REVIEW

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Update of the 2006 Evidence-Based Review

Denise M. Oliansky,[1] Richard A. Larson,[2] Daniel Weisdorf,[3] Hildy Dillon,[4] Thomas A. Ratko,[5] Donna Wall,[6] Philip L. McCarthy, Jr.,[1] Theresa Hahn[1]

Clinical research published since the first evidence-based review on the role of hematopoietic stem cell transplantation (SCT) in the treatment of acute lymphoblastic leukemia (ALL) in adults is presented and critically evaluated in this update. Treatment recommendations changed or modified based on new evidence include: (1) myeloablative allogeneic SCT is an appropriate treatment for adult (<35 years) ALL in first complete remission for all disease risk groups; and (2) reduced-intensity conditioning may produce similar outcomes to myeloablative regimens. Treatment recommendations unchanged or strengthened by new evidence include: (1) allogeneic SCT is recommended over chemotherapy for ALL in second complete remission or greater; (2) allogeneic is superior to autologous SCT; and (3) there are similar survival outcomes after related and unrelated allogeneic SCT. New treatment recommendations based on new evidence include: (1) in the absence of a suitable allogeneic donor, autologous SCT may be an appropriate therapy, but results in a high relapse rate; (2) it is appropriate to consider cord blood transplantation for patients with no HLA well-matched donor; and (3) imatinib therapy before and/or after SCT (for Ph+ ALL) yields significantly superior survival outcomes. Areas of needed research in the treatment of adult ALL with SCTwere identified and presented in the review.

Biol Blood Marrow Transplant 18: 18-36 (2012)

KEY WORDS: Acute lymphoblastic leukemia, Hematopoietic stem cell transplatation, Evidence-based review, Therapy, Adult

INTRODUCTION

In 1999, the American Society for Blood and Marrow Transplantation (ASBMT) began the development of systematic evidence-based reviews (EBRs) and position statements on the effectiveness of autologous and allogeneic hematopoietic stem cell transplantation (SCT) for specific diseases. In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly at approximately 5-year intervals. This constitutes the first update of the adult acute lymphoblastic leukemia (ALL) EBR originally published in 2006.

UPDATE OF THE ADULT ALL EBR

This adult ALL EBR update adheres to the methodology and grading systems presented in Appendix A (online only). In the original adult ALL EBR [1], each article was summarized in detail in the text, accompanied by summary tables comparing study designs and patient outcomes. To streamline this update, a concise summary of outcomes is provided in each section of text, whereas descriptions of the study design, patient population, and clinical outcomes of each article are presented in detailed summary tables.

Evidence in each section is presented with the highest quality studies first; studies of equal quality are presented in descending order by study population size. New evidence is provided first in each table, followed by the highest quality studies (ratings 1++

From the [1]Roswell Park Cancer Institute, Buffalo, New York; [2]University of Chicago, Chicago, Illinois; [3]University of Minnesota, Minneapolis, Minnesota; [4]The Leukemia & Lymphoma Society, White Plains, New York; [5]Blue Cross Blue Shield Association Technology Evaluation Center, Chicago, Illinois; and [6]University of Manitoba/CancerCare Manitoba, Winnipeg, Manitoba, Canada.

Financial disclosure: See Acknowledgments on page 33.

Correspondence and reprint requests: Theresa Hahn, PhD, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263 (e-mail: Theresa.hahn@roswellpark.org).

Received May 17, 2011; accepted July 25, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.07.019

and 2++) used to make treatment recommendations in the original adult ALL EBR. Both Level 1 and Level 2 evidence is presented in the tables for each study that provided biologic assignment (donor versus no donor) and randomized (autologous SCT versus chemotherapy) results.

TREATMENT RECOMMENDATIONS

Table 1 contains the summary of consensus treatment recommendations made by the expert panel based on the summarized evidence on the use of SCT to treat adult ALL. The consensus process is detailed in Appendix A (online only) and involves a teleconference during which panelists critically discuss the evidence for each section of the review and develop treatment recommendations rated according to the categories in Table 1 and in Appendix A, Table 2.

Table 1 presents new treatment recommendations based on the adult ALL evidence published since January 2005. In addition, the treatment recommendations from the original adult ALL EBR are incorporated into the respective tables when applicable. It is indicated whether the new evidence strengthens, modifies, or does not change the original recommendation. Four treatment options included in the original adult ALL EBR treatment recommendations table were removed in this update for the following reasons. First, there were no new studies of purged or unpurged autologous SCT, which is no longer relevant based on current treatment preferences. In addition, noncomparative studies of related and unrelated allogeneic SCT were included in the original adult ALL EBR because there were no comparative studies of these techniques; however, in this update, comparative evidence is presented, making these separate categories unnecessary. Additional evolution of SCT techniques, including advances in donor selection through high-resolution HLA typing and matching and in supportive care, all influence the current findings and limit their direct comparability to earlier reports.

TRANSPLANTATION VERSUS CHEMOTHERAPY FOR ADULT ALL

There were 11 studies published since the original adult ALL EBR, and briefly summarized below, which compared the efficacy of transplantation versus chemotherapy as treatment for adult (≥18 years) patients with ALL in first complete remission (CR1). Table 2 presents a detailed summary of the study designs, patient populations, and outcomes from this new evidence. Six high-quality (1++ to 2++) studies comparing transplantation versus chemotherapy in CR1 that were used to make treatment recommendations in the original adult ALL EBR are also presented in Table 2.

Table 3 presents two studies published since January 2005 that compared transplantation versus chemotherapy as treatment for relapsed or refractory adult ALL. The quality ratings for these two studies were 2++ and 2+. There were no studies in the original adult ALL EBR that compared transplantation versus chemotherapy for refractory or relapsed ALL, or for ALL in second complete remission (CR2).

Transplantation versus Chemotherapy for Adult ALL in CR1

The 11 new studies presented in Table 2 provided 15 analyses, including four meta-analyses, four randomized autologous SCT versus chemotherapy, four donor versus no donor, and three allogeneic SCT versus chemotherapy ± imatinib for the treatment of adult ALL in CR1. The quality ratings of these studies ranged from 1++ to 2+.

Meta-analyses

To briefly summarize, in a meta-analysis of aggregate data from 13 studies, Ram et al. [2] reported a significant reduction in all-cause mortality in favor of adult ALL patients in CR1 who underwent an allogeneic SCT versus chemotherapy alone or an autologous SCT in studies which analyzed data by intention to treat. In a meta-analysis of individual patient data from four studies, Orsi et al. [3] reported a significant difference in event-free survival (EFS) in favor of ALL patients in CR1 who had a donor versus those with no donor. Similarly, in a meta-analysis of aggregate data from seven studies, Yanada et al. [4] reported a significant advantage in overall survival (OS) for those patients with a donor versus those with no donor. In a meta-analysis of individual patient data from three studies, Dhédin et al. [5] found no significant difference in 10-year disease-free survival (DFS) or OS between ALL patients in CR1 who underwent autologous SCT versus those who received chemotherapy alone.

Autologous SCT versus Chemotherapy

In a prospective, multicenter study (UKALL XII/ECOG 2993) by Goldstone et al. [6], 456 patients were randomized to receive an autologous SCT or chemotherapy alone. A significant difference in 5-year EFS and OS was reported in favor of chemotherapy for standard or high-risk patients. Marks et al. [7] analyzed a subset of T-lineage ALL patients from the UKALL XII/ECOG 2993 trial and found no significant difference in 5-year OS between those randomized to autologous SCT versus chemotherapy alone. Ribera et al. [8] found no significant difference in 5-year DFS or OS between high-risk ALL patients in CR1 randomized to autologous SCT versus chemotherapy alone. Similarly, Hunault et al. [9] found no significant difference in 7-year relapse-free

Table 1. Summary of Updated Treatment Recommendations for Adult ALL

Indication for SCT	Original vs. New Rec	Tx Rec Grade*	Highest Level of Evidence†	Ref. No.‡	Treatment Recommendation Comments
TRANSPLANTATION VS. CHEMOTHERAPY					
Allogeneic SCT vs. chemotherapy for ALL in first complete remission	New evidence changed original recommendation	A	1++	2, 3, 5 (Table 2)	Myeloablative allogeneic SCT is an appropriate treatment for adult ALL in CR1 for all disease risk groups. Allogeneic SCT provides a significant improvement in overall and leukemia-free survival in younger (<35 years), standard risk, Ph-negative ALL patients compared with less intensive chemotherapy regimens. In older (>35 years), standard risk, Ph-negative ALL patients, a higher TRM diminishes the significant survival advantage with allogeneic SCT.
Autologous SCT vs. chemotherapy for ALL in first complete remission	New recommendation based on new evidence	A	1++	2, 5 (Table 2)	In the absence of a suitable allogeneic donor, autologous SCT may be an appropriate therapy due to similar survival outcomes and a shorter treatment duration when compared to chemotherapy alone, but results in a high relapse rate. Maintenance therapy, biologic therapy, or tyrosine kinase inhibitors may improve outcomes in selected patients, but these approaches need further study.
Allogeneic SCT vs. chemotherapy for ALL in ≥CR2	New evidence strengthened original recommendation	B	2++	20 (Table 3)	Allogeneic SCT is recommended over chemotherapy for ALL in CR2 or greater.
TRANSPLANTATION TECHNIQUES					
Allogeneic vs. autologous SCT	New evidence did not change original recommendation	B	2++	22 (Table 4)	There is a preponderance of evidence favoring allogeneic over autologous SCT. There are insufficient data to determine if this effect is more apparent in disease risk subgroups, including Ph+ ALL.
Related vs. unrelated allogeneic SCT	New evidence strengthened original recommendation	B	2++	28, 29 (Table 5)	There are similar, and possibly equivalent, survival outcomes after related and unrelated allogeneic SCT. Post-SCT complications may differ.
Unrelated donor BM vs. cord blood SCT	New recommendation based on new data published since the original review	B	2++	34 (Table 6)	It is appropriate to consider cord blood transplantation for patients with no HLA-well-matched donor option or those needing an urgent transplant.
Imatinib vs. no imatinib therapy pre- and/or post-SCT in Ph-positive ALL	New recommendation based on new data published since the original review	B	2++	36, 37 (Table 6)	Available data suggest imatinib therapy before and/or after SCT yields significantly superior outcomes in OS and LFS. Ongoing studies using other tyrosine kinase inhibitors may enhance this recommendation.
Comparison of induction therapies before SCT	No treatment recommendation based on new data published since the original review		1++	40 (Table 6)	There are insufficient data to make a treatment recommendation regarding the benefit of any one induction regimen.
Comparison of SCT conditioning regimens	New evidence modified original recommendation	B	2++	42 (Table 6)	There are not enough data to make a recommendation regarding the superiority of any one conditioning regimen. There appears to be a benefit to TBI-containing regimens compared to non-TBI-containing regimens. Reduced intensity conditioning may produce similar outcomes to myeloablative regimens, but available data are limited, thus reduced intensity regimens are appropriate only for patients with ALL in remission who are unsuited for myeloablative conditioning.

ALL indicates acute lymphoblastic leukemia; SCT, stem cell transplantation; LFS, leukemia-free survival; CR, complete remission; BM, bone marrow; TRM, treatment-related mortality; OS, overall survival; TBI, total-body irradiation.

*__Definitions for Grade of Recommendation__ (see Appendix A, Table 2): A = at least 1 meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results; B = A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as **1++** or 1+; C = a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++; D = evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.

†__Definitions for Levels of Evidence__ (see Appendix A, Table 1): **1++** High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias; **1+** well-conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; 1− Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; **2++** high-quality systematic reviews of case-control or cohort studies; or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal; **2+** Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal; 2− Case-control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal; 3 Nonanalytic studies (eg, case reports, case series); 4 Expert opinion.

