Biol Blood Marrow Transplant 20 (2014) 829–836

Survival Improvements in Adolescents and Young Adults after Myeloablative Allogeneic Transplantation for Acute Lymphoblastic Leukemia

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Article history:
Received 21 November 2013
Accepted 25 February 2014

Key Words:
Adolescent and young adults
Hematopoietic cell transplantation
Allogeneic
Survival

A B S T R A C T

Adolescents and young adults (AYAs, ages 15 to 40 years) with cancer have not experienced survival improvements to the same extent as younger and older patients. We compared changes in survival after myeloablative allogeneic hematopoietic cell transplantation (HCT) for acute lymphoblastic leukemia (ALL) among children (n = 981), AYAs (n = 1218), and older adults (n = 469) who underwent transplantation over 3 time periods: 1990 to 1995, 1996 to 2001, and 2002 to 2007. Five-year survival varied inversely with age group. Survival improved over time in AYAs and paralleled that seen in children; however, overall survival did not change over time for older adults. Survival improvements were primarily related to lower rates of early treatment-related mortality in the most recent era. For all cohorts, relapse rates did not change over time. A subset of 222 AYAs between the ages of 15 and 25 at 46 pediatric or 49 adult centers were also analyzed to describe differences by center type. In this subgroup, there were differences in transplantation practices among pediatric and adult centers, although HCT outcomes did not differ by center type. Survival for AYAs undergoing myeloablative allogeneic HCT for ALL improved at a similar rate as survival for children.

INTRODUCTION

Adolescents and young adults (AYAs, ages 15 to 40) with cancer are considered by the National Cancer Institute to be a vulnerable subgroup, in part because survival improvements over time have lagged behind survival improvements for older and younger patients with cancer [1,2]. AYAs with acute lymphoblastic leukemia (ALL) have garnered particular interest because of apparent survival disparities related to treatment in pediatric versus adult oncology settings. Several retrospective analyses have demonstrated superior survival for AYAs with ALL who are treated on pediatric protocols, such as a Children's Cancer Group versus Cancer and

Financial disclosure: See Acknowledgments on page 835.
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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.02.021

Leukemia Group B comparison, in which 5-year event-free survival and overall survival (OS) rates favored AYAs treated on pediatric studies (63% versus 34%, $P < .001$ and 67% versus 46%, $P < .001$ respectively) [3]. The reasons for these disparities are not entirely clear, though some have suggested differences in the type and amount of antileukemic drugs in pediatric versus adult treatment protocols [4]. Others have also pointed to differences in the way care is delivered to AYAs in pediatric versus adult settings, favoring improved access to care through insurance coverage [5], better adherence, and a higher proportion of on-time receipt of therapy in the pediatric setting [6].

In hematopoietic cell transplantation (HCT), outcomes have improved over time, in part because of improvements in supportive care and a corresponding reduction in transplantation-related mortality [7,8]. However, few studies specifically addressed outcomes among AYAs undergoing HCT [9], and it is unclear whether the benefits of improvements in supportive care have been realized equally in the vulnerable AYA population. For these reasons, we sought to determine whether outcomes for AYAs after myeloablative allogeneic HCT for ALL have improved to a similar degree as those for older and younger patients. Further, we wished to determine whether significant differences existed in care delivery characteristics associated with pediatric versus adult HCT settings for AYAs with ALL. We analyzed data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) to address these questions.

METHODS

Data Source and Patients

The CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on allogeneic and autologous HCTs to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Centers are required to report all consecutive transplantations and patients are followed over time, with yearly follow-up. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with the Privacy Rule as a public health authority and in compliance with all applicable federal regulations pertaining to the protection of human research participants as determined by continuous review of the institutional review board of the NMDP.

For this study, we included patients who had received their first allogeneic HCT for ALL using either an HLA-identical sibling donor (matched sibling donor) or unrelated donor (URD) from 1990 to 2007 at a transplantation center in the United States. Only patients who underwent transplantation after myeloablative conditioning and were in either first or second complete remission (CR) were included in this analysis. Recipients of umbilical cord blood grafts were excluded. Patients were divided into 3 groups based on age at transplantation: children (<15 years), AYAs (15 to 40 years), and older adults (>40 years), to match the recommended National Cancer Institute Progress Review Group age definition for AYAs [10].

Outcomes and Study Definitions

The primary objective of this study was to compare change over time in rates of OS, leukemia-free survival (LFS), relapse, and treatment-related mortality (TRM) among children, AYAs, and older adults. For OS, death from any cause was considered an event. LFS was defined as survival in CR after HCT. Relapse was defined as leukemia recurrence. TRM was defined as death in CR. All outcomes were assessed from the date of transplantation.

The NMDP classification of HLA-matching status was used for URD recipients (well matched, partially matched, or mismatched) [11]. Where information was available, cytogenetic risk was classified as high risk (t [4,11], t [9,22], t [8,14], hypodiploidy, or near triploidy, or more than 5 cytogenetic abnormalities), normal (normal cytogenetics), or other (any other abnormality) [12,13].

