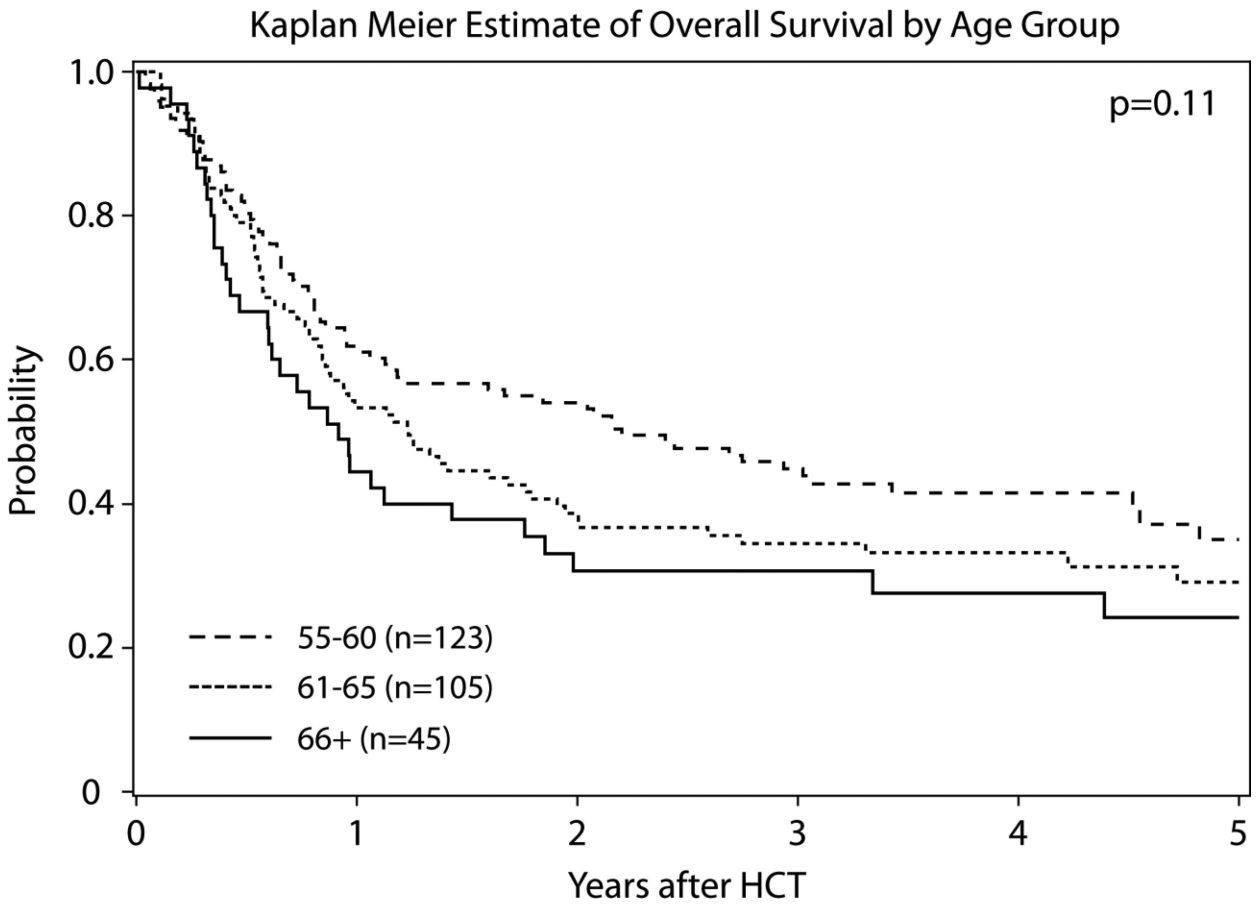

Figure 1B.
Kaplan-Meier estimate of overall survival by age group

Table 1

Patients, Disease, and Transplantation Characteristics

Variable	Total N (%)			
Number of patients / centers	273 / 95			
Gender	F: 141 (52)			
Recipient age	**Total N (%)**	**55-60**	**61-65**	**66+**
Year of HCT				
2001-2003	29 (11)	12 (10)	16 (15)	1 (2)
2004-2007	57 (21)	28 (23)	21 (20)	8 (18)
2008-2011	187 (68)	83 (67)	68 (65)	36 (80)
Karnofsky score				
<=80	101 (37)	45 (37)	34 (32)	22 (49)
90-100	153 (56)	69 (56)	66 (63)	18 (40)
Missing	19 (7)	9 (7)	5 (5)	5 (11)
HCT-CI				
0	71 (26)	29 (24)	29 (28)	13 (29)
1 +	117 (43)	54 (44)	39 (37)	24 (53)
Earlier than 2007	73 (27)	33 (27)	33 (31)	7 (16)
Missing	12 (4)	7 (6)	4 (4)	1 (2)
Disease status				
CR1	195 (71)	92 (75)	69 (66)	34 (76)
>=CR2	47 (17)	22 (18)	19 (18)	6 (13)
PIF/Rel	29 (11)	8 (7)	17 (16)	4 (9)
Missing	2 (<1)	1 (<1)	0	1 (2)
Time from diagnosis to HCT				
<6 months	123 (45)	61 (50)	43 (41)	19 (42)
6 - 12 months	86 (32)	30 (24)	38 (36)	18 (40)
>12 months	64 (23)	32 (26)	24 (23)	8 (18)
Median (range)	7 (2-121)	6 (2-85)	7 (3-121)	7 (4-43)
Conditioning regimen				
Low-dose TBI based (2Gy)				
TBI+Flu	84 (31)	35 (32)	32 (29)	17 (32)
TBI+other	8 (3)	2 (2)	5 (5)	1 (2)
Alkylating agent based				
Bu (≤8mg/kg po ≤6.4mg/kg IV) + Flu	62 (23)	27 (21)	24 (23)	11 (30)
Flu+Mel (<150mg/m^2)	80 (29)	44 (34)	30 (28)	6 (16)