‡The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in each section of the review.

Table 2. Transplantation vs. Chemotherapy for Adult Acute Lymphoblastic Leukemia in First Complete Remission

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Yeas Median (range)	% WBC >100,000	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS /LFS†	% OS (95%CI)	Signif. OS†
Update data published since January 2005													
[2] Ram 2010 1986-2006 accrual dates Meta-analysis Aggregate data from 11 studies (9 ITT)	1++	Total Allo SCT Other (auto or chemo) (7 ITT trials)	1863	NR (7-60)	NR	NR	NR	Overall Mean 62 (30-110)	NR	NR	NR	Reduced ACM for Allo SCT RR, .89 (0.82-0.97)	**$P = .009$**
		Total Auto SCT Chemotherapy (5 randomized trials)	903									No difference in ACM RR, 1.02 (0.88-1.19)	$P = .76$
[3] Orsi 2007 2000-2007 accrual dates Meta-analysis Individual data from 4 pre-2005 studies	1++	Total Donor No Donor	772 293 479	NR	NR	NR	NR	NR	NR	5-year EFS 44.2% ± 2.9% 36.7% ± 2.2%	**$P = .011$** Donor vs. No Donor	NR	NR
[5] Dhédin 2006 1985-2001 accrual dates Meta-analysis Individual data from 3 randomized trials: LALA-85, -87, -94	1++	Total Autologous SCT Chemotherapy	349 175 174	 28 (15-50) 33 (15-50)	≥30,000 43% 36%	5% 	 42% 43%	120 (NR)	 6% 2%	ITT 10-yr DFS 28% (21-35%) 19% (13-26%)	$P = .12$	10-year OS 30% (23-38%) 22% (16-30%)	$P = .48$
[4] Yanada 2006 1986-2002 accrual dates Meta-analysis Aggregate data from 7 studies	1+	Total Donor No Donor	1274 503 771	NR	NR	NR	NR	NR	NR	NR	NR	Summary HR for OS was 1.29 (1.02-1.63) favoring Donor vs. No Donor	**$P = .037$** Donor vs. No Donor
[6] Goldstone 2008 1993-2006 Prospective, Multicenter MRC UKALL XII & ECOG E2993 (Included in Ram, 2010 meta-analysis)	1+	Total Autologous SCT Chemotherapy (Randomized) (includes 16 Ph+ pts.)	456 229 227	NR (15-64)	NR	4%	NR	59 (1-167)	NR	5-yr EFS 32% 41%	**$P = .02$** Chemo vs. Auto SCT	5-year OS 37% (31-44%) 46% (39-53%)	**$P = .03$** Chemo vs. Auto SCT
	2++	Total Donor (MSD Allo) No Donor (chemo or auto) **(Ph- patients only)**	1031 443 588	NR (15-64)	NR	0%	NR	59 (1-167)	NR	NR	NR	5-year OS **SR** 62% 52% **HR‡** 41% 35%	**$P = .02$** Donor vs. No Donor $P = .20$
[7] Marks 2009 1993-2006 Prospective, Multicenter MRC UKALL XII & ECOG E2993	1+	Total Autologous SCT Chemotherapy (Randomized)	99 54 45	29 (15-59)	27%	NR	100%	84 (3-192)	 NR NR	NR	NR	5-year OS 51% (37-64%) 51% (36-65%)	$P = .90$

(*Continued*)

Table 2. (*Continued*)

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Yeas Median (range)	% WBC >100,000	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS /LFS†	% OS (95%CI)	Signif. OS†
T-lineage ALL only	2+	Total	249										
		Donor (MSD Allo)	110						22%	NR	NR	61% (51-70%)	***P* = .02**
		No Donor (chemo or auto)	139						12%			46% (38-55%)	
[8] Ribera 2005	1+	Total	98		NR	14%		70 (27-113)		ITT 5-year DFS	*P* =.19	5-year OS	*P* = .17
1993-2002		Autologous SCT	50	25 (25-50)			34%		2%	35% ± 12%		37% ± 12%	
Prospective, Multicenter		Chemotherapy	48	27 (15-50)			25%		2%	44% ± 12%		50% ± 12%	
Spanish PETHEMA ALL-93		(Randomized)											
HR§ ALL in CR1	2+	Total	222	27 (15-50)	NR	23%	30%	70 (27-113)		ITT 5-year DFS	*P* not signif	5-year OS	*P* not signif
(Included in Ram, 2010		Donor (MRD Allo)	84						10%	39% (30-48%)		44% (35-52%)	
and Yanada, 2006		No Donor (chemo or auto)	98						2%	33% (23-41%)		35% (25-44%)	
meta-analyses)													
[9] Hunault 2007	1+	Total	27			NR	100%	85.2 (NR)	NR	ITT 7-year RFS	*P* not signif	7-year OS	*P* not signif
1994-1998		Autologous SCT	10	21 (15-59)	0%					60% ± 15%		70% ± 14%	
Prospective, Multicenter		Maintenance Chemo	17	NR	0%					65% ± 12%		65% ± 12%	
GOELAMS T-LBL/ALL GOELAL02		(Randomized)											
T-lineage ALL only													
[11] Fielding 2009	2++	Total	158	40 (15-60)	NR	100%	< 1%	98 (38-171)				ITT 5-year OS	*P* = .20
1993-2004		Donor (MSD Allo)	81						NR			34% (24-45%)	
Prospective, Multicenter		No Donor (ITT)	77						NR			25% (15-34%)	
MRC UKALL XII and ECOG E2993										5-year EFS	***P* <.001**	5-year OS	***P* = .001**
Ph+ ALL in CR1	2++	MSD Allo SCT	45						27%	41% (27-56)	Any Allo	44% (29-59%)	Any Allo
		MUD Allo SCT	31						39%	36% (19-52)	vs. Chemo	36% (19-52%)	vs. Chemo
		Chemotherapy (By actual treatment)	82						NR	9% (3-15%)		19% (10-28%)	
[12] Li 2010	2++	Total	110		>30,000		NR			2-year DFS	***P* = .003**	2-year OS	***P* < .001**
1996-2007		Allo SCT	22	32 (16-51)	40.9%	54.5%		18 (7-14)	5%	48.2% ± 13.9%	Allo SCT	53.1% ± 12.7%	Allo SCT
Retrospective, Single Ctr		Chemo + Imatinib (ICT)	41	36 (15-59)	53.7%	58.5%		12.5 (2-46)	2%	22.1% ± 8.8%	vs. CT	41.6% ± 10%	vs. CT
Ph+ or BCR-ABL+ ALL 87.3% in CR1		Chemotherapy (CT) (pre-imatinib era pts)	47	33 (15-56)	63.8%	51.1%		11 (2-32)	2%	0%	***P* = .016** ICT vs. CT	23.2% ± 6.9%	***P* = .009** ICT vs. CT
[13] Yanada 2006	2+	Total	102	48 (15-63)	NR	NR	NR	13.1 (2-35)		NR	NR	1-year OS	*P* = .94
2002-2005		MSD, MRD, MUD Allo, or UCBT	49						27%			73.3% ± 6.9%	
Prospective, Multicenter JALSG ALL-202 (Chemo + Imatinib) vs. JALSG ALL-93 (Chemo only)		No Allo SCT (Chemo+imatinib or chemo alone)	53						NR			84.8% ± 7.1%	
Ad hoc, 49 Allo SCT **BCR-ABL+** ALL													

(*Continued*)

Table 2. (*Continued*)

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Yeas Median (range)	% WBC >100,000	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS /LFS†	% OS (95%CI)	Signif. OS†
Original Adult ALL EBR data													
[14] Fière 1993 1986-1991 Prospective, Multicenter LALA-87	1+	Total Autologous BMT Chemotherapy (Randomized)	191 95 96	 25 (15-50) 28 (15-48)	> 30,000 37% 33%	 7% 21	 40% 30%	38 (NR)	 4% 3%	ITT 3-year DFS 39% ± 5% 32% ± 5%	*P* = .80	3-year OS 49% ± 5% 42% ± 6%	*P* =.90
[18] Thomas 2004 1994-2002 Prospective, Multicenter LALA-94	1+	Total¶ Autologous SCT Chemotherapy (Randomized)	129 70 59	33 (15-55)	NR	23%	26%	62 (NR)	 7% 0%	3-year DFS 39% 24%	*P* not signif	3-year OS 44% 35%	*P* not signif
	2+	Total Related donor Allo No donor (chemo or auto)	259 100 159						 18% 7%	3-year DFS 47% 34%	***P* = .007** Donor vs. No Donor	NR	NR
[17] Sebban 1994 1986-1991 Prospective, Multicenter LALA-87 ALL in CR1 or CR2	2++	Total Related donor Allo No donor (chemo or auto)	257 116 141	 26 (15-40) 24 (15-40)	> 30,000 42% 40%	 6% 13%	 33% 38%	62 (10-90)	 16% 3%	ITT 5-year DFS 45% ± 5 31% ± 4	*P* = .10	5-year OS 48% ± 5 35% ± 5	*P* =.08
[19] Zhang 1995 1980-1987 Retrospective, Multictr IBMTR & two trials	2++	Total MSD Allo BMT Chemotherapy	718 234 484	NR (15-45)	NR	NR	NR	 100 (28-162) 89 (12-156)	 53% 5%	9-year LFS 34% (28-40%) 32% (27-37%)	*P* >.20	NR	NR
[16] Oh 1998 1988-1990 Retrospective, Multictr IBMTR and JALSG All-87	2++	Total MSD Allo BMT Chemotherapy	290 214 76	 26 (15-51) 29 (15-55)	 19% 16%	 13% 8%	 29% 21%	 48 (7-81) 54 (2-80)	 **≤ 30 y** 32% 3% **> 30 years** 57% 13%	5-year LFS **≤ 30 y** 53% (44-63%) 30% (15-48%) **> 30 years** 30% (20-41%) 26% (13-41%)	 ***P* =.02** Allo vs. Chemo *P* = .70	NR	NR
[15] Messerer 1991 Prospective German ALL/AUL	2++	Total MSD Allo BMT Chemotherapy	76 38 38	NR (15-44)	NR	NR	NR	NR	NR	3-year DFS 34% (16-52%) 34% (16-52%)	*P* not signif	NR	NR

ACM indicates all-cause mortality; ALL, acute lymphoblastic leukemia; Allo, allogeneic; Auto, autologous; BFM, Berlin-Frankfurt-Münster; BMT, bone marrow transplantation; Chemo, chemotherapy; CI, confidence interval; CR, complete remission; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; GOELAMS, Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang; HR, high risk; IBMTR, International Bone Marrow Transplant Registry; ITT, intention-to-treat analysis; JALSG, Japan Adult Leukemia Study Group; LALA, Leucémie Aiguës Lymphoblastique de l'Adulte; LFS, leukemia-free survival; MMRD, mismatched related donor; MRC, Medical Research Council; MRD, matched related donor; MSD, matched sibling donor; MUD, matched unrelated donor; NR, not reported; Ph+, Philadelphia chromosome-positive; OS, overall survival; PETHEMA, Programa para el Tratamiento de Hemopatías Malignas; SCT, stem cell transplantation; SR, standard risk; TRM, treatment-related mortality; UCBT, unrelated cord blood transplant; WBC, white blood cell.

*Quality and strength of evidence definitions are listed in Appendix A, Table 1.

†Not significant: *P* > .05.

‡HR = age >35, WBC ≥100 × 10^9/L; SR = all others.