As a secondary objective, we evaluated whether the type of transplantation center (adult versus pediatric) was associated with OS for a subgroup of AYAs between 15 and 25 years of age. We used several data sources to determine whether transplantation centers were primarily adult or pediatric transplantation programs. First, we used information available from the CIBMTR and the NMDP, where centers report their patients' characteristics, including age. However, some centers with distinct adult and pediatric programs report as 1 center to the CIBMTR and/or NMDP. For these centers, we used data collected as part of a national CIBMTR survey to designate centers as adult versus pediatric [Navneet Majhail, personal communication]. Furthermore, we also contacted each "combined center" to determine (1) whether these centers performed transplantations exclusively for pediatric patients, adult patients, or both; (2) in cases where both adults and children underwent transplantation at the center, if there were separate pediatric and adult transplantation teams; and (3) the age cutoff that a center used to determine whether a patient would be cared for by the adult or pediatric service. Based on information obtained from these various above listed sources, centers were classified as either adult or pediatric.

Statistical Methods

Summaries of patient-, disease-, and treatment-related characteristics were produced for the 3 age groups. The chi-square test was used to compare categorical variables, and the Kruskal-Wallis test was used for continuous variables. Univariate probabilities of OS and LFS were calculated using the Kaplan-Meier estimator [14]. Probabilities of relapse and TRM were estimated using a cumulative incidence function method [15]. To evaluate changes in outcomes over time, we divided the cohort into 3 time periods based on the year of transplantation (1990 to 1995, 1996 to 2001, and 2002 to 2007).

Cox proportional hazards models were used to adjust for significant covariates while comparing the 3 age groups. All factors were examined for proportional hazards using a time-dependent covariate to appropriately model early versus later events. A backward regression model selection technique was used to identify significant covariates to be included in the models. The main effects tested in all multivariate analysis models were age and time period of transplantation. Consistent with the primary study question, potential interactions between age and time period were also examined. In addition to age and time period of transplantation, the patient and disease characteristic covariates considered in the multivariable models included gender, race/ethnicity, Karnofsky performance status, disease status, cell of origin (T versus B cell), cytogenetic risk, and time from diagnosis to HCT. As time from diagnosis to first CR (CR1) was confounded by disease status (CR1 versus second CR [CR2]), the 2 covariates were combined for multivariable analysis (CR1 versus CR2 with duration of CR1 $<$ 36 months versus CR2 with duration of CR1 $\geq$ 36 months versus CR2 with duration of CR1 unknown).

For the subgroup analysis that focused on adult versus pediatric center comparison for AYAs between 15 and 25 years of age, we describe the characteristics of patients who underwent transplantation at the 2 types of center. Univariate probabilities of OS, LFS, TRM, and relapse were analyzed as described above. Because of limited number of patients, we were not able to perform multivariable analyses to study the association of center type with patient outcomes.

All computations were performed using the SAS statistical package (SAS Institute, Cary, NC). All P values are 2 sided.

RESULTS

Patient Characteristics

In total, 2668 patients with ALL in CR1 or CR2 reported to the CIBMTR from 1990 to 2007 met the study eligibility criteria, including 981 children, 1218 AYAs, and 469 older adults (Table 1). From 1996 to 2007, transplantation volume increased by 7% in children, 50% in AYAs, and 180% in older adults. The proportions of patients receiving peripheral blood stem cell transplants and of patients receiving HCT using well-matched URD HCT increased over time in all 3 age groups. The proportions of Hispanic recipients increased among children and AYAs over time (in children, 6% in the period from 1990 to 1995 to 17% in the period from 2002 to 2007, and in AYAs, 4% in the period from 1990 to 1995 to 15% in the period from 2002 to 2007), but remained unchanged in older adults (5% in the period from 1990 to 1995 to 6% in the period from 2002 to 2007).

Outcomes Over Time

Univariate analyses for OS, LFS, relapse, and TRM of children, AYAs, and older adults over time are presented in Table 2. Survival was inversely related to age, with older

Table 1
Patient, Disease, and Transplantation Characteristics for Patients Receiving First Myeloablative Allogeneic HCT for ALL

