Biol Blood Marrow Transplant 24 (2018) 945–955

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Allogeneic: Adult

Pretransplant Consolidation Is Not Beneficial for Adults with ALL Undergoing Myeloablative Allogeneic Transplantation

Nelli Bejanyan [1,*], Mei-Jie Zhang [2,3], Hai-Lin Wang [3], Aleksandr Lazaryan [1], Marcos de Lima [4], David I. Marks [5], Brenda M. Sandmaier [6], Veronika Bachanova [1], Jacob Rowe [7], Martin Tallman [8], Partow Kebriaei [9], Mohamed Kharfan-Dabaja [10], Robert Peter Gale [11], Hillard M. Lazarus [12], Celalettin Ustun [1], Edward Copelan [13], Betty Ky Hamilton [14], Gary Schiller [15], William Hogan [16], Shahrukh Hashmi [17,18], Matthew Seftel [19], Christopher G. Kanakry [20], Richard F. Olsson [21,22], Rodrigo Martino [23], Wael Saber [3], H. Jean Khoury [24], Daniel J. Weisdorf [1]

[1] *Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, Minnesota*
[2] *Division of Biostatistics, Insitute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *CIBMTR (Center for International Blood and Marrrow Trasnsplantation), Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Department of Medicine, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, Ohio*
[5] *Adult Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom*
[6] *Division of Medical Oncology, University of Washington and Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[7] *Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel*
[8] *Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[9] *Department of Stem Cell Transplantation, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[10] *Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*
[11] *Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom*
[12] *Seidman Cancer Center, University Hospitals Cleveland Medical Center, Cleveland, Ohio*
[13] *Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, North Carolina*
[14] *Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio*
[15] *Hematological Malignancy/Stem Cell Transplant Program, David Geffen School of Medicine at UCLA, Los Angeles, California*
[16] *Departments of Hematology and Transplant Center, Mayo Clinic Rochester, Rochester, Minnesota*
[17] *Department of Internal Medicine, Mayo Clinic, Minnesota*
[18] *Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[19] *Department of Medical Oncology and Hematology, CancerCare Manitoba, Winnipeg, Canada*
[20] *Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*
[21] *Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden*
[22] *Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden*
[23] *Divison of Clinical Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[24] *Emory University Hospital, Atlanta, Georgia*

Article history:
Received 15 August 2017
Accepted 13 December 2017

Key Words:
ALL
Consolidation chemotherapy
Myeloablative conditioning
Allogeneic transplant

A B S T R A C T

Allogeneic hematopoietic cell transplantation (alloHCT) is curative for patients with acute lymphoblastic leukemia (ALL) who achieve complete remission (CR1) with chemotherapy. However, the benefit of consolidation chemotherapy remains uncertain in patients undergoing alloHCT. We compared clinical outcomes of 524 adult patients with ALL in CR1 who received ≥2 (n = 109), 1 (n = 93), or 0 cycles (n = 322) of consolidation before myeloablative alloHCT from 2008 to 2012. As expected, time to alloHCT was longer with increasing cycles of consolidation. Patients receiving ≥2, 1, or 0 cycles of consolidation had an adjusted 3-year cumulative incidence of relapse of 20%, 27%, and 22%; 1-year transplant-related mortality (TRM) of 16%, 18%, and 23%; adjusted 3-year leukemia-free survival (LFS) of 54%, 48%, and 47%; and 3-year overall survival (OS) of 63%, 59%, and 54% (all *P* values >.40). Multivariable analysis confirmed that consolidation was not prognostic for LFS (relative risk, 1.20, 95% confidence interval, .86 to 1.67; *P* = .28 for no consolidation; RR, 1.18, 95% confidence interval, .79 to 1.76; *P* = .41 for 1 cycle versus ≥2 cycles = reference). Similarly, consolidation was not associated with OS, relapse, TRM, or graft-versus-host disease. We conclude that consolidation chemotherapy does not appear

Financial disclosure: See Acknowledgments on page 953.
* Correspondence and reprint requests: Nelli Bejanyan, MD, Division of Hematology, Oncology and Transplantation, University of Minnesota, 420 Delaware Street SE, Mayo Mail Code 480, Minneapolis, MN 55455.
E-mail address: nbejanya@umn.edu (N. Bejanyan).

https://doi.org/10.1016/j.bbmt.2017.12.784

to provide added benefit in adult ALL patients with available donors who undergo myeloablative alloHCT in CR1.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative treatment for adult acute lymphoblastic leukemia (ALL) patients achieving initial complete remission (CR1) with cytoreductive chemotherapy [1-3]. Although most adult ALL treatment protocols include post-remission consolidation chemotherapy, it remains uncertain whether consolidation is beneficial in patients with an immediately available donor who is being considered for a prompt alloHCT. The MRC UKALL XII/ECOG 2993 trial mandated 2 cycles of induction chemotherapy (phase I and phase II) followed by intensification with high-dose methotrexate for adult ALL patients assigned to the alloHCT arm, even when CR1 was achieved after initial phase 1 induction [1,4]. Similarly, the GRAALL-2003 and LALA-94 prospective study protocols allowed alloHCT for high-risk CR1 ALL only after completion of several cycles of postinduction consolidation chemotherapy [5,6]. In contrast, other ALL induction protocols allowed patients with available donors to proceed with alloHCT whenever CR1 was achieved [7-9]. Because time from CR to postremission therapy has been found to be an independent predictor for relapse and overall survival (OS) in adults with ALL [10], postremission consolidation chemotherapy is routinely used in clinical practice while the donor search is in progress. However, among ALL patients in CR1 with an available allogeneic donor, the impact of further consolidation chemotherapy on clinical outcomes after transplantation remains uncertain. We hypothesized that consolidation chemotherapy is not associated with a survival benefit among alloHCT recipients with adult ALL in CR1. Therefore, we sought to determine the role of pretransplant consolidation chemotherapy in adult ALL in CR1 before an early (as soon as CR is achieved) versus delayed (postconsolidation) alloHCT therapeutic strategy for patients with an available donor.

METHODS

Data Source

The Center of International Blood and Marrow Transplant Research (CIBMTR) collects detailed data on consecutive alloHCT from a volunteer network of more than 450 transplant centers worldwide. CIBMTR data are reported to a centralized statistical center of the research headquarters located at the Medical College of Wisconsin and the National Marrow Donor Program. Patients reported to the CIBMTR are longitudinally observed on a yearly basis. Data quality is ensured via computerized checks for errors and on-site audits. All observational studies conducted by the CIBMTR are in compliance with all applicable federal regulations to ensure the protection of all human research subjects. The Institutional Board and the Privacy Officer of the Medical College of Wisconsin granted a waiver of informed consent for the present study that is in compliance with Health Insurance Portability and Accountability Act regulations.