§HR = at least one of the following: age 30-50, WBC ≥25 × 10^9/L, Ph+, t(4;11) or other 11q23 rearrangement, t(1;19).

¶Patient characteristic and median follow-up data based on 922 total patients in study.

Table 3. Transplantation vs. Chemotherapy for Refractory or Relapsed Adult Acute Lymphoblastic Leukemia

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (range)	% WBC >100,000	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS/ LFS†	% OS (95%CI)	Signif. OS†
Update data published since January 2005													
[20] Fielding 2007 Prospective, Multicenter Subset analysis of MRC UKALL XII & ECOG 2993 ALL in 1st relapse (Duration of CR1 NR)	2++	Total MSD Allo SCT MUD Allo SCT Autologous SCT Chemotherapy (By actual treatment)	302 42 65 13 182	NR (15-60)	NR	33%	NR	54 (1-131)	NR	NR	NR	5-year OS 23% (10%-36%) 16% (7%-26%) 15% (0%-35%) 4% (1%-7%)	***P* <.001** Any SCT vs. Chemo
[21] Cornillon 2005 1993-2000 Retrospect., Single Ctr Refractory ALL (63%) Total (ALL & AML) n = 97 ALL only n = 46 (Duration of CR1 NR)	2+	Total Donor (MSD Allo) No Donor (chemo or auto) (By actual treatment)	46 21 25	20 (4-50)	NR	53%	NR	54 (20-118)	NR	NR	NR	4-year OS Data not provided 4-year OS for ALL overall 12%	***P* <.007** Donor vs. No Donor

ALL indicates acute lymphoblastic leukemia; Allo, allogeneic; AML, acute myeloid leukemia; Auto, autologous SCT; Chemo, chemotherapy; CI, confidence interval; CR, complete remission; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; LFS, leukemia-free survival; MRC, Medical Research Council; MSD, matched related donor; MUD, matched unrelated donor; NR, not reported; OS, overall survival; TRM, treatment-related mortality; SCT, stem cell transplantation; WBC, white blood cell.

*Quality and strength of evidence definitions are listed in Appendix A, Table 1.

†Not significant: $P > .05$.

survival or OS among adult patients with T-lineage ALL in CR1 randomized to autologous SCT versus chemotherapy alone.

Donor versus No Donor

Goldstone et al. [6] also compared Philadelphia chromosome-negative (Ph-negative) patients in a donor versus no-donor analysis and reported a significant difference in 5-year OS in favor of standard risk Ph-negative patients with a donor versus no donor, but no difference in OS for high-risk Ph-negative patients. An unplanned subset analysis [10] reported the benefit of having a donor was greater in high-risk younger (<35 years) versus older patients; however, the difference was not significant.

Marks et al. [7] reported a significant benefit in 5-year OS for T-lineage ALL patients receiving sibling donor SCT versus no donor therapy (autologous SCT or chemotherapy); a difference that was maintained at 10 years.

Ribera et al. [8] reported no significant difference in 5-year DFS or OS between high risk patients with ALL in CR1 who had a donor versus those with no donor. Fielding et al. [11] found no significant difference in 5-year OS between Ph+ ALL patients in an intention-to-treat donor versus no-donor analysis; however, a significant difference in 5-year EFS and OS was reported in favor of Ph+ ALL patients whose actual treatment was an HLA-matched related or HLA-matched unrelated allogeneic SCT versus those who received chemotherapy alone.

Allogeneic SCT versus Chemotherapy ± Imatinib in Ph+/BCR-ABL+ ALL

In a retrospective study by Li et al. [12], Ph+ or BCR-ABL+ ALL patients who received chemotherapy combined with imatinib or underwent an HLA-matched related donor or HLA-compatible donor unrelated allogeneic SCT had significantly better 2-year DFS and 2-year OS compared with patients (preimatinib era) who received chemotherapy alone. Patients who underwent allogeneic SCT also had better survival outcomes than those in the chemotherapy + imatinib group, although there was no statistical significance.

In a prospective, multicenter study, Yanada et al. [13] reported no significant difference in 1-year OS between adult patients with BCR-ABL+ ALL who underwent an HLA-matched related or unrelated allogeneic SCT versus those who did not undergo transplantation, but received chemotherapy + imatinib or chemotherapy alone.

Original ALL EBR Studies

The six high-quality studies [14-19] from the original adult ALL EBR provided seven analyses, including two randomized autologous SCT versus chemotherapy, two donor versus no donor, and three allogeneic bone marrow transplantation (BMT) versus chemotherapy for the treatment of adult ALL in CR1. The quality ratings of these studies ranged from 1+ to 2+. The majority of these studies reported no significant outcome differences; however, one study reported a donor versus no donor (autologous SCT or chemotherapy) advantage in 3-year DFS [18]. Another study reported a significantly better 5-year leukemia-free survival (LFS) in favor of an HLA-matched sibling allogeneic SCT versus chemotherapy alone, but only for patients ≤30 years of age [16].

Transplantation versus Chemotherapy for Refractory or Relapsed Adult ALL

Table 3 presents two studies published since the original ALL EBR, which compared transplantation versus chemotherapy as treatment for relapsed or refractory adult ALL.

Fielding et al. [20] reported a significantly better 5-year OS for adult patients with ALL in first relapse whose actual treatment was any type of SCT (HLA-matched sibling or HLA-matched unrelated allogeneic SCT or autologous SCT) versus those who received chemotherapy alone.

Cornillon et al. [21] reported a significant improved in 4-year OS for adult patients with refractory ALL who actually received an HLA-matched sibling allogeneic SCT versus chemotherapy or autologous SCT (based on donor availability).

There were no studies in the original adult ALL EBR that compared transplantation versus chemotherapy for refractory or relapsed ALL, or for ALL in CR2.

AUTOLOGOUS VERSUS ALLOGENEIC SCT FOR ADULT ALL

There were two studies published since the original ALL EBR, and briefly summarized below, which compared the outcomes of autologous versus myeloablative allogeneic SCT as treatment for adult ALL. The quality of these studies were 2++ and 2+. Table 4 summarizes the study designs, patient populations, and outcomes from this new evidence.

A donor (allogeneic SCT) versus no-donor (autologous SCT) analysis by Cornelisson et al. [22] reported a significantly better 5-year DFS for adult standard risk ALL patients with an HLA-matched related donor who underwent allogeneic SCT versus those without a donor who underwent autologous SCT.

Bishop et al. [23] found equivalent outcomes in 5-year LFS or OS for high-risk adult ALL patients in CR1 or CR2 who underwent an unrelated donor allogeneic SCT versus an autologous SCT.

Table 4. Allogeneic SCT vs. Autologous SCT for Adult ALL

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (range)	% WBC >100,000	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS/ LFS†	% OS (95%CI)	Signif. OS†
Update data published since January 2005													
[22] Cornelissen 2009 1992-2005 Prospective, Multicenter HOVON-18 and -37 SR ALL in CR1	2++	Total Donor (Allo SCT) No Donor (Auto SCT)	257 96 161	 31 (16-55) 26 (15-54)	 15% 11%	 22% 16%	 29% 24%	NR	 16% 3%	5-year DFS 60% ± 5% 42% ± 4%	***P* = .01** Donor vs. No Donor	5-year OS 61% ± 5% 47% ± 5%	*P* =.08
[23] Bishop 2008 1989-1998 Retrospective, Registry NMDP & CIBMTR HR‡ ALL in CR1 or CR2 (46% in CR2)	2+	Total URD Allo SCT Autologous SCT	260 159 101	 27 (18-51) 28 (18-51)	>50,000 52% 68%	NR	 16% 21%	 84 (36-170) 74 (12-141)	2-year 45% 9%	5-year LFS 33% 29%	*P* = .50	5-year OS 34% 29%	*P* =.46
Original adult ALL EBR data													
[24] Ringden 2000 1987-1999 Retrospective, Multictr EBMTR ALL in CR1 (39%)	2++	Total ALL only MSD Allo SCT Twin Allo SCT Autologous SCT	1785 346 23 1416	Overall 27 (1-66) 30 (1-70) 34 (1-77)	NR	NR	Overall 5% 3% 4%	32 (NR)	2-year 9% 17% 9% (ALL)	5-year LFS 61% ± 3% 54% ± 11% 44% ± 1% (ALL)	***P* < .0001** Any Allo vs. Auto (ALL)	NR	NR
[27] Hunault 2004 1994-1998 Prospective, Multicenter GOELAMS GOELAL02 ALL (86% in CR1)	2+	Total Donor (MSD Allo) No Donor (Auto SCT)	156 41 115	 34 (15-52) 27 (15-59)	14%	 24% 13%	 7% 6%	61 (NR)	6 month 15% 3%	6-year DFS 72% ± 7% 33% ± 6%	***P* = .0004** Donor vs. No Donor	6-year OS 75% ± 7% 39% ± 7%	***P* = .0027** Donor vs. No Donor
[18] Thomas 2004 1994-2002 Prospective, Multictr LALA-94 **Ph+/BCR-ABL+ only** ALL in CR1	2+	Total MRD or MUD Allo SCT Autologous SCT	140 75 65	33 (15-55)	NR	100%	0%	62 (NR)	NR	3-year DFS 34% 15%	***P* = .001** Allo vs. Auto	3-year OS 36% 17%	***P* = .009** Allo vs. Auto
[25] Attal 1995 1990-1992 Prospective, Multicenter ALL in CR1	2+	Total Donor (MSD Allo) No Donor (Auto SCT)	120 42 77	31 (15-55)	NR	 12% 18%	 37% 24%	 30.3 (NR) 29.1 (NR)	 12% 2%	3-year DFS 68% (51%-80%) 26% (16%-37%)	***P* < .001** Donor vs. No Donor	NR	NR
[26] Dombret 2002 1994-2000 Prospective, Multicenter LALA-94 **Ph+/BCR-ABL+ only** **ALL in CR1**	2+	Total Donor (MRD or MUD) No Donor (Auto SCT)	103 60 43	42 (17-56)	NR	100%	0%	54 (NR)	NR	NR	NR	ITT 3-year OS 37% (24%-49%) 12% (4%-24%)	***P* = .02**

ALL indicates acute lymphoblastic leukemia; Allo, allogeneic; Auto, autologous; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete remission; EBMTR, European Group for Blood and Marrow Transplantation; EFS, event-free survival; GOELAMS, Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang; HOVON, Dutch-Belgian Cooperative Trial Group for Hematology Oncology; ITT, intention-to-treat; LALA, Leucémie Aiguës Lymphoblastique de l'Adulte; MRD, matched related donor; MSD, matched sibling data; MUD, matched unrelated donor; NMDP, National Marrow Donor Program; NR, not reported; OS, overall survival; Ph+, Philadelphia chromosome-positive; SCT, stem cell transplantation; SR, standard risk; TRM, treatment-related mortality; URD, unrelated donor; WBC, white blood cell.

*Quality and strength of evidence definitions are listed in Appendix A, Table 1.

†Not significant: $P > .05$.

‡HR = t(4;11), 11q23, Ph+, t(8;14), t(1;19), or hypodiploidy.