Characteristics	Children (<15 yr)			AYAs (15-40 yr)			Older Adults (>40 yr)		
	1990-1995	1996-2001	2002-2007	1990-1995	1996-2001	2002-2007	1990-1995	1996-2001	2002-2007
No. of patients	267	343	371	309	362	547	60	106	303
No. of centers	44	59	57	75	103	118	34	49	77
Age at HCT, median (range), yr	7.2 (.5-14.9)	7.6 (.5-14.9)	8.2 (.5-14.9)	23.9 (15.0-39.8)	23.7 (15.0-39.9)	26.2 (15.0-39.9)	44.8 (40.1-58.2)	47.0 (40.0-61.1)	49.1 (40.0-66.2)
Male	175 (66)	196 (57)	230 (62)	198 (64)	227 (63)	356 (65)	37 (62)	51 (48)	158 (52)
Race/ethnicity									
Non-Hispanic white	213 (80)	242 (71)	232 (63)	253 (82)	273 (75)	298 (73)	53 (88)	91 (86)	257 (85)
African-American	13 (5)	26 (8)	28 (8)	12 (4)	17 (5)	20 (4)	0	6 (6)	10 (3)
Asian/Pacific Islander	12 (4)	15 (4)	15 (4)	14 (5)	19 (5)	21 (4)	2 (3)	2 (2)	7 (2)
Hispanic	16 (6)	55 (16)	63 (17)	12 (4)	49 (14)	84 (15)	3 (5)	5 (5)	18 (6)
Other/unknown	13 (5)	5 (1)	33 (9)	18 (6)	4 (1)	24 (4)	2 (3)	2 (2)	11 (4)
KPS at HCT									
≥90	238 (89)	293 (85)	307 (83)	240 (78)	273 (75)	383 (70)	43 (72)	75 (71)	186 (60)
<90	27 (10)	45 (13)	20 (5)	65 (21)	84 (23)	122 (22)	17 (28)	29 (27)	94 (31)
Disease status at HCT									
CR1	77 (29)	114 (33)	127 (34)	159 (51)	160 (44)	279 (51)	47 (78)	73 (69)	232 (77)
CR2, CR1 duration <36 mo	137 (51)	162 (47)	182 (49)	104 (34)	153 (42)	192 (35)	10 (17)	29 (27)	54 (18)
CR2, CR1 duration ≥ 36 mo	37 (14)	57 (17)	52 (14)	35 (11)	42 (12)	53 (10)	2 (3)	3 (3)	13 (4)
CR2, CR1 duration unknown	16 (6)	10 (3)	10 (3)	11 (4)	7 (2)	23 (4)	1 (2)	1 (1)	4 (1)
Time from diagnosis to HCT									
<6 mo	44 (16)	75 (22)	90 (24)	105 (34)	83 (23)	180 (33)	33 (55)	39 (37)	153 (50)
6-12 mo	59 (22)	55 (16)	57 (15)	76 (25)	100 (28)	133 (24)	15 (25)	42 (40)	90 (30)
≥12 mo	164 (61)	213 (62)	224 (60)	128 (41)	179 (49)	234 (43)	12 (20)	25 (24)	60 (20)
Cell of origin									
B cell	171 (64)	249 (73)	280 (75)	155 (50)	233 (64)	428 (78)	33 (55)	72 (68)	246 (81)
T cell	30 (11)	31 (9)	60 (16)	55 (18)	55 (15)	83 (15)	7 (12)	6 (6)	26 (9)
Other/unknown	66 (25)	63 (18)	31 (8)	99 (32)	74 (20)	36 (7)	20 (33)	28 (26)	31 (10)
Graft type									
Bone marrow	266 (100)	319 (93)	291 (78)	303 (98)	304 (84)	209 (38)	59 (98)	82 (77)	82 (27)
Peripheral blood	1 (<1)	24 (7)	80 (22)	6 (2)	58 (16)	338 (62)	1 (2)	24 (23)	221 (73)
HLA match									
HLA-identical sibling	104 (39)	93 (27)	58 (16)	203 (66)	74 (20)	102 (19)	39 (65)	38 (36)	82 (27)
Unrelated, well matched	27 (10)	66 (19)	168 (45)	27 (9)	107 (30)	289 (53)	6 (10)	17 (16)	148 (49)
Unrelated, partially matched	54 (20)	113 (33)	96 (26)	28 (9)	111 (31)	121 (22)	10 (17)	33 (31)	56 (18)
Unrelated, mismatched	81 (30)	66 (19)	46 (12)	49 (16)	68 (19)	27 (5)	5 (8)	17 (16)	11 (4)
Conditioning									
TBI/Cy	198 (74)	285 (83)	337 (91)	187 (61)	288 (80)	398 (73)	38 (63)	77 (73)	182 (60)
Cy/Bu	23 (9)	33 (10)	4 (1)	32 (10)	28 (8)	25 (5)	7 (12)	9 (8)	27 (9)
TBI/etoposide	18 (7)	17 (5)	17 (5)	82 (27)	35 (10)	78 (14)	13 (22)	15 (14)	58 (19)
TBI/other	26 (10)	5 (1)	6 (2)	7 (2)	7 (2)	24 (4)	2 (3)	4 (4)	22 (7)
Other	2 (1)	3 (1)	7 (2)	1 (<1)	4 (1)	22 (4)	0	1 (1)	14 (5)
GVHD prophylaxis									
CsA + MTX +/− other	122 (46)	162 (47)	165 (44)	139 (45)	188 (52)	134 (24)	26 (43)	57 (54)	71 (23)
FK506 + MTX +/− other	2 (1)	24 (7)	101 (27)	7 (2)	54 (15)	263 (48)	1 (2)	20 (19)	140 (46)
T cell depletion	66 (25)	96 (28)	57 (16)	46 (15)	73 (20)	31 (5)	15 (25)	14 (13)	19 (7)
Other	77 (29)	61 (18)	48 (19)	117 (38)	47 (15)	119 (23)	18 (30)	15 (15)	73 (26)