Patient Selection

We included patients age 16 years and older with ALL in CR1 who received their first myeloablative alloHCT from 2008 to 2012. Patients were excluded if they had French American British (FAB) type L3 ALL (Burkitt's leukemia), received transplant from an identical twin or haploidentical related donor, or were missing their 100-day comprehensive research data collection form or informed consent form, or those missing pre-HCT treatment details. Conditioning intensity was defined using CIBMTR's consensus criteria [11]. In vivo T-cell depletion was defined as use of antithymocyte globulin or alemtuzumab in conditioning. HLA-matching for unrelated donor (URD) transplantation was classified using recommended criteria by CIBMTR [12]. Poor risk cytogenetics was defined as a complex karyotype with ≥3 chromosomal abnormalities, hypodiploid karyotype, or chromosomal translocations t(9;22), t(4;11), t(8;14), and t(14;18). Other cytogenetic risk was defined as having normal karyotype or chromosomal abnormalities other than poor cytogenetics. We defined remission induction chemotherapy cycles as those intensive chemotherapy cycles administered before achieving CR1. CR was defined as no morphological evidence of leukemia and <5% of bone marrow blasts after treatment [13]. We defined consolidation chemotherapy cycles as those intensive chemotherapy cycles administered after CR1, but before alloHCT. Intensive chemotherapy consisted of multiagent cytoreductive chemotherapy regimens administrated such as HyperCVAD [7,8], CALGB [9,14-16], and MRC UKALL XII/ECOG 2993 [1,4] or similar ALL "adult"-type treatment protocols. Tyrosine-kinase inhibitor (TKI) administration before or after transplantation was considered as TKI treatment or maintenance therapy. Central nervous system (CNS) leukemia prophylaxis was defined as receiving intrathecal chemotherapy, systemic high-dose intravenous methotrexate, cranial irradiation, spinal irradiation, or a combination thereof for prevention of CNS involvement with leukemia.

Study Endpoints

The primary endpoint of the study was LFS of ALL patients in CR1 receiving ≥2, 1, or 0 cycles of consolidation chemotherapy before alloHCT. LFS was defined as the time from transplantation to death or leukemia relapse. Secondary endpoints included treatment-related mortality (TRM), incidence of relapse (systemic or CNS), acute and chronic graft-versus-host disease (GVHD), and OS. TRM was defined as death from any cause without any evidence of leukemia relapse considering relapse as a competing event. Acute and chronic GVHD grading was performed according to consensus criteria [17,18]. Overall survival was defined as the time from transplant to death from any cause; patients who were alive and remained in CR were censored at the last follow-up.

Statistical Analysis

Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables were used to compare patient-, disease-, treatment-, and transplant-related characteristics between patients receiving ≥2, 1, or 0 cycles of consolidation chemotherapy before alloHCT. Univariate probabilities of LFS and OS were estimated by the Kaplan-Meier method. Cumulative incidence function was used to calculate probabilities of TRM, and relapse was considered a competing risk and the converse for relapse with TRM as a competing risk. Potential risks factors for clinical outcomes were tested using Cox proportional hazards regression model. The assumption of proportional hazards for each factor was tested using time-dependent covariates, and a backward stepwise model was used to select all significant risk factors. Factors that were significant at a 5% level were retained in the final model. The main effect of consolidation cycle numbers, donor type and recipient age were included in each step of model building regardless of their significance, and the potential interactions between main effect and all significant covariates were tested. The variables that were considered in the multivariable models included number of consolidation cycles, recipient age, Karnofsky performance status, HCT comorbidity index, cytogenetic risk, WBC count at diagnosis, time from diagnosis to CR1, detectable disease status at transplant, recipient cytomegalovirus serostatus, donor type, graft source, and in vivo T-cell depletion. Adjusted probabilities of LFS and survival, and adjusted cumulative incidence functions of TRM and relapse, were calculated using the multivariate models, stratified on cycles of consolidation (≥2 versus 1 versus 0) and weighted by the pooled sample proportion value for each prognostic factor [19,20]. All study analyses were performed using SAS software (SAS version 9.3 Institute, Cary, NC).

RESULTS

Patient Characteristics

We identified 524 adult patients with ALL in CR1 from 116 transplant centers undergoing alloHCT with myeloablative conditioning from 2008 to 2012: 109 patients received ≥2 cycles of consolidation chemotherapy, 93 patients received 1 cycle, and 322 patients received 0 cycles. Overall median follow-up of survivors was 59 months (range, 6 to 79 months). Patient, disease, treatment, and transplant characteristics are summarized in Table 1. The median age was 35, 36, and 40 years for patients receiving ≥2, 1, or 0 cycles of