Table 5. Related vs. Unrelated Allogeneic SCT for Adult ALL

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (range)	Median Duration CR1 (Months)	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS / LFS†	% OS (95%CI)	Signif. OS†
Update data published since January 2005													
[28] Ringden 2009 1995-2004 Retrospective, Registry CIBMTR Total n = 4099 ALL 16% (stratified) (Others—AML, CML)	2++	Total (ALL only) MSD Allo SCT MUD Allo SCT	672 483 189	Overall 38 (18-60) 39 (18-60)	> 12 months 29% 35% (Overall)	NR	NR	Overall 60.3 (1-137) 72.2 (10-135)	NR for ALL only	5-year LFS RR, 1.05 (0.84-1.32) No difference between MSD and MUD for ALL patients	$P = .67$	NR	NR
[29] Lee 2007 1995-2004 Retrospective, Single Ctr ALL (75% in CR1) 88.6% HR	2++	Total MSD Allo SCT MUD/MMUD Allo SCT	201 152 49	 31 (15-52) 22 (15-48)	NR	 34.2% 30.6%	 14.4% 12.2%	63 (25-139+)	NRM 21.4% 29.3%	5-year DFS 49.5% ± 4.1% 42.9% ± 7.1%	$P = .086$	5-year OS 52.4% ± 4.1% 42.1% ± 7.2%	$P = .067$
[30] Dahlke 2006 1990-2001 Retrospective, Single Ctr HR ALL (51% in CR1) 58% ≥ 18 years	2+	Total MRD/MMRD Allo SCT MUD/MMUD Allo SCT	84 46 38	23 (1-60) (Mean)	NR	31%	17%	18 (1-133)	27%	3-year DFS 46% 44%	$P = .86$	3-year OS 44% 42%	$P = .71$
[31] Chim 2007 1990-NR Retrospective, Single Ctr ALL (67% in CR1)	2−	Total MSD Allo BMT MUD Allo BMT	108 87 21	33 (15-56)	NR	35.2%	NR	20.5 (1-195)	 17.3% 14.9%	15-year DFS 28.2% 63.2%	**$P = .03$**	15-year OS 31.6% 67.8%	$P = .10$
[32] Cho 2009 2000-2007 Prospective, Single Ctr HR ALL (81% in CR1) RIC	2−	Total MSD Allo SCT MUD/MMUD Allo SCT	37 27 10	45 (15-63)	NR	43.2%	10.8%	36 (12-96+)	17.7%	3-year DFS 65% ± 9.6% 56% ± 17.1%	$P = .72$	3-year OS 67.8% ± 9.7% 52.5% ± 18.6%	$P = .58$

ALL indicates acute lymphoblastic leukemia; Allo, allogeneic; AML, acute myeloid leukemia; BMT, bone marrow transplantation; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CML, chronic myeloid leukemia; CR, complete remission; DFS, disease-free survival; EFS, event-free survival; HR, high risk; LFS, leukemia-free survival; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MSD, matched sibling donor; MUD, matched unrelated donor; NR, not reported; Ph+, Philadelphia chromosome-positive; OS, overall survival; RIC, reduced-intensity conditioning; SCT, stem cell transplantation; TRM, treatment-related mortality.

*Quality and strength of evidence definitions are listed in Appendix A, Table 1.

†Not significant: $P > .05$.

The details of one high-quality registry study (2++) [24] and four multicenter studies (rated 2+) [18,25-27], which were used to make a treatment recommendation in the original adult ALL EBR regarding the use of autologous SCT versus allogeneic SCT, are presented in Table 4. All five studies found a significant improvement in DFS or LFS, and/or OS for patients who underwent an HLA-matched related or HLA-matched unrelated donor allogeneic SCT versus autologous SCT.

RELATED VERSUS UNRELATED ALLOGENIC SCT FOR ADULT ALL

There were five studies published since the original ALL EBR, and summarized briefly below, which compared related versus unrelated donor allogeneic SCT as treatment for adult patients with ALL. Table 5 presents a detailed summary of the study designs, patient populations, and outcomes from this new evidence, ranging in quality from 2++ to 2−. Recent and continuing improvements in unrelated donor HLA typing and selection impacting overall outcomes are not reflected in the earlier reports.

In a retrospective analysis of the Center for International Blood and Marrow Transplant Research data, Ringden et al. [28] reported no difference in 5-year LFS between adult ALL patients who underwent an HLA-matched sibling allogeneic SCT versus an HLA-matched unrelated donor allogeneic SCT.

In a retrospective analysis of single center data, Lee et al. [29] reported comparable 5-year DFS and 5-year OS in adult ALL patients who underwent an HLA-matched sibling donor allogeneic SCT versus an HLA-matched or mismatched unrelated donor allogeneic SCT.

Dahlke et al. [30] reported comparable 3-year DFS and 3-year OS in older adult patients (58% ≥58 years) who underwent an HLA-matched or mismatched related allogeneic SCT versus an HLA-matched or mismatched unrelated donor allogeneic SCT.

In a long-term retrospective analysis of single center data, Chim et al. [31] reported significantly better 15-year DFS, but no difference in 15-year OS, in adult ALL patients who underwent an HLA-matched unrelated donor allogeneic BMT versus an HLA-matched sibling allogeneic BMT.

Cho et al. [32] reported no significant difference in 3-year DFS or 3-year OS in a prospective, single center study of adult patients with ALL (majority in CR1) who underwent an HLA-matched sibling allogeneic SCT versus an HLA-matched or unmatched unrelated donor allogeneic SCT following a reduced-intensity conditioning (RIC) regimen.

In the original adult ALL EBR there was one multicenter study that compared related versus unrelated allogeneic SCT. Kiehl et al. [33] reported no significant difference in 5-year DFS in 221 patients with ALL in CR1 who underwent an HLA-matched related versus an HLA-matched unrelated allogeneic SCT (2+ rating; not presented in Table 5).

OTHER COMPARATIVE STUDIES OF ADULT ALL

There were 12 comparative studies published since the original ALL EBR, and summarized briefly below, which investigated the impact of transplantation-related factors, such as hematopoietic cell source (unrelated bone marrow versus cord blood, n = 2 studies), pre- and/or post-SCT imatinib therapy (n = 4 studies), induction therapy regimen (n = 2 studies), induction versus no reinduction therapy (n = 1 study), and conditioning regimen (n = 3 studies) on survival outcomes in adult patients with ALL. Table 6 presents a detailed summary of the study designs, patient populations, and outcomes from this new evidence. The quality ratings of these 12 studies ranged from 1++ to 2+. There were no comparable studies in the original adult ALL EBR.

Unrelated Donor Bone Marrow (BM) versus Cord Blood SCT

Ferrá et al. [34] reported no significant difference in 5-year DFS or 5-year OS between adult high risk ALL patients who underwent an unrelated donor BMT versus a cord blood transplantation. Similarly, Atsuta et al. [35] reported no significant difference in 2-year LFS or 2-year OS between adult ALL patients who underwent an unrelated donor BMT versus a cord blood transplantation.

Imatinib versus No Imatinib Therapy

In a retrospective, registry analysis, Mizuta et al. [36] reported significantly improved 3-year DFS and 3-year OS in adult Ph+ ALL patients who received imatinib therapy pre- and/or post-allogeneic SCT versus those in a preimatinib era historical control who did not. In a prospective, multicenter study, Bassan et al. [37] also reported significant improvement in 5-year DFS and 5-year OS in adult Ph+ ALL patients who received imatinib therapy pre- and/or post-SCT (autologous or allogeneic) versus those who did not receive imatinib. In addition, Lee et al. [38] reported significantly improved 3-year DFS and 3-year OS in adult Ph+ ALL patients who received imatinib therapy pre- and/or post-allogeneic SCT versus those in a preimatinib era historical control who did not. In a retrospective, single center study, Burke et al. [39] reported no significant difference in 2-year LFS or 2-year OS between adult Ph+ ALL patients who received imatinib therapy pre- and/or postallogeneic SCT versus those who did not receive imatinib or who received it only after relapse.

Table 6. Other Comparative Studies of Adult ALL

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (Range)	Median Duration CR1 (Months)	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS /LFS†	% OS (95%CI)	Signif. OS†
Update data published since January 2005													
UNRELATED DONOR BMT VS. UNRELATED CORD BLOOD TRANSPLANT													
[34] Ferrá 2010	2++	Total	149	29 (15-59)	NR					5-year DFS	*P* = NS	5-year OS	*P* = NS
2000-2007		URD Allo SCT	87			59%	16%	20 (.3-96)	48%	21% (11-31%)		22 (11%-33%)	
Retrospective, Multictr		single UCBT	62			63%	23%	23 (2.7-101)	31%	22% (8-36%)		33 (18%-48%)	
HR ALL (54% in CR1)													
[35] Atsuta 2009	2+	Total (ALL only)	336		NR		NR	NR	2-year	2-year LFS	*P* = .06	2-year OS	*P* = .40
2000-2005		URD Allo BMT	222	32 (16-59)			23%			25%	51%	57%	
Retrospective, Registry		single UCBT	114	34 (16-58)			38%			24%	45%	49%	
JCBBN & JMDP													
Total n = 820 (inc. AML)													
ALL 41% (stratified)													
57% ALL in CR1													
IMATINIB VS. NO IMATINIB THERAPY PRE- AND/OR POST-SCT IN PH+ ALL													
[36] Mizuta 2010	2++	Total	173		NA	100%	NR			3-year DFS	***P* = .039**	3-year OS	***P* = .015**
2002-2005		Imatinib Pre Allo	51	38 (15-64)				31.2 (12-55)		58% (42-71%)		65% (49%-78%)	
Retrospective, Registry		No Imatinib (pre-imatinib	122	38 (15-57)				82.8 (12-137)		37% (29-46%)		44% (35%-52%)	
JALSG ALL 202,		historical control)											
JSHCT, and JMDP													
Ph+ ALL in CR1													
[37] Bassan 2010	2++	Total	94		NA	100%	NR	60 (7-110)		5-year DFS	***P* =.044**	5-year OS	***P* = .009**
2000-NR		Imatinab Pre/Post SCT	59	45 (20-66)					18%	39% (26-52%)		38% (19-57%)	
Prospective, Multicenter		No Imatinib Pre/Post SCT	35	50 (20-66)					13%	25% (8-37%)		23% (8-34%)	
NILG 09/00 trial													
Ph+ ALL (87% in CR1)		(SCT = Allo or Auto)											
[38] Lee 2005	2+	Total	62		NA	100%	NR		NRM	3-year DFS	***P* < .001**	3-year OS	***P* < .001**
2000-2003		Imatinib Pre Allo	29	36 (18-55)				25 (12-45+)	18.7%	78.1% ± 11.6%		78.1% ± 11.6%	
1996-2000 Historical										5-year DFS		5-year OS	
Prospective, Single Ctr		No Imatinib (pre-imatinib	33	35 (15-48)				51 (40-72+)	27%	38.7% ± 8.8%		38.7% ± 8.8%	
Ph + ALL (86% in CR)		historical control)											
[39] Burke 2009	2+	Total	32	Mean	NR		NR	11 (1-58)		2-year RFS	*P* = .12	2-year OS	*P* = .19
1999-2006		Imatinab Pre/Post Allo SCT	15	18 (1-42)		87%			20%	67%		61%	
Retrospective, Single Ctr		No Imatinab Pre/Post SCT	17	29 (3-55)		100%			29%	35%		41%	
Ph+ ALL (63% in CR1)		(or only after relapse)											
COMPARISON OF INDUCTION THERAPIES													
[40] Labar 2010	1++	Total	325		CR rate			79.2 (6-140)		6-year EFS	*P* = .82	6-year OS	*P* = .45
1995-2003		Dexamethasone	163	32 (15-68)	80.4%	18%	31%		18.3%	25.9% ± 3.6%		30.6%	
Prospective, Multicenter		Prednisolone	162	34 (15-72)	76.5%	17%	25%		10.5%	28.7% ± 3.5%		35.2%	
EORTC ALL-4		(Randomized)											
Untreated ALL		(prior to allo, auto, or chemo)											

(*Continued*)

Table 6. (*Continued*)