ALL indicates acute lymphoblastic leukemia; AYAs, adolescent and young adults; KPS, Karnofsky performance status; HCT, hematopoietic cell transplantation; CR, complete remission; HLA, human leukocyte antigen; TBI, total body irradiation; Cy, cyclophosphamide; Bu, busulfan; GVHD, graft-versus-host disease; CSA, cyclosporine; MTX, methotrexate.
Data presented are n (%) unless otherwise indicated.

Table 2
Unadjusted Probability of Outcomes by Time Period and Age Group Five Years after HCT

Outcome	1990-1995	1996-2001	2002-2007
Overall survival			
Children	49 (43-55)	53 (47-58)	58 (53-63)
AYAs	34 (29-40)	34 (29-39)	43 (39-47)
Older adults	41 (29-54)	22 (14-30)	36 (30-41)
Leukemia-free survival			
Children	47 (41-53)	33 (43-53)	53 (48-58)
AYAs	33 (28-39)	31 (26-36)	38 (34-43)
Older adults	41 (29-55)	19 (12-27)	33 (28-39)
Relapse			
Children	23 (18-28)	26 (21-31)	28 (24-33)
AYAs	24 (19-29)	28 (23-33)	31 (27-35)
Older adults	4 (0-10)	28 (20-37)	26 (21-31)
Treatment-related mortality			
Children	30 (25-36)	26 (22-31)	19 (15-23)
AYAs	43 (37-49)	41 (36-46)	31 (27-35)
Older adults	55 (42-68)	53 (44-63)	41 (36-47)

AYAs indicates adolescent and young adults; HCT, hematopoietic cell transplantation.
Data presented are probability (95% confidence interval).

patients having lower 5-year OS and LFS rates than AYAs, who in turn had lower OS and LFS rates than children, particularly in the 2 most recent time periods. For all time periods, higher TRM probability estimates were directly related to increasing age, with AYAs having higher 5-year TRM than children and adults having higher TRM than AYAs. The probabilities of relapse were similar across cohorts for each of the time periods.

Results for multivariate analyses for OS, LFS, relapse, and TRM are shown in Table 3. After adjusting for patient and disease characteristics, older age was shown to be associated with poorer survival (hazard ratio [HR], 2.04 for older adults and 1.57 for AYAs versus children, $P < .001$). No significant interactions were observed between age and time period. Figure 1 displays 5-year adjusted OS probabilities for each age group over time, highlighting that OS for AYAs improved and did not lag behind any survival improvements in the other age groups. Similar findings were observed for LFS and TRM, in which older patients again had inferior outcomes compared with AYAs, who in turn had inferior outcomes compared with children. Again, there was no significant interaction between age and time period.

For the entire cohort, late relapse rates (>12 months from HCT) for AYAs were higher than overall relapse rates for children (HR, 2.1; $P < .001$), whereas early relapse rates for AYAs were not significantly different than overall relapse rates for children (HR, 1.1; $P = .42$). The difference between overall relapse rates for older adults and those for children was of borderline significance (HR, 1.3; $P = .05$). Relapse rates after HCT were not significantly different in the period from 2002 to 2007 when compared with the period from 1990 to 1995 (HR, 1.2; $P = .10$).

An analysis of outcomes stratified by donor type for the 3 age cohorts in the most recent time period, 2002 to 2007, was also performed, with results presented in Table 4. In unadjusted outcomes, children maintained superior survival outcomes to AYAs and older adults, including recipients of both matched sibling and URD transplants. TRM was higher in AYAs and in older adults than in children for both types of transplantations.

Differences in Pediatric versus Adult Centers for AYAs

Table 5 shows transplantation characteristics for 15 to 25-year-old patients who underwent HCT at either a pediatric or adult transplantation center. For this analysis, there were 130 AYAs within this age group who underwent transplantation at 46 pediatric centers and 92 AYAs who underwent transplantation at 49 adult centers. OS, LFS, relapse, and TRM did not appear to differ by center type (Figure 2), but sample size precluded formal statistical comparison with adjustment for relevant patient and transplantation characteristics.