Table 1
Patient Characteristics

Variable	Consolidation Chemotherapy			
	0 Cycles	1 Cycle	≥2 Cycles	*P* Value
Number of patients	322	93	109	
Number of centers	89	45	62	
Age in decades				.17
16–29 yr	97 (30)	36 (39)	39 (36)	
30–39 yr	62 (19)	16 (17)	30 (28)	
40–49 yr	90 (28)	20 (22)	22 (20)	
50–59 yr	62 (19)	16 (17)	17 (16)	
60–69 yr	11 (3)	5 (5)	1 (<1)	
Median (range), yr	40 (16–68)	36 (17–67)	35 (16–65)	.01
Gender				.55
Male	191 (59)	51 (55)	59 (54)	
Female	131 (41)	42 (45)	50 (46)	
Karnofsky score				.07
<90%	102 (32)	17 (18)	35 (32)	
≥90%	215 (67)	76 (82)	72 (66)	
Missing	5 (2)	0	2 (2)	
ALL immunophenotype				.55
B-lineage	265 (82)	75 (81)	92 (84)	
T-lineage	51 (16)	14 (15)	13 (12)	
Missing	6 (2)	4 (4)	4 (4)	
WBC count at diagnosis				.62
≤10	116 (36)	40 (43)	38 (35)	
10–29	43 (13)	8 (9)	10 (9)	
30–100	36 (11)	13 (14)	12 (11)	
>100	22 (7)	8 (9)	11 (10)	
Missing	105 (33)	24 (26)	38 (35)	
Median (range)	8 (<1–432)	8 (1–429)	8 (1–1410)	.95
HCT comorbidity index				.04
0	191 (59)	64 (69)	61 (56)	
1–2	78 (24)	16 (17)	33 (30)	
≥3	52 (16)	10 (11)	14 (13)	
Missing	1 (<1)	3 (3)	1 (<1)	
Cytogenetics scoring*				.30
Normal	72 (22)	18 (19)	22 (20)	
Poor	188 (58)	55 (59)	66 (61)	
Other	45 (14)	9 (10)	16 (15)	
Missing	17 (5)	11 (12)	5 (5)	
Ph+				.22
No	163 (51)	51 (55)	66 (61)	
Yes	153 (48)	38 (41)	40 (37)	
Missing	6 (2)	4 (4)	3 (3)	
Extramedullary disease at diagnosis				1.00
No	264 (82)	77 (83)	91 (83)	
Yes	48 (15)	13 (14)	15 (14)	
Missing	10 (3)	3 (3)	3 (3)	
Extramedullary or CNS leukemia at diagnosis				.88
No	281 (87)	81 (87)	99 (91)	
Yes	31 (10)	9 (10)	7 (6)	
Missing	10 (3)	3 (3)	3 (3)	
Number of induction cycles				.72
1	278 (86)	77 (83)	93 (85)	
2	30 (9)	14 (15)	11 (10)	
3	11 (3)	2 (2)	4 (4)	
4	3 (<1)	0	1 (<1)	
CNS prophylaxis†				.005
No	96 (30)	18 (19)	17 (16)	
Yes	226 (70)	75 (81)	92 (84)	
Time from diagnosis to CR1				<.001
0–2 mo	136 (42)	61 (66)	80 (73)	
2–6 mo	138 (43)	24 (26)	25 (23)	
≥6 mo	28 (9)	3 (3)	2 (2)	
Missing	20 (6)	5 (5)	2 (2)	
Number of consolidation cycles				<.001
0	322	0	0	
1	0	93	0	
2	0	0	59 (54)	
3	0	0	22 (20)	
4	0	0	17 (16)	
≥5	0	0	10 (9)	
Missing	0	0	1 (<1)	
Time from CR1 to HCT				<.001
0–2 mo	144 (45)	17 (18)	9 (8)	
2–4 mo	89 (28)	44 (47)	33 (30)	

(*Continued on next page*)

Table 1
(*continued*)

Variable	Consolidation Chemotherapy			
	0 Cycles	1 Cycle	≥2 Cycles	*P* Value
4–6 mo	38 (12)	15 (16)	31 (28)	
≥6 mo	31 (10)	12 (13)	34 (31)	
Missing	20 (6)	5 (5)	2 (2)	
Cytogenetic CR status at HCT (n = 379; poor + other)				.33
No	16 (7)	2 (3)	6 (7)	
Yes	191 (82)	59 (92)	70 (85)	
Missing	26 (11)	3 (5)	6 (7)	
Molecular CR status at HCT (n = 231; Ph+ patients only)				.66
No	43 (28)	8 (21)	10 (25)	
Yes	77 (50)	24 (63)	20 (50)	
Missing	33 (22)	6 (16)	10 (25)	
TBI				.63
No	26 (8)	8 (9)	6 (6)	
Yes	296 (92)	85 (91)	103 (94)	
<600 cGy	23	3	9	
600–1200 cGy	148	40	62	
>1200 cGy	125	42	32	
Conditioning regimen				.47
TBI + Cy	150 (47)	35 (38)	43 (39)	
TBI + Cy + other	75 (23)	20 (20)	32 (29)	
TBI + VP16	62 (19)	21 (23)	23 (21)	
TBI + other	15 (5)	11 (12)	9 (8)	
Bu + Cy	7 (2)	3 (3)	1 (<1)	
Bu + Flu	13 (4)	3 (3)	1 (<1)	
In vivo T-cell depletion				.11
No	266 (83)	80 (86)	82 (75)	
Yes	56 (17)	13 (14)	27 (25)	
Type of donor				.40
HLA-identical sibling	130 (40)	37 (40)	38 (35)	
Well matched URD	96 (30)	23 (25)	31 (28)	
Partially matched URD	22 (7)	10 (11)	10 (9)	
Mismatched URD	2 (<1)	1 (1)	3 (3)	
UCB	72 (23)	22 (23)	27 (25)	
6/6 UCB	5	1	0	
5/6 UCB	6	2	4	
≤4/6 UCB	31	4	11	
Matching unknown	30	15	12	
Graft type				.42
Bone marrow	39 (12)	19 (20)	14 (13)	
Peripheral blood	211 (66)	52 (56)	68 (62)	
Single UCB	22 (7)	5 (5)	6 (6)	
Double UCB	50 (16)	17 (18)	21 (19)	
Donor/Recipient CMV match				.05
–/–	92 (29)	16 (17)	39 (36)	
–/+	112 (35)	33 (35)	35 (32)	
+/–	36 (11)	13 (14)	7 (6)	
+/+	81 (25)	31 (33)	24 (22)	
Missing	1 (<1)	0	4 (4)	
Donor/Recipient sex match				.44
M/M	115 (36)	28 (30)	30 (28)	
M/F	73 (23)	28 (30)	21 (19)	
F/M	71 (22)	23 (25)	24 (22)	
F/F	52 (16)	14 (15)	26 (24)	
Double UCB with sex mismatch	11 (3)	0	8 (7)	
GVHD prophylaxis				.16
Tacrolimus based	219 (68)	57 (61)	73 (67)	
Cyclosporine based	87 (27)	29 (31)	35 (32)	
Other	16 (5)	7 (8)	1 (<1)	
TKI maintenance (pre- or post-HCT) (n = 231; Ph+ patients only)				.10
No	82 (54)	17 (45)	14 (35)	
Yes	71 (46)	21 (55)	26 (65)	
Year of HCT				.40
2008	97 (30)	28 (30)	33 (30)	
2009	65 (20)	20 (22)	27 (25)	
2010	56 (17)	15 (16)	13 (12)	
2011	67 (21)	13 (14)	17 (16)	
2012	37 (11)	17 (18)	19 (17)	
Median follow-up of survivors (range), mo	50 (4–78)	61 (12–76)	52 (15–74)	

CMV indicates cytomegalovirus; M, male; F, female.

* Cytogenetics scoring: poor: complex (≥3 abnormalities), t(9;22), t(4;11), t(8;14), t(14;18), hypodiploid (other: everything else except poor and normal.