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (Range)	Median Duration CR1 (Months)	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/LFS (95% CI)	Signif. EFS/DFS /LFS†	% OS (95%CI)	Signif. OS†
[41] Wassmann 2006 2001-2004 Prospective, Multicenter **Ph+** ALL (77% in CR1)	2+	Total Alternating Chemo + Imatinib Concurrent Chemo + Imatinib (prior to allo or auto SCT)	92 47 45	 46 (21-65) 41 (19-63)	CR rate 78% 56%	100%	NR	NR		NR	NR	2-year OS 36.2% ± 7% 43% ± 9%	$P = .97$
COMPARISON OF REINDUCTION VS. NO REINDUCTION THERAPY PRE-ALLO SCT ± DLI FOR REFRACTORY/RELAPSED ALL													
[42] Terwey 2008 1995-2006 Retrospective analysis Single Center Refract/Relapsed ALL	2+	Total No Reinduction (31% DLI) Reinduction (40% DLI) (prior to allo SCT)	60 19 41	 34 (18-49) 26 (17-54)	NR	 37% 17%	 10% 29%	 68 (28-109) 25.8 (17-141)	 26% 34%	NR	NR	5-year OS 47% 18%	**$P = .039$**
COMPARISON OF CONDITIONING REGIMENS													
[43] Marks 2010 1995-2006 Retrospective, Registry CIBMTR **Ph-negative** ALL (53% in CR1)	2++	Total Myeloablative RIC (MSD or URD Allo SCT)	1521 1428 93	 28 (16-62) 45 (17-66)	>12 mo 54% 61%	0%	 21% 20%	 54 (3-166) 38 (3-93)	3-year 33% 32%	3-year DFS 41% (38%-44%) 32% (22%-43%)	$P = .12$	3-year OS 43% (40-46%) 38% (28-49%)	$P = .39$
[44] Kojima 2005 1998-2002 Retrospective, Multictr Total 207 ALL n = 35 (stratified) (AML, CML, MDS)	2+	Total (ALL only) Myeloablative RIC (prior to allo SCT)	35 27 8	(Overall) 52 (50-59) 57 (50-59)	NA	NR	NR	(Overall) 31.6 (10-64) 20.3 (10-38)	(ALL) 41% 25%	NR	NR	2-year OS (ALL) 33% (16%-51%) 50 (15%-85%)	$P = NR$
[45] Deconinck 2005 1986-1992 Retrospective, Multictr LALPOF (standard) GOLEAL1 (intensive) ALL in CR1	2+	Total Standard Ind. & Cond. Intensive Ind. and Cond. (actually rec'd allo SCT)	35 18 15	 20 (17-40) 29 (19-46)	NA	 11% 27%	 33% 20%	 121 (114-157) 47 (39-51)	 11% 40%	4-year EFS 66% ± 11% 35% ± 11%	**$P = .02$**	4-year OS 71% ± 12% 36% ± 13%	**$P = .009$**

ALL indicates acute lymphoblastic leukemia; Allo, allogeneic; AML, acute myeloid leukemia; Auto, autologous; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CML, chronic myeloid leukemia; Cond., conditioning; CR, complete remission; DFS, disease-free survival; DLI, donor lymphocytic infusions; EFS, event-free survival; EORTC, European Organization for Research and Treatment of Cancer; GOLEAL, Groupe Ouest Est des Leucémies Aiguës Lymphoblastiques; HR, high risk; Ind., induction; JALSG, Japan Adult Leukemia Study Group; JCBBN, Japan Cord Blood Bank Network; JMDP, Japan Marrow Donor Program; LALPOF, Leucémie Aiguë Lymphoblastique Paris-Ouest-France; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NILG, Northern Italy Leukemia Group; NR, not reported; Ph+, Philadelphia chromosome-positive; OS, overall survival; RIC, reduced-intensity conditioning; SCT, stem cell transplantation; TRM, treatment-related mortality, UCBT, unrelated cord blood transplant; URD, unrelated donor.

*Quality and strength of evidence definitions are listed in Appendix A, Table 1.

†Not significant: $P > .05$.

Comparison of Induction Therapies

In a prospective, multicenter study Labar et al. [40] reported no significant difference in 6-year EFS or 6-year OS between adult ALL patients randomized to receive dexamethasone versus prednisolone as part of their induction therapy prior to receiving further chemotherapy or undergoing allogeneic or autologous SCT.

Wassman et al. [41] reported no significant difference in 2-year OS between adult patients with Ph+ ALL who received alternating or concurrent schedules of chemotherapy and imatinib as induction therapy prior to undergoing an allogeneic or autologous SCT.

Comparison of Reinduction versus No-Reinduction Therapy for Refractory/Relapsed ALL

A retrospective analysis of a prospective, single-center treatment algorithm by Terwey et al. [42] found that adult patients with refractory or relapsed ALL who did *not* received reinduction chemotherapy prior to allogeneic SCT (31% received prophylactic donor lymphocytic infusions [DLI] starting after day + 60) had significantly better 5-year OS than patients who *did* receive reinduction chemotherapy prior to allogeneic SCT (40% received prophylactic DLI).

Comparison of Conditioning Regimens

Marks et al. [43] reported no significant differences in 3-year DFS or 3-year OS, and Kojima et al. [44] reported no significant difference in 2-year OS, in comparisons of RIC versus myeloablative conditioning prior to allogeneic SCT in adult ALL patients.

In a retrospective analysis of two prospective trials, Deconinck et al. [45] reported significantly worse 4-year EFS and 4-year OS in patients who underwent an intensified versus standard dose induction, consolidation, and myeloablative conditioning regimen prior to allogeneic SCT, primarily because of an increased toxic death rate in the intensive protocol.

NONCOMPARATIVE STUDIES OF TRANSPLANTATION FOR ADULT ALL

There were 14 noncomparative cohort studies [46-59] published since the original EBR that examined the use of SCT as therapy for adult ALL. The design, methodology, and outcomes data from these noncomparative studies are summarized in Appendix B (online only). The studies represent non-randomized single- or multi-institutional experiences with various transplantation techniques or retrospective analyses of transplant registry data. The quality of the noncomparative SCT studies ranged from 2+ to 2−. These noncomparative data on SCT for ALL provide additional, though lower level evidence, on SCT for ALL and thus are cited to provide added perspective on the published data.

AREAS OF NEEDED RESEARCH AND ONGOING STUDIES

After reviewing the updated evidence on the use of SCT for adult ALL, the expert panel identified several important areas of needed research. Some of these areas are being investigated by ongoing studies that are currently accruing patients, maturing follow-up, or which have been published in abstract form. The areas of needed research are grouped by topic, numbered, and followed by a brief description of some relevant ongoing studies, with some comment on their potential contribution to future treatment decisions. None of these studies were used as evidence for the review or for making treatment recommendations. This section is provided for the reader's information only.

Allogeneic SCT versus Chemotherapy

1. Reevaluate allogeneic SCT versus more intensive chemotherapy regimens, especially in younger (<35 years) adults, and in the context of biologic therapies and Tyrosine Kinase Inhibitors (TKIs) (for Ph+ ALL).

The ongoing studies summarized below follow a biologic allocation and comparison based upon donor availability in an attempt to perform a statistically randomized study that avoids bias. Intent-to-treat, donor versus no-donor comparisons avoid the bias of assessing only those with a donor and who were considered medically suitable to proceed with SCT; however, they can still result in confounding because of other types of SCT performed in those without a matched related donor.

A meta-analysis by Pidala et al. [60] consisted of aggregate outcome data from 14 trials and provided a donor versus no-donor comparison in 3215 adult patients to determine whether or not there is a survival benefit to allogeneic SCT for ALL in CR1.

Litzow et al. [61] presented the UKALLXII/E2993 trial on 1229 adult (14-65 years) Ph-negative B-ALL patients who were randomized to autologous SCT or to consolidation and maintenance chemotherapy. Patients <55 years of age with a matched sibling donor were biologically assigned to myeloablative allogeneic SCT. Analyses included chemotherapy versus autologous SCT and donor versus no-donor comparisons.

Leguay et al. [62] reported the outcomes of 75 young adult (15-59) with Ph-negative ALL. Of the 70 patients who attained CR, 54 (77%) were considered high risk and eligible for allogeneic SCT. Of these, 30 had a donor and received a SCT, and 24 received intensification and maintenance chemotherapy (donor/no-donor comparison). Of the remaining

16 patients in CR, two died before evaluation and 14 with low-risk ALL received chemotherapy alone followed by maintenance therapy.

A clinical trial (NCT00792948) sponsored by the Southwest Oncology Group is currently accruing patients to compare combination therapy (HyperCVAD + dasatinib) with or without allogeneic SCT for patients with Ph+ or BCR-ABL+ ALL. The estimated enrollment is 85 patients, and the primary clinical outcomes of interest are 1-year relapse-free survival and OS. This trial will provide preliminary estimates of efficacy, but future study of newer TKIs may yield better outcomes or identify situations where one agent, dose, or schedule is preferred.

Allogeneic SCT versus Chemotherapy ± TKI Therapy

2. Assess the ability of TKIs to reduce the leukemia murden pre- or post-SCT in Ph+ ALL patients and evaluate whether this can improve survival outcomes after autologous and allogeneic. Study of different TKIs, dose, and schedule will be important.

In a prospective, Northern Italy Leukemia Group study, Rambaldi et al. [63] investigated the clinical outcomes of adult Ph+ ALL patients who underwent allogeneic SCT (n = 58) versus standard chemotherapy (n = 33), or autologous SCT (n = 9) with or without imatinib as part of induction/consolidation therapy.

Fielding et al. [64] reported the final results of the UKALLXII/COG2993 trial, comparing the outcomes of three nonrandomized subgroups of Ph+ ALL patients on imatinib versus no imatinib, early versus late imatinib, and allogeneic SCT versus chemotherapy maintenance including imatinib.

There are several ongoing clinical trials investigating SCT with or without TKI therapy. The Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) is sponsoring a phase II trial (NCT00458848) comparing the effectiveness of combination chemotherapy with or without imatinib and/or peripheral blood SCT for adult Ph+ ALL patients. The estimated enrollment is 253 patients, and the primary outcomes of interest are 1-year DFS and OS.

The Group for Research in Adult Acute Lymphoblastic Leukemia is sponsoring a randomized clinical trial (NCT00327678) comparing standard versus intensified induction for Ph-negative T or B ALL, rituximab versus no rituximab with or without allogeneic SCT for Ph-negative B ALL, and imatinib-based induction versus chemotherapy plus imatinib induction with or without allogeneic SCT based on donor availability and minimal residual disease status after induction for Ph+ ALL. The primary outcomes of interest are EFS and OS and the percentage of patients with minimal residual disease after induction or consolidation therapy. The estimated enrollment is 1080 patients.

A clinical trial (NCT01256398) sponsored by the Cancer and Leukemia Group B and the National Cancer Institute is investigating the use of dasatinib followed by allogeneic or autologous SCT as treatment for older (≥50 years) adult patients with *de novo* Ph+ ALL. The estimated enrollment is 66 patients, and the primary outcome measure is 3-year DFS.

The Sheba Medical Center is sponsoring a clinical trial (NCT00750659) investigating the use of nilotinib pre- and post-allogeneic SCT for adult Ph+ ALL or advanced chronic myeloid leukemia patients. The estimated enrollment is 24 patients, and the primary measures are safety and response at one year.

Minimal Residual Disease (MRD)

3. Improvement in the detection and monitoring of MRD during initial treatment to guide individual patient eligibility and timing of allogeneic SCT.