There were several differences between pediatric and adult centers in baseline patient characteristics and transplantation techniques. AYAs between 15 and 25 years of age

Table 3
Multivariate Analyses for Outcomes by Time Period and Age Group

Variable	Hazard Ratio	95% Confidence Intervals	*P* Value
Overall survival*			
Age group			
Children	1.00	-	<.001†
AYAs	1.57	1.40-1.77	<.001
Older adults	2.04	1.75-2.39	<.001
Year of transplantation			
1990-1995	1.00	-	<.001†
1996-2001 (≤4 mo)‡	.82	.67-.99	.04
1996-2001 (>4 mo)‡	1.21	1.01-1.46	.04
2002-2007 (≤4 mo)‡	.44	.36-.54	<.001
2002-2007 (>4 mo)‡	1.12	.94-1.33	.22
Leukemia-free survival§			
Age group			
Children	1.00	-	<.001†
AYAs	1.50	1.34-1.69	<.001
Older adults	1.84	1.58-2.14	<.001
Year of transplantation			
1990-1995	1.00	-	
1996-2001 (≤2 mo)‡	.74	.58-.94	.02†
1996-2001 (>2 mo)‡	1.22	1.04-1.43	.02
2002-2007 (≤2 mo)‡	.40	.31-.51	<.001
2002-2007 (>2 mo)‡	1.06	.91-1.24	.44
Relapse‖			
Age group			
Children	1.00	-	<.001†
AYAs (≤ 12 mo)‡	1.08	.89-1.32	.42
AYAs (>12 mo)‡	2.09	1.59-2.75	<.001
Older adults	1.28	1.00-1.63	.05
Year of transplantation			
1990-1995	1.00	-	.08†
1996-2001	1.28	1.03-1.58	.03
2002-2007	1.18	.97-1.45	.10
Treatment-related mortality¶			
Age group			
Children	1.00	-	<.001†
AYAs	1.66	1.42-1.95	<.001
Older adults	2.37	1.94-2.88	<.001
Year of transplantation			
1990-1995	1.00	-	<.001†
1996-2001 (≤4 mo)‡	.79	.64-.97	.03
1996-2002 (>4 mo)‡	1.28	.96-1.71	.09
2002-2007 (≤4 mo)‡	.42	.34-.52	<.001
2002-2007 (>4 mo)‡	1.29	.98-1.70	.07

* Multivariable models adjusted for the following covariates: disease status, cell of origin, cytogenetic risk, and Karnofsky performance score at transplantation.
† Overall *P* value.
‡ Nonproportional hazards; hazard ratio differed by time since transplantation (eg, ≤4 months or >4 months for overall survival and treatment-related mortality).
¶ Multivariable models adjusted for the following covariates: cytogenetic risk, interval from diagnosis to transplantation, and Karnofsky performance score at transplantation.
§ Multivariable models adjusted for the following covariates: disease status, cell of origin, cytogenetic risk, and Karnofsky performance score at transplantation.
‖ Multivariable models adjusted for the following covariates: disease status.

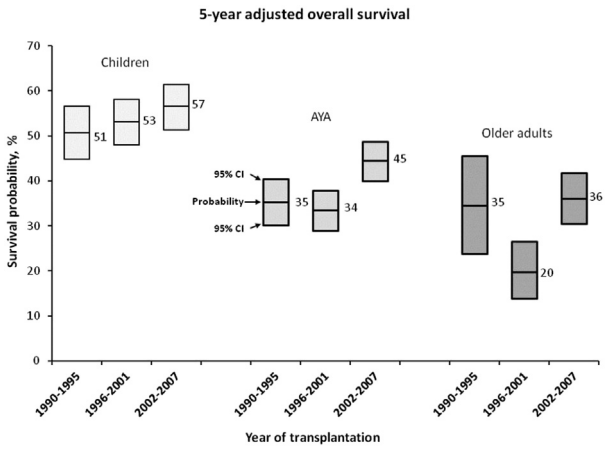

Figure 1. Five-year adjusted overall survival probabilities for each age group over time (the lines in the box represent survival probability and the ends of the box represent 95% confidence intervals).

at pediatric centers were more likely to have a high pre-HCT Karnofsky performance status (78% with Karnofsky performance status ≥ 90 in pediatric centers versus 66% in adult centers, $P = .005$). In pediatric centers, patients had a shorter interval from diagnosis to CR1 ($P = .003$) and had a longer time from diagnosis to transplantation ($P = .02$). AYAs who underwent transplantation at pediatric centers were more likely to receive bone marrow grafts than AYAs at adult centers (57% versus 26%, $P < .001$). AYAs who underwent transplantation at pediatric centers were more likely to receive cyclosporine-based graft-versus-host disease (GVHD) prophylaxis (41% versus 21%, $P < .01$) and were more likely to receive cyclophosphamide/total body irradiation conditioning (78% versus 68%, $P = .04$).