Cy+Flu	15 (5)	6 (5)	7 (7)	2 (5)
Other Alkylating agents	13 (5)	4 (3)	5 (5)	4 (11)
Other regimen	11 (4)	5 (4)	2 (4)	4 (4)
In-vivo T-cell depletion (ATG or campath)				

Variable	Total N (%)			
No	189 (69)	87 (71)	69 (66)	33 (73)
Yes	83 (30)	36 (29)	35 (33)	12 (27)
Missing	1 (<1)	0	1 (<1)	0
Graft type				
Bone marrow	19 (7)	7 (6)	10 (10)	2 (4)
Peripheral blood	233 (85)	105 (85)	88 (84)	40 (89)
Single UCB	4 (1)	2 (2)	2 (2)	0
Double UCB	17 (6)	9 (7)	5 (5)	3 (7)
Type of donor				
Matched sibling	92 (34)	46 (37)	36 (34)	10 (22)
MUD	104 (38)	39 (32)	41 (39)	24 (53)
UCB	21 (8)	11 (9)	7 (7)	3 (7)
Other[&]	56 (21)	27 (22)	21 (20)	8 (18)
Prior fungal infections[*]				
No	108 (91)	47 (90)	45 (94)	16 (84)
Yes	10 (8)	4 (8)	3 (6)	3 (16)
Missing	1 (<1)	1 (2)	0	0
Cytogenetics[*]				
t(9;22) present	59 (50)	31 (60)	20 (42)	8 (42)
t(9;22) absent	33 (28)	13 (25)	14 (29)	6 (32)
Missing	27 (23)	8 (15)	14 (29)	5 (26)
Extramedullary disease at diagnosis[*]				
No	104 (87)	46 (88)	42 (88)	16 (84)
Yes	14 (12)	6 (12)	6 (13)	2 (11)
Missing	1 (<1)	0	0	1 (5)
Time to achieve CR1[*]				
<=8 weeks	48 (40)	21 (40)	21 (44)	6 (32)
>8 weeks	51 (43)	22 (42)	19 (40)	10 (53)
N/A, CR1 not achieved	5 (4)	2 (4)	2 (4)	1 (5)
Missing	15 (13)	7 (13)	6 (13)	2 (11)
Median (range), weeks	8 (2-57)	8 (2-41)	7 (2-57)	11 (2-33)
Median follow-up of survivors (range), months	49 (3-145)	73 (3-145)	61 (13-118)	62 (20-74)