† Cranial or spinal radiation therapy, intrathecal chemotherapy or high-dose IV methotrexate.

consolidation chemotherapy ($P = .01$), respectively. In addition, there were no reported comorbidities at HCT in 56%, 69%, and 59% of patients receiving ≥2, 1, or 0 cycles of consolidation chemotherapy ($P = .04$), respectively. Philadelphia positive (Ph+) chromosomal abnormality was present in 44% of all study patients, and only 21% of all patients had normal cytogenetics. Only a minority of patients had hyperleukocytosis (defined as WBC count of $>100 \times 10^9$/L; 8%) at diagnosis or CNS involvement by leukemia (9%) at any time point before HCT. An HLA-identical sibling donor was used in 205 (39%) patients, URD in 198 (38%; 150 well matched, 42 partially matched, and 6 mismatched), and umbilical cord blood (UCB) in 121 (23%; 33 single and 88 double UCB). Peripheral blood (63%) was the most commonly used graft source, followed by UCB (23%) or bone marrow (14%). The majority of all patients (>80%) achieved CR1 with only 1 cycle of induction chemotherapy; however, the median time from diagnosis to CR1 was significantly longer among patients receiving no consolidation chemotherapy (2 months) than among patients receiving 1 cycle (1 month) or ≥2 cycles (1 month) of consolidation chemotherapy ($P < .001$). In contrast and as expected, the median time from CR1 to HCT was longer for patients receiving ≥2 cycles (5 months) than for patients receiving 1 cycle (3 months) or no cycles (2 months) of consolidation chemotherapy ($P < .001$). About half of patients (54%) receiving ≥2 cycles of consolidation received only 2 cycles of consolidation chemotherapy. Detectable minimal residual disease (MRD) status before HCT either by cytogenetics or by molecular assessment was present only in a minority of patients in the entire cohort, and it was similar among the 3 groups (14%, 11%, and 18% [$P = .12$], respectively). For those receiving ≥2, 1, or 0 cycles of consolidation, pretransplant CNS prophylaxis was used in 84%, 81%, or 70% ($P = .005$) of patients, respectively; and pre- or post-HCT TKI maintenance chemotherapy among Ph+ patients (n = 231) was used in 65%, 55%, or 46% ($P = .10$), respectively. Other patient, disease, treatment and transplant characteristics were similar among the 3 study groups.

Relapse and TRM

The cumulative incidence of relapse at 3-years for ≥2, 1, or 0 cycles of consolidation chemotherapy was 20%, 26%, and 21%, respectively ($P = .71$; Table 2 and Figure 1). In addition, when relapse was evaluated among the Ph + subgroup of patients, we identified no influence of consolidation on risks of relapse after alloHCT. In multiple regression analysis consolidation chemotherapy did not influence risk of relapse (Table 3). In addition, MRD before HCT did not influence the relapse risk. Adjusted probabilities of 1-year TRM were 17%, 18%, and 23%, respectively ($P = .56$). In univariable analysis, the donor type and graft source influenced TRM; however, none of the other factors tested was significantly associated with relapse incidence after alloHCT. Consolidation did not influence the risks of TRM, but the choice of partially or mismatched URD (mmURD) (relative risk [RR], 3.11; 95% CI, 1.87 to 5.18; $P < .0001$) or UCB donor (RR, 2.46; 95% CI, 1.64 to 3.71; $P < .0001$) significantly increased the risk of TRM after alloHCT.

LFS and OS

Univariate LFS probabilities at 3-years for ≥2, 1, and 0 cycles of consultation therapy were similar at 54%, 48%, and 48%, respectively ($P = .48$). Similarly, univariate OS probabilities at 3 years were 63%, 58%, and 54%, respectively ($P = .21$). Donor type was the only factor associated with LFS and OS. In contrast, LFS or OS were not affected by patient age, Karnofsky performance status, HCT comorbidity index, cytogenetics, WBC count at diagnosis, detectable disease status before HCT, time from diagnosis to CR1, recipient cytomegalovirus serostatus, in vivo T-cell depletion, or type of GVHD prophylaxis. In multiple regression analysis, consolidation chemotherapy did not influence treatment failure (inverse of LFS) or overall mortality. mmURD and UCB donor types increased the risk of

Table 2
Univariate Analysis

	Consolidation Chemotherapy					
	0 Cycles (n = 322)		1 Cycle (n = 93)		≥2 Cycles (n = 109)	
Outcomes	n	Probability (95% CI)	n	Probability (95% CI)	Probability (95% CI)	*P* Value
aGVHD grade II-IV	321		93		109	.86
100-day		37 (32-43)		41 (31-51)	41 (32-51)	
cGVHD	321		93		109	.68
1 yr		48 (42-53)		47 (36-57)	52 (42-61)	
3 yr		56 (50-62)		NE*	58 (48-67)	
5 yr		57 (51-62)		NE*	NE*	
Relapse	321		92		109	.71
1 yr		17 (13-22)		18 (11-27)	17 (11-25)	
3 yr		21 (17-26)		26 (17-36)	20 (13-28)	
5 yr		22 (18-27)		26 (17-36)	20 (13-28)	
TRM	321		92		109	.56
1 yr		23 (18-28)		18 (11-27)	17 (10-24)	
3 yr		31 (26-36)		26 (17-35)	26 (18-35)	
5 yr		33 (28-39)		34 (23-45)	28 (19-37)	
LFS	321		92		109	.48
1 yr		60 (55-65)		63 (53-73)	66 (57-75)	
3 yr		48 (42-53)		48 (38-59)	54 (44-63)	
5 yr		45 (39-50)		40 (29-52)	52 (42-62)	
OS	322		93		109	.21
1 yr		71 (66-76)		72 (63-81)	78 (70-85)	
3 yr		54 (49-60)		58 (48-68)	63 (53-72)	
5 yr		48 (42-54)		49 (37-60)	61 (51-70)	

aGVHD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NE, not evaluable.
* <15 cases at risk at specified time point.