In a Polish Adult Leukemia Group study (PALG 5-2007), Giebel et al. [65] compared the outcomes of 108 adult patients with ALL who received an individualized therapeutic approach with treatment intensity adjusted to MRD status and age, versus those from the PALG4-2002 trial in which MRD status was not taken into account for treatment decisions. In both studies, patients with standard risk ALL received induction/consolidation followed by maintenance, whereas those with high-risk disease were referred for allogeneic SCT.

The Johann Wolfgang Goethe University Hospitals clinical trial (NCT00198991) is a multicenter study of treatment optimization in adult ALL based on the risk of relapse and MRD status. The primary outcomes measures are remission rate, remission duration, DFS, and OS. Secondary measures include realization of SCT, toxicity, and course of MRD. The estimated enrollment is 1250 patients.

4. Monitoring of MRD after SCT to detect early post-SCT relapse in need of preemptive therapy. This may indicate patients at higher risk of early recurrence, but effective therapy will also need to be developed.

Tang et al. [66] retrospectively analyzed the MRD status at day +100 post-allogeneic SCT of 52 high-risk adult patients with ALL (n = 25; acute myelogenous leukemia [AML], n = 27) to evaluate the prognostic value of MRD pre- and post-SCT.

RIC for Allogeneic SCT

5. Indications for using RIC versus myeloablative conditioning regimens for allogeneic SCT. The broad range of conditioning intensity will need further study, adjusted for a patient's tolerance of conditioning toxicity balanced against the risk of relapse. It is likely that randomized comparative trials will be essential.

The Asan Medical Center is sponsoring a clinical trial (NCT01037764) of adult patients with

ALL, comparing busulfan-cyclophosphamide versus busulfan-fludarabine-antithymocyte globulin conditioning regimens followed by BMT or peripheral blood stem cell transplantation (PBSCT), respectively, using HLA-matched sibling donors, HLA-matched unrelated donors, or HLA-mismatched related donors. Patients with an HLA-matched unrelated or mismatched related donor will receive the busulfan-fludarabine-antithymocyte globulin conditioning and PBSCT. The outcome measures of interest include 3-year relapse rate, LFS, treatment-related mortality (TRM), and OS, and the estimated enrollment is 100 patients. Heterogeneity in patients, donor types, and disease risk status may confound conclusions in this modest sized trial.

Cord Blood Transplantation

6. Evaluation of cord blood transplantation techniques, such as single unit, double unit, and ex vivo expansion, to improve survival outcomes and reduce TRM. Larger multicenter experience will be needed to more fully evaluate the broader applicability of cord blood grafting for adults with ALL.

Brunstein et al. [67] investigated the effect of unrelated donor stem cell source on outcomes in adult ALL (n = 62) or AML (n = 523) patients, comparing PBSCT versus double cord blood transplantation after an RIC regimen.

Rocha et al. [68] compared acute leukemia patients (38% ALL, 62% AML) who underwent a double versus single cord blood transplantation in CR1, CR2, or CR3. The clinical outcome of interest was 3-year LFS and stratified by disease.

Post-SCT Patient Status and Management

7. Assessment of patient quality of life and functional status after successful SCT.

A clinical trial sponsored by the University Health Network, Toronto (NCT01148927) is evaluating the quality of life of long-term survivors of adult ALL who were treated with a modified Dana Farber Cancer Institute ALL protocol (91-01). Patients over 18, and who have completed the protocol at least three months prior and are in complete rmission are included. The patients complete several well-validated questionnaires assessing various quality of life issues of concern to these patients. Enrollment is estimated at 50 patients.

8. Assess the impact of management plans and follow-up care to facilitate better quality of life for ALL patients, regardless of treatment.

There are no ongoing studies specifically for ALL that address this area of needed research.

STRENGTHS/LIMITATIONS AND DISCUSSION

The strengths of this updated systematic evidence-based review are the details about each study's design and outcomes conveyed in the summary tables for each major section, and the consensus treatment recommendations made by the adult ALL expert panel.

A limitation is the exclusion of nonpeer-reviewed data. Unpublished data can represent "negative" findings that could lead to publication bias; however, the inclusion of high-quality, peer-reviewed publicly available data was of paramount importance. With the exception of the Ongoing Studies section, data published in abstract form were not included in this review because of the inadequate details of study design or patient characteristics, making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial difficult.

The quality of this systematic EBR is affected by treatment modalities that vary over time. Chemotherapy regimens, HLA typing techniques, novel pre- and post-SCT biologic and TKI therapies, and post-SCT supportive care change considerably over the course of these reviews and updates. The clinical research process is lengthy, making data from many of these studies outmoded by the time of publication. Much of the new data presented in this updated EBR may be obsolete in terms of the current standard of care, stressing the need for more timely updates of the EBRs. In addition, the lengthy process of conducting and reporting clinical research emphasizes the need to identify surrogate endpoints or molecular markers that are predictive of long-term survival in adult ALL patients. Further delineation of clinical risk factors may facilitate appropriate selection of ALL patients for SCT.

ACKNOWLEDGMENTS

Financial disclosure: Major funding for this review was provided by the National Marrow Donor Program. The authors have no financial conflicts of interest to disclose.

The American Society for Blood and Marrow Transplantation and Drs. Hahn and McCarthy are indebted to the members of the Adult ALL EBR Update Expert Panel and the ASBMT Evidence-Based Review Steering Committee, who voluntarily and enthusiastically participated in this endeavor. The authors of this Adult ALL EBR Update and the American Society for Blood and Marrow Transplantation thank the National Marrow Donor Program, and especially Jeffrey Chell, MD, and Michael Boo, for their support of this project. The authors acknowledge C. Fred LeMaistre, MD, for pioneering and supporting this effort and

Thomas Joseph, MPS, CAE, for his invaluable administrative assistance. The authors are grateful to all the patients who participated in the clinical trials, which led to the evidence upon which this EBR update is based. Major funding for this study was provided by the National Marrow Donor Program.

REFERENCES

1. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant*. 2006;12:1-30.
2. Ram R, Gafter-Gvili A, Vidal L, et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission. *Cancer*. 2010;116:3447-3457.
3. Orsi C, Bartolozzi B, Messori A, Bosi A. Event-free survival and cost-effectiveness in adult acute lymphoblastic leukaemia in first remission treated with allogeneic transplantation. *Bone Marrow Transplant*. 2007;40:643-649.
4. Yanada M, Matsuo K, Suzuki T, Naoe T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. *Cancer*. 2006;106:2657-2663.
5. Dhedin N, Dombret H, Thomas X, et al. Autologous stem cell transplantation in adults with acute lymphoblastic leukemia in first complete remission: analysis of the LALA-85, -87 and -94 trials. *Leukemia*. 2006;20:336-344.
6. 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.
7. Marks DI, Paietta EM, Moorman AV, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). *Blood*. 2009;114:5136-5145.
8. Ribera JM, Oriol A, Bethencourt C, et al. Comparison of intensive chemotherapy, allogeneic or autologous stem cell transplantation as post-remission treatment for adult patients with high-risk acute lymphoblastic leukemia. Results of the PETHEMA ALL-93 trial. *Haematologica*. 2005;90:1346-1356.
9. Hunault M, Truchan-Graczyk M, Caillot D, et al. Outcome of adult T-lymphoblastic lymphoma after acute lymphoblastic leukemia-type treatment: a GOELAMS trial. *Haematologica*. 2007;92:1623-1630.
10. Goldstone AH, Richards SM, Fielding AK, Rowe JM. Response: chemotherapy or allografting for young adults with high-risk ALL? *Blood*. 2008;111:5755 (Response to Letter to the Editor.).
11. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. *Blood*. 2009;113:4489-4496.
12. Li Y, Zou D, Zhao Y, et al. Clinical characteristics and outcomes of adults with Philadelphia chromosome positive and/or bcr-abl positive acute lymphoblastic leukemia: a single center study from China. *Leuk Lymphoma*. 2010;51:488-496.
13. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol*. 2006;24:460-466.
14. Fiere D, Lepage E, Sebban C, et al. Adult acute lymphoblastic leukemia: a multicentric randomized trial testing bone marrow transplantation as postremission therapy. The French Group on Therapy for Adult Acute Lymphoblastic Leukemia. *J Clin Oncol*. 1993;11:1990-2001.
15. Messerer D, Neiss A, Aydemir U, Hoelzer D, Arnold R. How can disease-free survival of adult ALL patients with or without transplants be compared? *Onkologie*. 1991;14:53-55.
16. Oh H, Gale RP, Zhang MJ, et al. Chemotherapy versus HLA-identical sibling bone marrow transplants for adults with acute lymphoblastic leukemia in first remission. *Bone Marrow Transplant*. 1998;22:253-257.
17. Sebban C, Lepage E, Vernant JP, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *J Clin Oncol*. 1994;12:2580-2587.
18. Thomas X, Boiron J-M, 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.
19. Zhang M-J, Hoelzer D, Horowitz M, et al. Long-term follow-up of adults with acute lymphoblastic leukemia in first remission treated with chemotherapy or bone marrow transplantation. *Ann Intern Med*. 1995;123:428-431.
20. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007;109:944-950.
21. Cornillon J, Fawaz A, Depil S, et al. Outcome of patients less than 55 years of age with high-risk acute leukemia who did not have an human leukocyte antigen-identical related donor: a long-term study of 97 consecutive patients. *Leuk Lymphoma*. 2005;46:841-849.
22. 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.
23. Bishop MR, Logan BR, Gandham S, et al. Long-term outcomes of adults with acute lymphoblastic leukemia after autologous or unrelated donor bone marrow transplantation: a comparative analysis by the National Marrow Donor Program and Center for International Blood and Marrow Transplant Research. *Bone Marrow Transplant*. 2008;41:635-642.
24. Ringdén O, Labopin M, Gorin NC, et al. Is there a graft-versus-leukaemia effect in the absence of graft-versus-host disease in patients undergoing bone marrow transplantation for acute leukaemia? *Br J Haematol*. 2000;111:1130-1137.
25. Attal M, Blaise D, Marit G, et al. Consolidation treatment of adult acute lymphoblastic leukemia: a prospective, randomized trial comparing allogeneic versus autologous bone marrow transplantation and testing the impact of recombinant interleukin-2 after autologous bone marrow transplantation. BGMT Group. *Blood*. 1995;86:1619-1628.
26. Dombret H, Gabert J, Boiron J-M, 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.
27. Hunault M, Harousseau J-L, Delain M, et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. *Blood*. 2004;104:3028-3037.
28. Ringden O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood*. 2009;113:3110-3118.
29. Lee S, Cho BS, Kim SY, et al. Allogeneic stem cell transplantation in first complete remission enhances graft-versus-leukemia effect in adults with acute lymphoblastic leukemia: antileukemic activity of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2007;13:1083-1094.