Abbreviations: F: Female, HCT-CI: Hematopoietic Stem Cell Transplant-Comorbidity Index, CR:Complete Remission, TBI: Total Body Irradiation, Flu: Fludarabine, Bu: Busulfaran, CsA: Cyclosporine, MTX:Methotrexate, MMF: mycophenolate mofetil, MUD: matched unrelated donor, UCB: Umbilical Cord Blood, ATG: Anti-Thymocyte Globulin

[*] Data limited to nested cohort of 119 subjects (55 centers)

[&] mismatched unrelated donor and mismatched related(haplo=9)

Table 2

Cumulative Incidences of 3-Year Relapse and Non-Relapse Mortality (NRM)

		Relapse 3 yr		NRM 3 yr	
Covariates	**N**	**Probability(95% CI)**	**p**	**Probability(95% CI)**	**p**
Age in decades			0.08		0.07
55-60	123	47 (38-56)%		23 (15-31)%	
61-65	105	53 (43-62)%		22 (14-30)%	
66+	45	33 (20-48)%		40 (26-56)%≠	
Karnofsky score			0.30		0.006
<=80	101	43 (33-53)%		34 (25-43)%	
90-100	153	50 (42-58)%		18 (12-24)%	
Disease status			0.13		0.72
CR1	195	43 (36-50)%		24 (18-30)%	
>=CR2	47	57 (43-71)%≠		28 (16-41)%≠	
PIF/Rel	29	56 (37-73)%≠		30 (14-48)%≠	
Conditioning regimen			0.90		0.44
Low-dose TBI based	92	45 (35-55)%		28 (19-37)%	
Alkylating agent based	170	48 (40-56)%		23 (17-30)%	
Other	11	50 (21-79)%≠		40 (13-70)%≠	
Type of donor			0.65		0.44
Matched sib	92	49 (39-60)%		20 (12-29)%	
MUD	104	44 (34-53)%		26 (18-35)%	
UCB	21	57 (36-77)%≠		25 (9-46)%≠	
Other&	56	45 (32-58)%≠		33 (21-46)%≠	
GVHD prophylaxis			0.81		0.48
CsA/tacrolimus + MTX	104	48 (38-58)%		21 (13-29)%	
CsA/tacrolimus + MMF	117	45 (36-54)%		28 (20-36)%	
Other	49	51 (36-65)%≠		25 (14-39)%≠	
***In-vivo* T-cell depletion**			0.004		0.73
No	189	41 (34-48)%		26 (20-32)%	
Yes	83	60 (49-70)%≠		24 (15-34)%	
Year of HCT			0.41		0.99
2000-2006	73	51 (39-63)%		25 (16-36)%	
2007-2012	200	45 (38-53)%		25 (19-32)%	
Prior fungal infections*			0.21		0.004
No	107	54 (44-63)%		20 (13-28)%	
Yes	10	33 (8-65)%≠		67 (35-92)%≠	

		Relapse 3 yr		NRM 3 yr	
Covariates	**N**	**Probability(95% CI)**	**p**	**Probability(95% CI)**	**p**
Cytogenetics*			0.75		0.95
t(9;22) present	58	54 (41-67)%		22 (12-34)%≠	
t(9;22) absent	33	58 (40-74)%≠		23 (10-39)%≠	
Time to achieve CR1*			0.16		0.84
<=8 weeks	47	41 (28-56)%		27 (15-41)%≠	
>8 weeks	51	60 (46-73)%≠		22 (12-34)%≠	