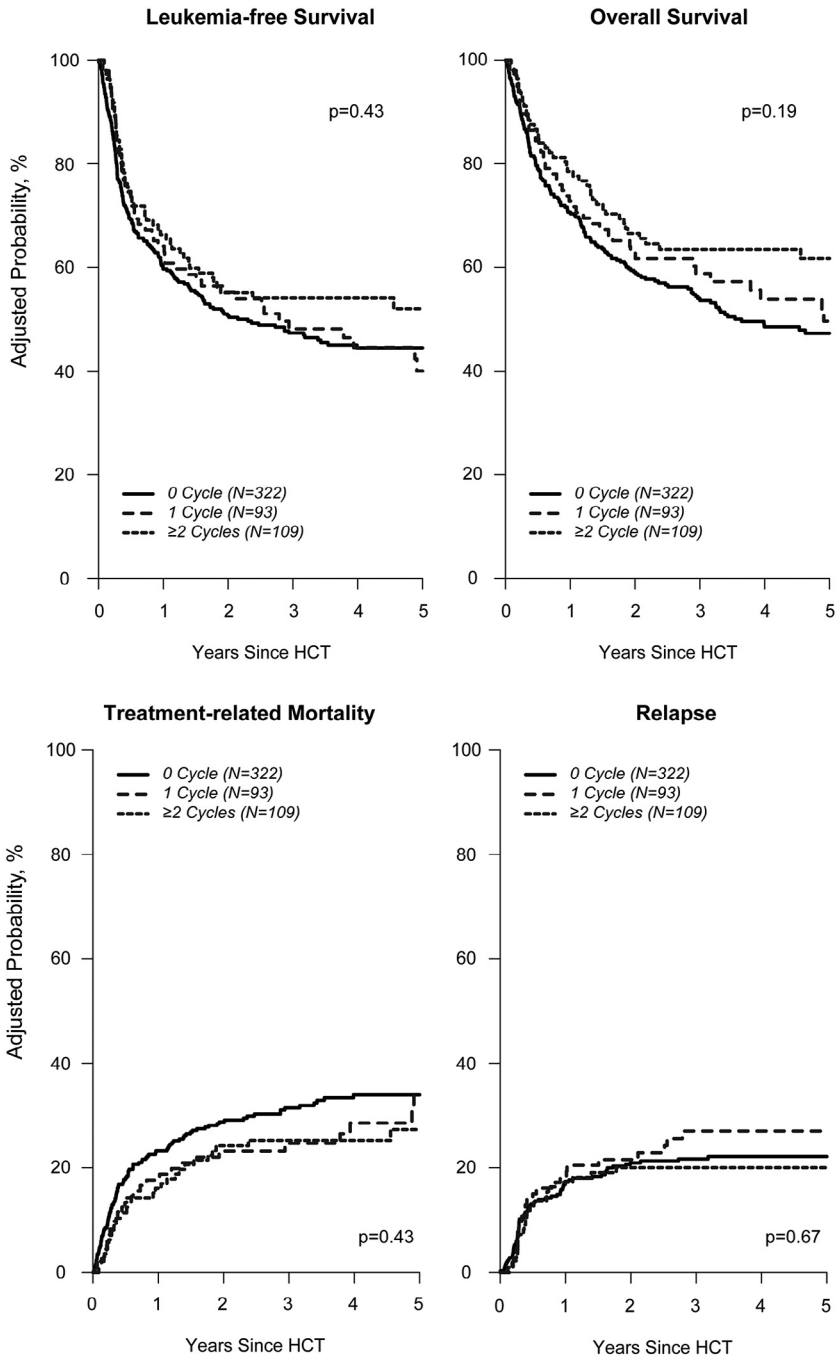

Figure 1. Adjusted clinical outcomes of patients receiving ≥2, 1, or 0 cycles of consolidation chemotherapy before alloHCT.

treatment failure (for mmURD: RR, 1.81; 95% CI, 1.19 to 2.73; $P = .005$; for UCB: RR, 1.50; 95% CI, 1.10 to 2.05; $P = .011$) and overall mortality (for mmURD: RR, 1.98; 95% CI, 1.29 to 3.05; $p = .002$; for UCB: RR, 1.68; 95% CI, 1.21 to 2.34; $P = .002$). In addition, among the Ph + subgroup, LFS after alloHCT was not associated with consolidation or MRD-positive status.

Acute and Chronic GVHD

The cumulative incidence of acute GVHD at day 100 for ≥2, 1, and 0 cycles of consolidation chemotherapy was 41%, 41%, and 37%, respectively ($P = .86$). Similarly, the cumulative incidence of chronic GVHD at 1 year was 52%, 47%, and 48%, respectively ($P = .68$). Consolidation chemotherapy was not associated with the incidence of GVHD; however, acute GVHD was influenced by graft source, and chronic GVHD was influenced by time to CR1, graft source, donor type, and in vivo T-cell depletion. In multiple regression analysis, consolidation was not found to be an independent predictor of acute or chronic GVHD. In contrast, well-matched URD (RR = 1.45, 95% CI, 1.05 to 2.01; $P = .026$) was associated with increased risk of acute GVHD as compared with HLA-identical sibling donor type, whereas in vivo T-cell depletion (RR, .55; 95% CI, .38 to .80; $P = .002$) significantly reduced the risk of chronic GVHD.

Table 3
Multivariable Analysis

	n	RR (95% CI)	*P* Value
1. aGVHD grade II-IV			
Number of consolidation cycles			.98
≥2	109	1	
0	322	.97 (.70-1.35)	.87
1	93	.96 (.63-1.47)	.85
Donor type			.10
HLA-identical sibling	205	1	
Well matched URD	150	1.45 (1.05-2.01)	.026
Partially/mismatched URD	48	1.41 (.87-2.29)	.17
UCB	121	1.42 (1.00-2.01)	.053
Recipient age at HCT			.36
16-39 yr	280	1	
≥40 yr	244	.88 (.67-1.16)	
2. cGVHD			
Number of consolidation cycles			.59
≥2	109	1	
0	322	.94 (.70-1.26)	.68
1	93	.82 (.56-1.20)	.31
Donor type			.082
HLA-identical sibling	205	1	
Well matched URD	150	1.01 (.75-1.36)	.96
Partially/mismatched URD	48	1.42 (.87-2.31)	.16
UCB	121	.74 (.53-1.02)	.066
In vivo T-cell depletion			.0019
No	428	1	
Yes	96	.55 (.38-0.80)	
Recipient age at HCT			.57
16-39 yr	280	1	
≥40 yr	244	.93 (.74-1.18)	
3. Treatment related mortality			
Number of consolidation cycles			.43
≥2 cycles	109	1	
0 cycles	322	1.30 (.86-1.96)	.22
1 cycle	93	1.12 (.66-1.91)	.67
Donor type			<.0001
HLA-identical sibling	205	1	
Well matched URD	150	1.33 (.87-2.04)	.19
Partially/mismatched URD	48	3.11 (1.87-5.18)	<.0001
UCB	121	2.46 (1.64-3.71)	<.0001
Recipient age at HCT			.10
16-39 yr	280	1	
≥40 yr	244	1.31 (.95-1.81)	
HCT comorbidity index			.56
0	316	1	
1	75	1.06 (.65-1.74)	.80
≥2	128	1.22 (.85-1.76)	.28
4. Relapse			
Number of consolidation cycles			.67
≥2	109	1	
0	322	1.15 (.71-1.87)	.57
1	93	1.31 (.73-2.34)	.37
Donor type			.63
HLA-identical sibling	205	1	
Well matched URD	150	.92 (.60-1.42)	.71
Partially/mismatched URD	48	.81 (.38-1.70)	.57
UCB	121	.71 (.42-1.21)	.21
Recipient age at HCT			.80
16-39 yr	280	1	
≥40 yr	244	.95 (.66-1.38)	
5. Treatment failure (1 - LFS)			
Number of consolidation cycles			.43
≥2	109	1	
0	322	1.23 (.90-1.69)	.19
1	93	1.19 (.80-1.77)	.38
Donor type			.0096
HLA-identical sibling	205	1	
Well matched URD	150	1.11 (.82-1.51)	.48
Partially/mismatched URD	48	1.81 (1.19-2.73)	.0051
UCB	121	1.50 (1.10-2.05)	.011
Recipient age at HCT			.22
16-39 yr	280	1	
≥40 yr	244	1.16 (.91-1.49)	