DISCUSSION

Although survival improvements for AYAs with cancer in general have lagged behind children and older adults, we found that survival after transplantation for AYAs improved over time in parallel to younger patients and more favorably than older adults. The observation that survival improvements in AYAs did not lag behind other age groups is similar to findings from a recent study of outcomes after myeloablative transplantation for acute myeloid leukemia [16]. Further, although sample size precluded a formal comparison of outcomes for AYAs treated at pediatric versus adult transplantation centers, in our study, survival rates appeared similar despite differences in patient selection and transplantation techniques. Taken together, these data provide reassurance that AYAs with ALL seem to be benefiting from survival improvements in HCT in similar ways to their younger counterparts and that treatment setting does not appear, at least preliminarily, to be a major determinant of outcome.

However, our study demonstrates broader observations about the influence of increasing age upon outcomes after

Table 4
Unadjusted Probability of Outcomes by Donor Type and Age Group Five Years after HCT for the Most Recent Cohort (2002 to 2007)

Outcome	Matched Sibling Donor	Unrelated Donor
Overall survival		
Children	68 (56-81)	56 (50-62)
AYAs	48 (38-59)	42 (37-47)
Older adults	33 (24-46)	37 (30-44)
Leukemia-free survival		
Children	61 (49-75)	52 (46-58)
AYAs	34 (34-54)	38 (33-43)
Older adults	31 (23-43)	34 (28-41)
Relapse		
Children	34 (21-47)	27 (22-32)
AYAs	31 (22-41)	31 (26-35)
Older adults	29 (19-40)	24 (18-30)
Treatment-related mortality		
Children	5 (1-13)	21 (16-26)
AYAs	25 (17-35)	32 (27-37)
Older adults	39 (28-50)	42 (34-49)

AYAs indicates adolescent and young adults; HCT, hematopoietic cell transplantation.
Data presented are probability (95% confidence interval).

Table 5
Patient Characteristics by Center Type (Pediatric versus Adult) for AYAs Ages 15 to 25 Years Who Received a Myeloablative Allogeneic HCT between 2002 and 2007

Characteristics	Pediatric Center	Adult Center	*P* Value
	n (%)	n (%)	
No. of patients	130	92	
No. of centers	46	49	
Age at HCT, yr			<.001
15-19	106 (82)	22 (24)	
20-25	24 (18)	70 (76)	
KPS at HCT			.005
≥90	101 (78)	61 (66)	
<90	18 (14)	28 (30)	
Disease status at HCT			.18
CR1	46 (35)	45 (49)	
CR2, CR1 duration <36 mo	29 (35)	36 (39)	
CR2, CR1 duration ≥36 mo	18 (14)	7 (8)	
CR2, CR1 duration unknown	7 (5)	4 (4)	
Interval from diagnosis to CR1, mo			.003
<1	54 (48)	21 (25)	
1-6	55 (49)	55 (65)	
≤6	4 (4)	8 (10)	
Time from diagnosis to HCT, mo			.019
<6	26 (20)	30 (33)	
6-12	23 (18)	22 (24)	
≥12	81 (62)	40 (43)	
Cytogenetic risk			.34
High risk	35 (27)	17 (18)	
Normal	33 (25)	31 (34)	
Other	35 (27)	22 (24)	
Not tested/unknown	27 (21)	22 (24)	
Graft type			<.001
Bone marrow	74 (57)	24 (26)	
Peripheral blood	56 (43)	68 (74)	
HLA match			.11
HLA-identical sibling	21 (16)	19 (21)	
Unrelated, well matched	68 (52)	49 (53)	
Unrelated, partially matched	26 (20)	22 (24)	
Unrelated, mismatched	12 (9)	1 (1)	
Unrelated, unknown degree of match	3 (2)	1 (1)	
Conditioning			.04
TBI/Cy	102 (78)	63 (68)	
Cy/Bu	4 (3)	4 (4)	
TBI/etoposide	15 (12)	12 (13)	
TBI/other	8 (6)	5 (5)	
Other	1 (1)	8 (9)	
GVHD prophylaxis			<.01
CSA+ MTX +/− other	53 (41)	19 (21)	
FK506 + MTX +/− other	35 (27)	44 (48)	
T cell depletion	21 (16)	3 (3)	
Other	21 (16)	26 (28)	

AYAs indicates adolescent and young adults; KPS, Karnofsky performance status; HCT, hematopoietic cell transplantation; CR, complete remission; HLA, human leukocyte antigen; TBI, total body irradiation; Cy, cyclophosphamide; Bu, busulfan; GVHD, graft-versus-host disease; CSA, cyclosporine; MTX, methotrexate.