30. Dahlke J, Kroger N, Zabelina T, et al. Comparable results in patients with acute lymphoblastic leukemia after related and unrelated stem cell transplantation. *Bone Marrow Transplant*. 2006; 37:155-163.
31. Chim CS, Lie AKW, Liang R, Au WY, Kwong YL. Long-term results of allogeneic bone marrow transplantation for 108 adult patients with acute lymphoblastic leukemia: favorable outcome with BMT at first remission and HLA-matched unrelated donor. *Bone Marrow Transplant*. 2007;40:339-347.
32. Cho BS, Lee S, Kim YJ, et al. Reduced-intensity conditioning allogeneic stem cell transplantation is a potential therapeutic approach for adults with high-risk acute lymphoblastic leukemia in remission: results of a prospective phase 2 study. *Leukemia*. 2009; 23:1763-1770.
33. Kiehl MG, Kraut L, Schwerdtfeger R, et al. Outcome of allogeneic hematopoietic stem-cell transplantation in adult patients with acute lymphoblastic leukemia: no difference in related compared with unrelated transplant in first complete remission. *J Clin Oncol*. 2004;22:2816-2825.
34. Ferra C, Sanz J, de la Camara R, et al. Unrelated transplantation for poor-prognosis adult acute lymphoblastic leukemia: long-term outcome analysis and study of the impact of hematopoietic graft source. *Biol Blood Marrow Transplant*. 2010;16:957-966.
35. Atsuta Y, Suzuki R, Nagamura-Inoue T, et al. Disease-specific analyses of unrelated cord blood transplantation compared with unrelated bone marrow transplantation in adult patients with acute leukemia. *Blood*. 2009;113:1631-1638.
36. Mizuta S, Matsuo K, Yagasaki F, et al. Pre-transplant imatinib-based therapy improves the outcome of allogeneic hematopoietic stem cell transplantation for BCR-ABL-positive acute lymphoblastic leukemia. *Leukemia*. 2010;25:41-47.
37. Bassan R, Rossi G, Pogliani E, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group Protocol 09/00. *J Clin Oncol*. 2010;28:3644-3652.
38. Lee S, Kim YJ, Min CK, et al. The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2005;105:3449-3457.
39. Burke MJ, Trotz B, Luo X, et al. Allo-hematopoietic cell transplantation for Ph chromosome-positive ALL: impact of imatinib on relapse and survival. *Bone Marrow Transplant*. 2009;43:107-113.
40. Labar B, Suciu S, Willemze R, et al. Dexamethasone compared to prednisolone for adults with acute lymphoblastic leukemia or lymphoblastic lymphoma: final results of the ALL-4 randomized, phase III trial of the EORTC Leukemia Group. *Haematologica*. 2010;95:1489-1495.
41. Wassmann B, Pfeifer H, Goekbuget N, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood*. 2006;108:1469-1477.
42. Terwey TH, Massenkeil G, Tamm I, et al. Allogeneic SCT in refractory or relapsed adult ALL is effective without prior reinduction chemotherapy. *Bone Marrow Transplant*. 2008;42:791-798.
43. Marks DI, Wang T, Perez WS, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. *Blood*. 2010;116:366-374.
44. Kojima R, Kami M, Kanda Y, et al. Comparison between reduced intensity and conventional myeloablative allogeneic stem-cell transplantation in patients with hematologic malignancies aged between 50 and 59 years. *Bone Marrow Transplant*. 2005;36:667-674.
45. Deconinck E, Hunault M, Milpied N, et al. Intensive therapy before or during the conditioning regimen of allogeneic marrow transplantation in adult acute lymphoblastic leukemia patients: we must choose to reduce toxicity—a Groupe Ouest-Est d'Etude des Leucémies et Autres Maladies du Sang study. *Biol Blood Marrow Transplant*. 2005;11:448-454.
46. Huang XJ, Liu DH, Liu KY, et al. Treatment of acute leukemia with unmanipulated HLA-mismatched/haploidentical blood and bone marrow transplantation. *Biol Blood Marrow Transplant*. 2009;15:257-265.
47. Fouillard L, Labopin M, Gratwohl A, et al. Results of syngeneic hematopoietic stem cell transplantation for acute leukemia: risk factors for outcomes of adults transplanted in first complete remission. *Haematologica*. 2008;93:834-841.
48. Marks DI, Perez WS, He W, et al. Unrelated donor transplants in adults with Philadelphia-negative acute lymphoblastic leukemia in first complete remission. *Blood*. 2008;112:426-434.
49. Hamaki T, Kami M, Kanda Y, et al. Reduced-intensity stem-cell transplantation for adult acute lymphoblastic leukemia: a retrospective study of 33 patients. *Bone Marrow Transplant*. 2005;35: 549-556.
50. Duval M, Klein JP, He W, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. *J Clin Oncol*. 2010;28:3730-3738.
51. Yanada M, Naoe T, Iida H, et al. Myeloablative allogeneic hematopoietic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia in adults: significant roles of total body irradiation and chronic graft-versus-host disease. *Bone Marrow Transplant*. 2005;36:867-872.
52. Mohty M, Labopin M, Tabrizzi R, et al. Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. *Haematologica*. 2008;93:303-306.
53. Shigematsu A, Kondo T, Yamamoto S, et al. Excellent outcome of allogeneic hematopoietic stem cell transplantation using a conditioning regimen with medium-dose VP-16, cyclophosphamide and total-body irradiation for adult patients with acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2008;14: 568-575.
54. Kebriaei P, Saliba RM, Ma C, et al. Allogeneic hematopoietic stem cell transplantation after rituximab-containing myeloablative preparative regimen for acute lymphoblastic leukemia. *Bone Marrow Transplant*. 2006;38:203-209.
55. Gutierrez-Aguirre CH, Gomez-Almaguer D, Cantu-Rodriguez OG, et al. Non-myeloablative stem cell transplantation in patients with relapsed acute lymphoblastic leukemia: results of a multicenter study. *Bone Marrow Transplant*. 2007; 40:535-539.
56. Song KW, Barnett MJ, Gascoyne RD, et al. Primary therapy for adults with T-cell lymphoblastic lymphoma with hematopoietic stem-cell transplantation results in favorable outcomes. *Ann Oncol*. 2007;18:535-540.
57. Kantarjian HM, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia in second or subsequent complete remission. *Leuk Lymphoma*. 2010;51:475-480.
58. Dudler C, Bargetzi M, Tichelli A, et al. DV-ICE, intensive induction and early transplantation for adult patients with acute lymphoblastic leukemia: a phase II study. *Eur J Haematol*. 2009;83:512-518.
59. Wassmann B, Pfeifer H, Stadler M, et al. Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood*. 2005;106:458-463.
60. Pidala J, Djulbegovic B, Anasetti C, Kharfan-Dabaja MA, Kumar A. Allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia in first complete remission: a systematic review and meta-analysis. *ASH Annu Meet Abstr*. 2010; 116:3511.
61. Litzow MR, Buck G, Dewald G, et al. Outcome of 1,229 adult Philadelphia chromosome negative B acute lymphoblastic leukemia (B-ALL) patients from the International UKALLXII/ E2993 trial: no difference in results between B cell immunophenotypic subgroups. *ASH Annu Meet Abstr*. 2010;116:524.

62. Leguay T, Pigneux A, Tabrizi R, et al. Allograft after pediatric-inspired therapy does not improve young patient's outcome with high risk Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-ALL): a single center report. *ASH Annu Meet Abstr*. 2010;116:3528.
63. Rambaldi A, Spinelli O, Oldani E, et al. Improved clinical outcome of adult patients with Ph+ ALL after a combined imatinib-chemotherapy induction/consolidation program followed by allogeneic hematopoietic stem cell transplantation: results from a prospective study of the Northern Italy Leukemia Group. *ASH Annu Meet Abstr*. 2010;116:682.
64. Fielding AK, Buck G, Lazarus HM, et al. Imatinib significantly enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukaemia: final results of the UKALLXII/ECOG2993 trial. *ASH Annu Meet Abstr*. 2010;116:169.
65. Giebel S, Holowiecki J, Krawczyk-Kulis M, et al. Improved outcome of adult acute lymphoblastic leukemia treated with individualized protocol adjusted to the status of minimal residual disease and age: interim analysis of PALG ALL 5-2007 study. *ASH Annu Meet Abstr*. 2010;116:2138.
66. Tang X, Sun X, Xue S, et al. Minimal residual disease status at day +100 post allogeneic hematopoietic stem cell transplantation is a powerful predictor for post-transplant outcome In patients with high risk acute leukemia. *ASH Annu Meet Abstr*. 2010;116:3550.
67. Brunstein C, Eapen M, Ahn Kw, et al. Reduced intensity conditioning (RIC) transplantation in acute leukemia: the effect of source of unrelated donor stem cells on outcomes. *ASH Annu Meet Abstr*. 2010;116:908.
68. Rocha V, Labopin M, Mohty M, et al. Outcomes after double unit unrelated cord blood transplantation (UCBT) compared with single UCBT in adults with acute leukemia in remission. An Eurocord and ALWP collaboration study. *ASH Annu Meet Abstr*. 2010;116:910.

APPENDIX A: METHODOLOGY FOR THE ADULT ACUTE LYMPHOBLASTIC LEUKEMIA EVIDENCE-BASED REVIEW UPDATE

Introduction

In 1999, the American Society for Blood and Marrow Transplantation (ASBMT) began developing systematic evidence-based reviews (EBR) and position statements on the effectiveness of autologous and allogeneic hematopoietic stem cell transplantation (SCT) for specific diseases. The purpose of these reviews is to provide evidence in support of clinical decisions and matters of public policy regarding SCT and achieve broader and more consistent coverage from payers for established indications for SCT. The ASBMT EBR Steering Committee developed specific policies outlining the methodology to be followed for these reviews [1,2]. Currently, eight reviews have been published in *Biology of Blood and Marrow Transplantation* (*BBMT*) on the use of SCT in the therapy of: diffuse large B cell lymphoma [3], multiple myeloma [4], pediatric acute lymphoblastic leukemia (ALL) [5], adult ALL [6], pediatric acute myeloid leukemia (AML) [7], adult AML [8], myelodysplastic syndromes [9], and follicular lymphoma [10].

In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly at approximately 5-year intervals. The purpose of the updates is to provide a summary of recent clinical evidence, provide timely treatment recommendations, and determine if new evidence strengthens or changes the treatment recommendations provided in original EBR. By providing these updates, physicians will have access to timely information that will facilitate and help disseminate advances in the field of transplantation. To guide its own activities and that of the expert panel associated with each review, the ASBMT EBR Steering Committee developed a policy statement specifying the methodology to be followed for updating each review [11]. The same expert panel members associated with the original EBR are invited to participate in the update process as well. The diffuse large B cell lymphoma update was the first to be published [12], and the adult and pediatric ALL updates are the next in the series, as requested by the ASBMT.

Expert Panel Selection for EBR Update

To achieve an appropriate balance, physicians who have extensive clinical experience and published research studies using SCT and other therapies in the treatment of the specific disease of interest are invited to join an independent expert panel that examines the summarized literature and provides subsequent treatment recommendations based on the available evidence. Potential panelists are restricted to U.S.-based institutions for two reasons: (1) ease of logistics in convening teleconferences, and (2) differences in the healthcare systems and health insurance coverage between the United States and other countries (including Canada, Europe, etc), which may result in different expert recommendations based on considerations of costs and access to care. In addition to clinical and research physicians, at least one third-party payer representative, a patient advocate,

Appendix A, Table 1. Grading the Quality of Design and Strength of Evidence

Levels of Evidence	
1++	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2−	Case-control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Nonanalytic studies (eg, case reports, case series)
4	Expert opinion

Reprinted with permission from Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J.* 2001;323:334-336.

Appendix A, Table 2. Grading the Strength of the Treatment Recommendation

Grades of Recommendation	
A	At least 1 meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Reprinted with permission from Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J.* 2001;323:334-336.

and a liaison to the ASBMT Steering Committee are invited to serve on the panel.

Literature Search Methodology for the Adult All EBR Update

The SCOPUS database, which includes PubMed and Medline, the Websites developed by the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were first searched on July 29, 2010, using the search terms "acute lymphoblastic leukemia" OR "ALL" AND "transplant" limited to "human trials," "English language," and a publication date of January 1, 2005 or later. An updated search was conducted on October 15, 2010. In addition to the online database searches, a manual search of the reference lists of the included articles and relevant reviews published since January 2005 was conducted.