(*Continued on next page*)

Table 3
(*continued*)

	n	RR (95% CI)	*P* Value
HCT comorbidity index			.56
0	316	1	
1	75	1.13 (.80-1.60)	.50
≥2	128	1.07 (.81-1.43)	.63
6. Overall mortality (1 - OS)			
Number of consolidation cycles			.19
≥2	109	1	
0	322	1.38 (.98-1.94)	.065
1	93	1.31 (.85-2.00)	.22
Donor type			.0015
HLA-identical sibling	205	1	
Well matched URD	150	1.14 (.83-1.57)	.43
Partially/mismatched URD	48	1.98 (1.29-3.05)	.0019
UCB	121	1.68 (1.21-2.34)	.0020
Recipient age at HCT			.14
16-39 yr	280	1	
≥40 yr	244	1.22 (.94-1.58)	
HCT comorbidity index			.16
0	316	1	
1	75	1.22 (.85-1.76)	.29
≥2	128	1.22 (.90-1.65)	.19
7. Relapse (Ph + subset)			
Number of consolidation cycles			.75
≥2	40	1	
0	153	1.05 (.47-2.35)	.91
1	38	1.35 (.54-3.40)	.53
Donor type			.46
HLA-identical sibling	87	1	
Well matched URD	65	.74 (.37-1.48)	.39
Partially/mismatched URD	21	.96 (.35-2.61)	.94
UCB	58	.53 (.24-1.20)	.13
Recipient age at HCT			.073
16-39 yr	99	1	
≥40 yr	132	.59 (.33-1.05)	
MRD status			.84
No	115	1	
Yes	67	1.21 (.63-2.32)	.57
Missing	49	1.14 (.52-2.49)	.74
8. Overall mortality (Ph + subset)			
Number of consolidation cycles			.84
≥2	40	1	
0	153	1.04 (.64-1.70)	.86
1	38	.89 (.48-1.67)	.73
Donor type			.64
HLA-identical sibling	87	1	
Well matched URD	65	1.22 (.78-1.90)	.38
Partially/mismatched URD	21	1.35 (.68-2.67)	.39
UCB	58	1.27 (.80-2.02)	.30
Recipient age at HCT			.68
16-39 yr	99	1	
≥40 yr	132	1.08 (.75-1.57)	
MRD status			.56
No	115	1	
Yes	67	1.02 (.67-1.57)	.92
Missing	49	1.27 (.80-2.02)	.31
HCT comorbidity index			.45
0	140	1	
1	30	.96 (.54-1.69)	.89
≥2	59	1.19 (.79-1.78)	.41

RR indicates relative risk.

DISCUSSION

We conducted a large analysis of CIBMTR data on 524 patients with ALL in CR1 to determine whether consolidation chemotherapy affected clinical outcomes of myeloablative alloHCT. We found that consolidation chemotherapy had no demonstrable benefit for myeloablative alloHCT recipients—an observation not previously reported. We observed similar rates of LFS, OS, relapse, and TRM in CR1 ALL patients independent of consolidation chemotherapy use. Since many ALL treatment protocols for adults still incorporate mandatory consolidation even for those undergoing alloHCT [21], this observation has practical importance for clinicians because it suggests that consolidation is not necessary for those patients with readily available donors undergoing prompt myeloablative alloHCT for ALL in CR1, especially when a negative MRD status can be verified. On the other hand, our analysis showed that consolidation had no negative effect on TRM or survival after alloHCT. Because a previous report found that the time from induction chemotherapy to consolidation was independently associated

with increased risk of relapse in ALL [10], our data suggest that consolidation can be safely used to prevent leukemia relapse in those waiting for suitable donor without increasing the risk of TRM.

In this study, factors including patient age, comorbidities, Ph + status, or WBC at diagnosis were not independently associated with clinical outcomes after alloHCT. In addition, exclusion of patients younger than age 18 years (n = 29) had no significant effect on any clinical outcomes after transplantation (data not shown). Notably, no consolidation group was enriched with older patients and patients with comorbidities. Although factors determining the choice of offering consolidation cannot be assessed in this retrospective study, older age and patient comorbidities are common reasons why consolidation might not be routinely administered in clinical practice. Despite this, however, in our study factors such as older age or comorbidities did not significantly increase the risk of TRM or mortality in patients receiving no consolidation.

Although the adverse influence of hyperleukocytosis [22-26] or CNS leukemia [27] on clinical outcomes of ALL were previously reported in several studies, this effect was not observed in our analysis. However, our study had only a smaller proportion of patients with hyperleukocytosis or CNS leukemia (<10% for each); therefore, the effect of these factors on transplant outcomes could not be robustly assessed. Despite the high proportion of Ph + ALL cases (44%) in our study cohort, we observed no influence of Ph + status on transplantation outcomes. Our observation is consistent with several prior reports of improved outcomes in myeloablative alloHCT recipients with Ph + ALL [28-32]. The increased use of TKI maintenance before or after alloHCT in recent years might have influenced, in part, the improved outcomes of the otherwise well-known adverse subgroup with Ph + ALL [31-33].