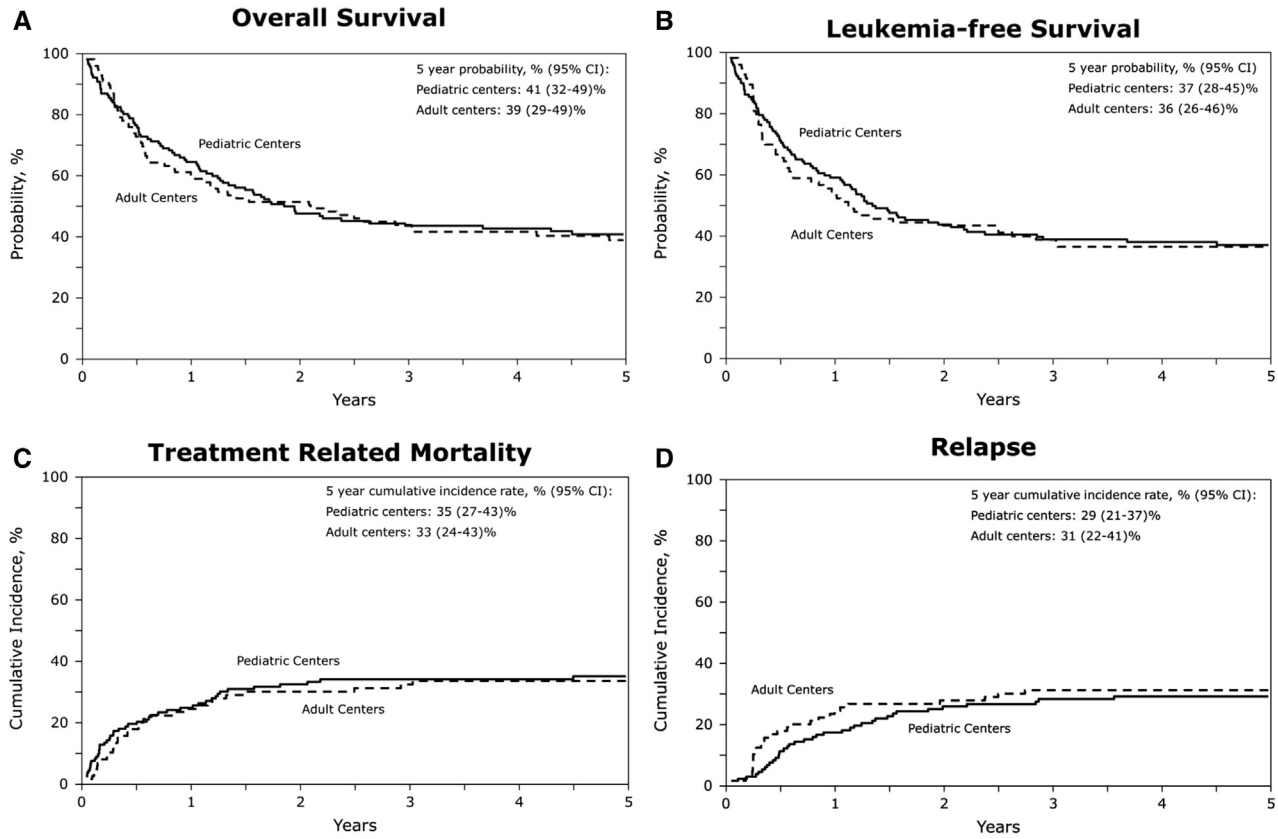

Figure 2. Outcomes for AYAs 15 to 25 years of age who underwent transplantation between 2002 and 2007. (A) Shows overall survival. (B) Shows leukemia-free survival. (C) Shows treatment-related mortality. (D) Shows relapse.

myeloablative transplantation for ALL. Across all time periods, children maintained a survival advantage over AYAs and older adults. Further, survival rates did not appear to improve in the older adult group over time. It appears that some of the survival improvement over time in the younger age groups was attributable to lower rates of TRM, especially in the early post-transplantation period. These data are consistent with larger trends in improvements in supportive care leading to decreased TRM after allogeneic HCT in general [7,8]. In the most recent time period, TRM remained higher for AYAs and for older adults than for children, including recipients of matched sibling donor transplants. This observation highlights the continued important contribution of TRM to outcomes after myeloablative transplantation in AYAs and older adults, even in the modern transplantation era. In this study, we were not able to analyze outcomes of GVHD and other potential contributors to TRM, which need to be addressed by future research. Another important observation was the lack of reduction over time in relapse rates for any age group. This highlights the need for more research to investigate novel methods to prevent relapse in these high-risk patients.

The observation that TRM is an important determinant of survival after myeloablative HCT for ALL is consistent with published data from large controlled trials. In the Medical Research Council/Eastern Cooperative Oncology Group study, the difference in survival between the donor and no-donor groups was significant only in standard-risk patients because of the higher TRM (36%) in the high-risk patients undergoing transplantation [17]. In this study, risk was defined in part by age older than or younger than 35. The Haemato Oncology Foundation for Adults in Netherlands (HOVON) study did not categorize risk by age in the same way as the Medical Research Council/Eastern Cooperative Oncology Group study, but the authors did conclude that the greatest benefit of myeloablative HCT for ALL in first CR was likely to be seen when TRM rates were less than 20% [18]. An individual patient data meta-analysis that included both of the above studies concluded that HCT for ALL in CR1 was beneficial only in patients younger than 35 years of age because of higher rates of TRM in older patients [19]. Within clinical trials, the reasons for differences in TRM as a function of age are not entirely known and may relate to disease-related and age-related biology.