Abbrevations: HCT-CI: Hematopoietic Stem Cell Transplant-Comorbidity Index, CR: Complete Remission, TBI: Total Body Irradiation, Flu: Fludarabine, Bu: Busulfaran, CsA: Cyclosporine, MTX: Methotrexate, MMF: mycophenolate mofetil, MUD: matched unrelated donor, UCB: Umbilical Cord Blood, ATG: Anti-Thymocyte Globulin

*Data limited to nested cohort of 119 subjects (55 centers)

&mismatched (haplo=9)

≠Less than 15 cases at risk at 3 years

Table 3

Univariate Cox Regression of LFS and OS

		Treatment failure (inversion of LFS)		Overall Mortality	
Covariates	**N**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age in decades					
55-60	123	1.0		1.0	
61-65	105	1.04 (0.76-1.42)	0.80	1.27 (0.92-1.75)	0.15
66+	45	1.15 (0.76-1.73)	0.51	1.51 (1.00-2.29)	0.05
Karnofsky score					
<=80	101	1.0		1.0	
90-100	153	0.85 (0.63-1.14)	0.28	0.78 (0.57-1.07)	0.13
Disease status					
CR1	195	1.0		1.0	
>=CR2	47	1.75 (1.21-2.54)	0.003	1.95 (1.36-2.80)	< 0.001
PIF/Rel	29	1.99 (1.33-2.99)	< 0.001	2.13 (1.36-3.34)	0.001
Conditioning regimen					
Low-dose TBI based	92	1.0		1.0	
Alkylating agent based	170	0.85 (0.63-1.14)	0.29	1.08 (0.79-1.49)	0.62
Other	11	1.32 (0.66-2.64)	0.44	2.18 (1.11-4.27)	0.02
Type of donor					
Matched sib	92	1.0		1.0	
MUD	104	1.02 (0.73-1.43)	0.90	1.23 (0.87-1.75)	0.24
UCB	21	1.39 (0.81-2.38)	0.23	0.96 (0.51-1.79)	0.89
Other	56	1.29 (0.87-1.92)	0.20	1.43 (0.94-2.17)	0.09
CMV match					
Recipient negative	90	1.0		1.0	
Recipient positive	167	1.01 (0.74-1.36)	0.97	1.09 (0.79-1.50)	0.61
GVHD prophylaxis					
CsA/tacrolimus + MTX	104	1.0		1.0	
CsA/tacrolimus + MMF	117	1.18 (0.86-1.62)	0.30	1.04 (0.74-1.44)	0.84
Other	49	1.14 (0.76-1.70)	0.52	1.27 (0.84-1.91)	0.26
Year of HCT					
2000-2006	73	1.0		1.0	
2007-2012	200	0.83 (0.60-1.14)	0.25	0.78 (0.56-1.08)	0.13
Prior fungal infection *					
No	108	1.0		1.0	
Yes	10	1.27 (0.63-2.55)	0.50	1.55 (0.77-3.11)	0.22
Cytogenetics *					
t(9;22) present	59	1.0		1.0	

		Treatment failure (inversion of LFS)		Overall Mortality	
Covariates	**N**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
t(9;22) absent	33	1.07 (0.66-1.74)	0.77	1.10 (0.66-1.86)	0.71
Time to achieve CR1*					
<=8 weeks	48	1.0		1.0	
>8 weeks	51	1.29 (0.82-2.02)	0.27	1.48 (0.91-2.39)	0.11

LFS: Leukemia-free survival; OS: overall survival, CI: confidence interval, HR: hazard ratio, MUD: matched unrelated donor; UCB: umbilical cord blood, CMV: cytomegalovirus, GVHD:graft-versus-host disease, HCT:hematopoietic cell transplantation, CSA: cyclosporine, MTX: methotrexate, MMF: mycophenolate mofetil, CR: complete remission

*Examined in nested cohort of 119 patients