Our study also highlights that achievement of CR1 with upfront therapy is an acceptable benchmark for disease control before myeloablative alloHCT. Several recent studies reported increased risk of ALL recurrence in patients undergoing alloHCT with positive MRD status using either flow cytometry or more sensitive polymerase chain reaction molecular techniques [34], particularly in a settings of reduced-intensity conditioning transplantation [31,35-38] or myeloablative alloHCT in CR2 [39]. In our analysis, MRD-positive status (though not quantitatively reported) among the Ph + subgroup of patients had no influence on ALL relapse or LFS after transplantation. This observation is consistent with the UKALL XII/ECOG2993 results demonstrating that MRD-positive status had no adverse effect on outcomes of myeloablative alloHCT [40], thereby emphasizing that myeloablative conditioning could potentially overcome the increased risk of relapse after transplantation of MRD-positive ALL in CR1. Although MRD status by high-sensitivity flow cytometry assessment might have differentially influenced our observation, such information was not available for our analysis. However, we analyzed data on either cytogenetic or molecular MRD status in a majority of study patients and there was a similar distribution of detectable MRD cases among the 3 study groups. Future studies could re-examine the role of consolidation in flow cytometry detectable MRD to allow a better definition of whether such patients require consolidation before transplant to improve outcomes. At present, our study findings must only be cautiously extrapolated to cases with flow cytometry evidence of MRD and may not be applicable for patients undergoing reduced-intensity conditioning alloHCT.

These patients received various upfront ALL chemotherapy regimens and generally only “adult”-type ALL therapy. More intense pediatric style intensification and consolidation therapy might alter this risk-benefit equation and in some subgoups might effectively substitute for the benefits of an allograft [41].

These data support the conclusion that consolidation chemotherapy does not appear to provide added benefit in adult ALL patients who have an available donor permitting prompt initiation of myeloablative alloHCT in CR1. Consolidation should still be administrated to maintain CR1 before alloHCT in those awaiting donor availability.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the following additional contributing coauthors from the writing committee: Mahmoud Aljurf, Edwin Alyea, Miguel Angel Diaz, Mouhab Ayas, Ulrike Bacher, Karen Ballen, Minoo Battiwalla, Amer Beitinjaneh, Jonathan Brammer, Michael Byrne, Jean-Yves Cahn, Mitchell Cairo, Jan Cerny, Stefan Ciurea, Brenda Cooper, Jorge Cortes, Chris Dandoy, Zachariah DeFilipp, Abhinav Deol, William Drobyski, Michael Franklin, Cesar Freytes, Sid Ganguly, Biju George, Usama Gergis, Michael Grunwald, Gregory Hale, Brandon Hayes-Lattin, Mark Hertzberg, Mary Horowitz, Nasheed Hossain, Yoshi Inamoto, Madan Jagasia, Antonio Jimenez, Rammurti Kamble, Nandita Khera, Elizabeth Krakow, Mary Laughlin, Ian Lewis, Michael Lill, Mark Litzow, Marlise Luskin, Amani Makkouk, Alan Miller, Giuseppe Milone, Guru Murthy, Velu Nair, Taiga Nishihori, Ian Nivison-Smith, Tracey O’Brien, Attaphol Pawarode, Muthalagu Ramanathan, Armin Rashidi, Olle Ringden, David Rizzieri, Ayman Saad, Lynn Savoie, Harry Schouten, Kirk Schultz, Steven Gore, Koen van Besien, Leo Verdonck, Ravi Vij, Edmund Waller, Mona Wirk, Jean Yared, Agnes Yong

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

Authorship statement: Contribution: N.B., A.L., and D.J.W. conceived the study; M.J.Z. and H.L.W. analyzed and interpreted data; N.B. wrote the manuscript; N.B., M.J.Z., H.L.W., A.L., M.L., D.I.M., B.M.S., V.B., J.R., M.T., P.K., M.K.D., R.P.G., H.M.L., C.U., E.C., B.K.H., G.S., W.H., S.H., M.S., C.G.K., R.F.O., R.M., W.S., H.J.K., and D.J.W. interpreted and edited the manuscript; and all authors approved the final manuscript.

CIBMTR SUPPORT LIST

The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement 5U24- CA076518 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 5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration; 2 Grants N00014-15-1-0848 and N00014-16-1-2020 from the Office of Naval Research; and grants from Alexion; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US; AstraZeneca; Be the Match Foundation; *Bluebird Bio, Inc.; *Bristol Myers Squibb Oncology; *Celgene Corporation; Cellular Dynamics International, Inc.; *Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd.; Genentech, Inc.; Genzyme Corporation; *Gilead Sciences, Inc.; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals, Inc.; Jeff Gordon Children’s Foundation; The Leukemia & Lymphoma Society; Medac, GmbH; MedImmune; The Medical College

of Wisconsin; *Merck & Co, Inc.; Mesoblast; MesoScale Diagnostics, Inc.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; Neovii Biotech NA, Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Otsuka America Pharmaceutical, Inc.; Otsuka Pharmaceutical Co, Ltd. – Japan; PCORI; Perkin Elmer, Inc.; Pfizer, Inc; *Sanofi US; *Seattle Genetics; *Spectrum Pharmaceuticals, Inc.; St. Baldrick's Foundation; *Sunesis Pharmaceuticals, Inc.; Swedish Orphan Biovitrum, Inc.; Takeda Oncology; Telomere Diagnostics, Inc.; University of Minnesota; and *Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration, or any other agency of the U.S. government.

*Corporate Members.