In contrast to the above-cited studies based on randomized controlled trials, our observational study also highlights significant practice variation in transplantation techniques for ALL. In pediatric versus adult treatment settings, we found differences in the characteristics of patients who underwent transplantation and the type of conditioning regimen, stem cell source, and GVHD prophylaxis used. These are all key elements of the clinical practice of HCT. Our study was not designed to assess the impact of these differences on outcomes. Although superficially these differences did not appear to impact the outcomes of 15 to 25-year-old AYAs undergoing transplantation, larger studies would be needed to confirm this observation. Whether these differences in practice patterns between pediatric and adult centers have any impact more generally on outcomes after HCT for ALL is not known. For example, characteristics of how patients come to transplantation at pediatric versus adult centers (time to CR1, time from diagnosis to transplantation)

may impact relapse rates after transplantation, particularly if, over time, reduced-intensity transplantation regimens are used with increasing frequency in adult settings. As another example, although marrow grafts are used more frequently in pediatric settings, perhaps because of the higher proportion of patients with nonmalignant diseases who underwent transplantation in pediatric centers, marrow versus peripheral blood use may affect post-transplantation graft-versus-leukemia or GVHD rates in patients who underwent transplantation for ALL [20]. Additionally, the distinction between pediatric and adult treatment programs is only 1 variable that impacts practice patterns [21]. Whether outcomes are influenced by center-specific differences in transplantation techniques among adult centers or among pediatric centers is also not known.

Our study does have several limitations inherent in a retrospective analysis with registry-level data. We were unable to address issues related to access to HCT or issues related to caregiver support, financial resources, medication and supportive care adherence, or other factors that may influence outcomes after HCT for AYAs and other age groups. We were also unable to address the issue of confounding due to selection, including the possibility that differences in explicit or implicit criteria for transplantation might differ by age group. For example, it is possible that younger patients may have been more likely to have adverse prognostic features at the time of transplantation than older patients, given differences in practice patterns in the pediatric versus adult settings. Finally, systematic differences by age group in pre-transplantation treatment might have affected relative outcomes among patients who were included in this analysis. Differences in pre-HCT therapy could conceivably affect TRM, as pediatric patients in our study had higher pre-HCT Karnofsky performance status than AYA and adult patients, and the relative contributions of differences in pre-HCT therapy versus host biological differences to this finding are not readily discernible with our data. Differences in pre-HCT therapy could also contribute to relapse rates. Some of the patients in the AYA group were likely treated on modified pediatric protocols and others on adult protocols, and we were not able to determine which patients were treated on which pre-HCT protocols with our available data.

Moving forward, additional studies will be needed to better understand reasons for persistent differences in late TRM in relationship to increasing patient age. The impact of conditioning regimen intensity on TRM and OS for comparable patients, the subject of an ongoing multicenter trial [22], also requires clarification. A retrospective CIBMTR study of patients with Philadelphia chromosome–negative ALL who underwent transplantation in first or second complete remission suggested similar age-adjusted survival after reduced-intensity or full-intensity conditioning [23]. In parallel, a more precise understanding of relapse risk as a function of pre-HCT “adult-like” or “pediatric-like” chemotherapy is also needed. After these issues are further clarified, individualized pre-HCT calculators of TRM and relapse risk may become possible, similar to the recent development of post-HCT calculators [24], in turn facilitating the personalized application of transplantation strategies for this disease.

In conclusion, our study shows that improvements in survival among AYAs undergoing allogeneic HCT for ALL parallel those seen among younger patients and are more favorable than those among older adults. However, our study also demonstrates persistent survival disparities across increasing age groups that warrant further study.

ACKNOWLEDGMENTS

Financial disclosure: CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA76518 from the National Cancer Institute, the National Heart, Lung and Blood Institute, and the National Institute of Allergy and Infectious Diseases; a Grant/Cooperative Agreement 5U01HL069294 from National Heart, Lung and Blood Institute and National Cancer Institute; a contract HHSH234200637015C with Health Resources and Services Administration; grants N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from Allos, Inc., Amgen, Inc., and Angioblast; anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; Blue Cross and Blue Shield Association; Buchanan Family Foundation; CaridianBCT; Celgene Corporation; CellGenix, GmbH; Children’s Leukemia Research Association; Fresenius-Biotech North America, Inc.; Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.; Genzyme Corporation; GlaxoSmithKline; HistoGenetics, Inc.; Kiadis Pharma; The Leukemia & Lymphoma Society; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; RemedyMD; Sanofi; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; Tarix Pharmaceuticals; Teva Neuroscience, Inc.; THERAKOS, Inc.; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, or any other agency of the US government.

Conflict of interest statement: There are no conflicts of interest to report.

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