Papers that were published before January 2005, included fewer than 25 ALL patients, or were not peer-reviewed were excluded. Also excluded were editorials, letters to the editor, Phase I (dose escalation or dose finding) studies, reviews, consensus conference papers, practice guidelines, and laboratory studies with no clinical correlates. Abstracts and presentations at national or international meetings were not used for the treatment recommendations in this update for reasons previously described [5]. However, abstracts are included in the "Areas of Needed Research and Ongoing Studies" section for the reader's information.

Several of the studies evaluated for inclusion in this adult ALL update included patients with AML; therefore, to be included, at least 65% of a study's patients had to have ALL, unless the results were stratified by disease.

Qualitative and Quantitative Grading of the Evidence

The hierarchy of evidence, including a grading system for the quality and strength of the evidence and strength of each treatment recommendation, was published as an editorial policy statement in *BBMT* in 2005 [2]. Appendix A, Tables 1 and 2, reprinted from the policy statement, define criteria used to grade the studies that were included in this update and criteria to grade the treatment recommendations, respectively. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment protocol also were considered in evaluating the studies. Clinical studies are described in the tables with sufficient detail to give a concise summary of study design and patient outcomes.

All data in the text and tables were abstracted from the original manuscripts by the first author (D.O.) and double checked for accuracy and clarity by 2 other authors (T.H. and P.L.M.). Some articles contained inconsistencies within the data reported; the data most consistent with the text of the article were included in this review.

Format of the Adult All EBR Update

Evidence is taken from studies published after January 2005 of adult ALL patients. For each section of the review, a summary paragraph provides an overall description of the number and types of studies included as evidence, as well as a brief synopsis of outcomes. As noted earlier, unlike the original ALL EBRs, in which each article was summarized in detail in the text, this update presents the study design, patient population, and clinical outcomes only in the detailed summary tables.

The highest quality studies are presented in the tables first, while studies of equal quality are presented in descending order by study population size. Individual studies that were also included in a meta-analysis are identified in the tables. New evidence is provided first in each table, followed by the highest quality studies (ratings from 1++ to 2++) used to make treatment recommendations in the original adult ALL EBR. Both Level 1 and Level 2 evidence is presented in the tables for each study that provided biologic assignment (donor versus no donor) and randomized (autologous SCT versus chemotherapy) results. When specific data elements of a study's patient population or disease characteristics were not included in a table, it was because the information was not provided in the article.

Consensus Process for Treatment Recommendations

The Treatment Recommendations Table (Table 1 in the Adult ALL EBR Update) contains the summary of consensus treatment recommendations made by the expert panel based on the summarized evidence. The consensus process involves a teleconference during which panelists critically discuss the evidence for each section of the review and develop initial treatment recommendations according to the categories in Appendix A, Table 2. The information is summarized by the primary authors in the Treatment Recommendations Table and distributed to the panelists for additional review and clarification. Any changes suggested by an individual panelist are circulated for review and approval by all panelists. This iterative process concludes when a final version of the Treatment Recommendations Table is approved by all panelists.

After the final draft of the Adult ALL EBR Update is approved by the expert panel it is reviewed by the ASBMT EBR Steering Committee and then submitted to the *BBMT* journal for peer-review. Any changes requested during the peer-review process must be reviewed and approved by all the expert panelists.

REFERENCES

1. Jones R, Horowitz M, Wall D, et al. ASBMT Policy Statement regarding the methodology of evidence-based reviews in evaluating the role of blood and marrow transplantation in the treatment of selected diseases. *Biol Blood Marrow Transplant*. 2000;6: 524-525.
2. Jones R, Nieto Y, Rizzo J, et al. The evolution of the evidence-based review: Evaluating the science enhances the art of medicine-statement of the Steering Committee for Evidence-Based Reviews of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2005;11: 819-822.
3. Hahn T, Wolff SN, Czuczman M, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2001;7: 308-331.
4. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. *Biol Blood Marrow Transplant*. 2003;9:4-37.
5. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children: an evidence-based review. *Biol Blood Marrow Transplant*. 2005;11.
6. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant*. 2006;12:1-30.
7. Oliansky DM, Rizzo JD, Aplan PD, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in children: an evidence-based review. *Biol Blood Marrow Transplant*. 2007;13:1-25.
8. Oliansky DM, Appelbaum F, Cassileth PA, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant*. 2008;14:137-180.
9. Oliansky DM, Antin J, Bennett J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. *Biol Blood and Marrow Transplant*. 2009;15:137-172.
10. Oliansky DM, Gordon LI, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2010;16:443-468.
11. Jones RB, Nieto Y, Wall D, et al. Methodology for updating published evidence-based reviews evaluating the role of blood and marrow transplantation in the treatment of selected diseases: a policy statement by the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2009;15:761-762.
12. Oliansky D, Czuczman M, Fisher R, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: Update of the 2001 evidence-based review. *Biol Blood Marrow Transplant*. 2011;17:20-47.

Appendix B. Noncomparative Studies of Transplantation for Adult ALL

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (Range)	Median Duration CR1 (Months)	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/ LFS (95% CI)	% OS (95%CI)
RELATED ALLOGENEIC SCT											
[46] Huang 2009 2001-2007 Retrospective, Single Ctr Total n = 250 57% ALL (stratified) (others AML) 61.3% ALL in CR	2+	Total ALL Unmanipulated Mismatched/ Haploidentical RD Allo	142	25 (2-56) Overall	NR	13%	9%	NR	5-year 30% ALL	3-year LFS 55.9% ± 5% ALL	NR
[47] Fouillard 2008 1975-2003 Retrospective, Registry EBMT Total n = 162 33% ALL (stratified) (others AML) Overall 72% in CR1	2+	Total ALL Syngeneic identical twin SCT	53	36 (16-68) Overall	NR	13%	NR	60 (1-275)	3%	1-year LFS 52% ± 10% ALL	NR
UNRELATED ALLOGENEIC SCT											
[48] Marks 2008 1995-2004 Retrospective, Registry CIMBTR Ph-negative ALL in CR1	2+	Total MUD or MMUD Allo	169	33 (16-59)	NA	0%	19%	54 (NR)	5-year 42%	NR	5-year OS 39%
RELATED OR UNRELATED ALLOGENEIC SCT											
[49] Hamaki 2005 2000-2003 Retrospective, Multictr ALL (39% in CR1) 18% previous SCT	2++	Total RIC prior to MRD, MMRD, or MUD Allo SCT	33	55 (17-68)	NR	30%	3%	11.6 (4-37)	27%	1-year RFS 29.8%	1-year OS 39.6%
[50] Duval 2010 1995-2004 Retrospective, Registry CIBMTR ALL Refractory/Relapse Total n = 2255 26% ALL (stratified)	2+	Total ALL MSD, MRD, MUD, or MMUD Allo SCT	582	29 (<1-60) ALL	8 (<1-97) ALL	NR	NR	61 (2-137) Overall	100 day 41%	NR	3-year OS 16% (13%-20%)

(*Continued*)

Appendix B. (*Continued*)

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (Range)	Median Duration CR1 (Months)	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/ LFS (95% CI)	% OS (95%CI)
[51] Yanada 2005 1991-2001 Retrospective, Registry JSHCT **Ph+** ALL (57% in CR)	2+	Total TBI regimen (84%) prior to MSD, MMRD, MUD, or MMUD Allo SCT	197	37 (16-59)	NR	100%	NR	57.6 (NR)	NR	NR	5-year OS 22%
[52] Mohty 2008 1996-2004 Retrospective, Registry EBMT ALL (29% in CR1) 35% previous SCT	2+	Total RIC prior to MSD or MUD Allo SCT	97	38 (17-65)	NR	38%	NR	33.6 (5-76)	NRM 28%	2-year LFS 21% ± 4%	2-year OS 31% ± 5%
[53] Shigematsu 2008 1993-2007 Retrospective, Single Ctr ALL (94.6% in CR1)	2+	Total Medium-dose VP16 + Cy + TBI prior to MRD, MUD, or MMUD	37	26 (15-58)	NR	32.3%	10.8%	35.1 (.9-163)	5.4%	NR	3-year OS 89.2%
[54] Kebriaei 2006 1999-2004 Prospective, Single Ctr ALL (26% in CR1)	2+	Total Cy + TBI + Rituximab prior to MSD or MUD Allo SCT	35	30 (15-55)	NR	32%	0%	21 (3-46)	2-year 24%	2-year PFS 30% (15%-46%)	2-year OS 47% (28%-63%)
[55] Gutierrez 2007 No study dates reported +Prospective, Multicenter ALL in CR2 63% > 16 years	2−	Total RIC prior to MSD Allo SCT	43	19 (1-55)	NR	NR	NR	7.8 (1-35)	21%	NR	3-year OS 31%
ALLOGENEIC OR AUTOLOGOUS SCT											
[56] Song 2007 1987-2005 Retrospective, Registry BMT Program of BC and BCCA Database T-lineage ALL (94% in CR1)	2+	Total MSD Allo SCT (4) or Auto SCT (25)	34 29 SCT	26 (18-56)	NA	NR	NR	51 (13-142)	NR	4-year EFS 68% (ITT)	4-year OS 72% (ITT)

(*Continued*)

Appendix B. (*Continued*)

Reference and Patient Populations	Quality/ Strength of Evidence*	Treatment Regimen	Sample Size	Age, Years Median (Range)	Median Duration CR1 (Months)	% Ph+	% T Lineage	Follow-Up (in Months) Med (Range)	% TRM	% EFS/DFS/ LFS (95% CI)	% OS (95%CI)
[57] Kantarjian 2010 1990 - NR Retrospective, Single Ctr ALL in ≥CR2	2−	Total MSD or MUD Allo (44) or Auto SCT (2)	172 46 SCT	32 (16-81)	≥12 months 25%	16%	NR	NR	NR	NR	3-year OS 25% (SCT patients only)
[58] Dudler 2009 1995-2005 Retrospective, 2 Centers ALL (76% in CR1)	2−	Total DV-ICE intensive induction, then immediate MSD, MUD, MMRD Allo SCT (24) or Auto SCT (7) based on donor availability	42 31 SCT	43 (17-67)	NR	29%	19%	55 (4-136)	21%	5-year DFS 16% ± 13% (ITT)	5-year OS 23% ± 15% (ITT)
POST-SCT IMATINIB FOR MRD$^+$ PH$^+$ ALL											
[59] Wassmann 2005 Study dates NR Prospective, Multicenter MRD$^+$ Ph$^+$ ALL	2−	Total MRD responders MRD nonresponders Allo (24) or Auto (3) SCT	27 14 13	48 (16-63)	NR	100%	NR	15.6 (2-31)	na	PFS 68% ± 21% 12 months 8% ± 7% 13 months	NR

ALL indicates acute lymphoblastic leukemia; Allo, allogeneic; AML, acute myeloid leukemia; Auto, autologous; BC, British Columbia; BCCA, British Columbia Cancer Agency; BMT, bone marrow transplantation; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CML, chronic myeloid leukemia; CR, complete remission; Cy, cyclophosphamide; DFS, disease-free survival; DV-ICE, dexamethasone/vincristine-idarubicine/cytosine-arabinoside/etoposide; EBMT, European Group for Blood and Marrow Transplant; EFS, event-free survival; HR, high risk; ITT, intention-to-treat; JSHCT, Japan Society of Hematopoietic Cell Transplantation; LFS, leukemia-free survival; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor or minimal residual disease; MSD, matched sibling donor; MUD, matched unrelated donor; NR, not reported; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome-positive; RD, related donor; RIC, reduced-intensity conditioning; RD, related donor; SCT, stem cell transplantation; TBI, total-body irradiation; TRM, treatment-related mortality; VP16, etoposide.

*Quality and strength of evidence definitions are listed in Appendix A, Table 1.