REFERENCES

1. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. 2008;111:1827-1833. doi:10.1182/blood-2007-10-116582.
2. Cornelissen JJ, van der Holt B, Verhoef GE, et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. *Blood*. 2009;113:1375-1382. doi:10.1182/blood-2008-07-168625.
3. Kako S, Morita S, Sakamaki H, et al. A decision analysis of allogeneic hematopoietic stem cell transplantation in adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission who have an HLA-matched sibling donor. *Leukemia*. 2011;25:259-265. doi:10.1038/leu.2010.260.
4. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*. 2005;106:3760-3767. doi:10.1182/blood-2005-04-1623.
5. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol*. 2009;27:911-918. doi:10.1200/JCO.2008.18.6916.
6. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol*. 2004;22:4075-4086. doi:10.1200/JCO.2004.10.050.
7. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol*. 2010;28:3880-3889. doi:10.1200/JCO.2009.26.9456.
8. Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood*. 2010;116:2070-2077. doi:10.1182/blood-2009-12-261586.
9. Stock W, Johnson JL, Stone RM, et al. Dose intensification of daunorubicin and cytarabine during treatment of adult acute lymphoblastic leukemia: results of Cancer and Leukemia Group B Study 19802. *Cancer*. 2013;119:90-98. doi:10.1002/cncr.27617.
10. Advani AS, Jin T, Ramsingh G, et al. Time to post-remission therapy is an independent prognostic factor in adults with acute lymphoblastic leukemia. *Leuk Lymphoma*. 2008;49:1560-1566. doi:10.1080/10428190802146078.
11. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628-1633. doi:10.1016/j.bbmt.2009.07.004.
12. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. *Biol Blood Marrow Transplant*. 2008;14:748-758. doi:10.1016/j.bbmt.2008.04.003.
13. Pui CH, Campana D. New definition of remission in childhood acute lymphoblastic leukemia. *Leukemia*. 2000;14:783-785.
14. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood*. 1995;85:2025-2037.
15. Larson RA, Dodge RK, Linker CA, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. *Blood*. 1998;92:1556-1564.
16. Wetzler M, Sanford BL, Kurtzberg J, et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. *Blood*. 2007;109:4164-4167. doi:10.1182/blood-2006-09-045351.
17. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18:295-304.
18. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med*. 1980;69:204-217.
19. Zhang X, Loberiza FR, Klein JP, Zhang MJ. A SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. *Comput Methods Programs Biomed*. 2007;88:95-101. doi:10.1016/j.cmpb.2007.07.010.
20. Zhang X, Zhang MJ. SAS macros for estimation of direct adjusted cumulative incidence curves under proportional subdistribution hazards models. *Comput Methods Programs Biomed*. 2011;101:87-93. doi:10.1016/j.cmpb.2010.07.005.
21. Fathi AT, DeAngelo DJ, Stevenson KE, et al. Phase 2 study of intensified chemotherapy and allogeneic hematopoietic stem cell transplantation for older patients with acute lymphoblastic leukemia. *Cancer*. 2016;122:2379-2388. doi:10.1002/cncr.30037.
22. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood*. 2015;125:3711-3719. doi:10.1182/blood-2015-02-627935.
23. Eguiguren JM, Schell MJ, Crist WM, Kunkel K, Rivera GK. Complications and outcome in childhood acute lymphoblastic leukemia with hyperleukocytosis. *Blood*. 1992;79:871-875.
24. Lowe EJ, Pui CH, Hancock ML, Geiger TL, Khan RB, Sandlund JT. Early complications in children with acute lymphoblastic leukemia presenting with hyperleukocytosis. *Pediatr Blood Cancer*. 2005;45:10-15. doi:10.1002/pbc.20178.
25. Kong SG, Seo JH, Jun SE, Lee BK, Lim YT. Childhood acute lymphoblastic leukemia with hyperleukocytosis at presentation. *Blood Res*. 2014;49:29-35. doi:10.5045/br.2014.49.1.29.
26. Hoelzer D, Thiel E, Loffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood*. 1988;71:123-131.
27. Lazarus HM, Richards SM, Chopra R, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. *Blood*. 2006;108:465-472. doi:10.1182/blood-2005-11-4666.
28. Kebriaei P, Saliba R, Rondon G, et al. Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact of tyrosine kinase inhibitors on treatment outcomes. *Biol Blood Marrow Transplant*. 2012;18:584-592. doi:10.1016/j.bbmt.2011.08.011.
29. Barrett AJ, Horowitz MM, Ash RC, et al. Bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 1992;79:3067-3070.
30. Chao NJ, Blume KG, Forman SJ, Snyder DS. Long-term follow-up of allogeneic bone marrow recipients for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 1995;85:3353-3354.
31. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia–results of the prospective multicenter LALA-94 trial. *Blood*. 2002;100:2357-2366. doi:10.1182/blood-2002-03-0704.
32. Wrzesien-Kus A, Robak T, Pluta A, et al. Outcome of treatment in adults with Philadelphia chromosome-positive and/or BCR-ABL–positive acute lymphoblastic leukemia-retrospective analysis of Polish Adult Leukemia Group (PALG). *Ann Hematol*. 2006;85:366-373. doi:10.1007/s00277-006-0099-z.
33. Bloomfield CD, Lindquist LL, Arthur D, et al. Chromosomal abnormalities in acute lymphoblastic leukemia. *Cancer Res*. 1981;41(11 pt 2):4838-4843.
34. Balduzzi A, Di Maio L, Silvestri D, et al. Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: is there any room for intervention? *Br J Haematol*. 2014;164:396-408. doi:10.1111/bjh.12639.
35. Spinelli O, Peruta B, Tosi M, et al. Clearance of minimal residual disease after allogeneic stem cell transplantation and the prediction of the clinical outcome of adult patients with high-risk acute lymphoblastic leukemia. *Haematologica*. 2007;92:612-618.
36. Sanchez-Garcia J, Serrano J, Serrano-Lopez J, et al. Quantification of minimal residual disease levels by flow cytometry at time of transplant predicts outcome after myeloablative allogeneic transplantation in ALL. *Bone Marrow Transplant*. 2013;48:396-402. doi:10.1038/bmt.2012.147.
37. Bachanova V, Burke MJ, Yohe S, et al. Unrelated cord blood transplantation in adult and pediatric acute lymphoblastic leukemia: effect of minimal residual disease on relapse and survival. *Biol Blood Marrow Transplant*. 2012;18:963-968. doi:10.1016/j.bbmt.2012.02.012.

38. Bachanova V, Marks DI, Zhang MJ, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. *Leukemia*. 2014;28:658-665. doi:10.1038/leu.2013.253.
39. Knechtli CJ, Goulden NJ, Hancock JP, et al. Minimal residual disease status before allogeneic bone marrow transplantation is an important determinant of successful outcome for children and adolescents with acute lymphoblastic leukemia. *Blood*. 1998;92:4072-4079.
40. Patel B, Rai L, Buck G, et al. Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993. *Br J Haematol*. 2010;148:80-89. doi:10.1111/j.1365-2141.2009.07941.x.
41. Seftel MD, Neuberg D, Zhang MJ, et al. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. *Am J Hematol*. 2016;91:322-329. doi:10.1002/ajh.24285.