1083-8791/06/1201-0001$32.00/0
doi:10.1016/j.bbmt.2005.10.018

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Acute Lymphoblastic Leukemia in Adults: An Evidence-based Review

Theresa Hahn,[1] Donna Wall,[2] Bruce Camitta,[3] Stella Davies,[4] Hildy Dillon,[5] Paul Gaynon,[6] Richard A. Larson,[7] Susan Parsons,[8] Jerome Seidenfeld,[9] Daniel Weisdorf,[10] Philip L. McCarthy, Jr[1]

[1]Roswell Park Cancer Institute, Buffalo, New York; [2]Texas Transplant Institute, San Antonio, Texas; [3]Midwest Children's Center, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, Wisconsin; [4]Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio; [5]The Leukemia and Lymphoma Society, White Plains, New York; [6]Children's Hospital of Los Angeles, Los Angeles, California; [7]University of Chicago, Chicago, Illinois; [8]Tufts-New England Medical Center, Boston, Massachusetts; [9]Blue Cross and Blue Shield Association Technology Evaluation Center, Chicago, Illinois; [10]University of Minnesota, Minneapolis, Minnesota

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

Received October 18, 2005; accepted October 19, 2005

ABSTRACT

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute lymphoblastic leukemia in adults (≥15 years) is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published medical literature and for grading the quality and strength of the evidence, and the strength of the treatment recommendations. Treatment recommendations based on the evidence are presented and were reached unanimously by a panel of acute lymphoblastic leukemia experts. The priority areas of needed future research for adult acute lymphoblastic leukemia are: definition of patients at high risk in first complete remission, beyond Philadelphia chromosome positive; outcomes of SCT in older (>50 years) adults; determination if reduced intensity versus myeloablative conditioning regimens yield an equivalent graft-versus-leukemia effect with reduced toxicity; monitoring of minimal residual disease to achieve disease control before SCT; and the use of cord blood and other alternative sources of stem cells for use in adult SCT recipients.

KEY WORDS

Acute lymphoblastic leukemia • Hematopoietic stem cell transplantation • Therapy • Adult

INTRODUCTION

The American Society for Blood and Marrow Transplantation (ASBMT) in 1999 began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of hematopoietic stem cell transplantation (SCT) in the therapy of selected diseases. The steering committee that was convened to oversee the projects invited an independent panel of disease-specific experts to conduct each review. Three reviews have been published in *Biology of Blood and Marrow Transplantation*: diffuse large cell B-cell non-Hodgkin's lymphoma in 2001 [1]; multiple myeloma in 2003 [2]; and pediatric acute lymphoblastic leukemia (ALL) in 2005 [3]. The following is the fourth review to result from this initiative. Its goals are to: (1) assemble and critically evaluate all of the evidence regarding the role of stem cell transplantation (SCT) in the therapy of adult ALL; (2) make treatment recommendations based on the available evidence; and (3) identify needed areas of research.

The published literature was graded on the quality of design and the strength of the evidence (Table 1) in

All terms abbreviated in this article are defined in a Glossary of Terms, Appendix A, at the end of the article.

Table 1. *Grading the Quality of Design and Strength of Evidence*

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of 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 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 (e.g., case reports, case series)
4	Expert opinion

RCTs indicates randomized controlled trials.

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.

a systematic manner. Treatment recommendations were subsequently graded based on the quality and strength of the evidence (Table 2). The treatment recommendations of the expert panel are detailed in Table 3.

LITERATURE SEARCH METHODOLOGY

PubMed and MEDLINE, the Web sites developed by the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were searched using the search terms "acute lymphoblastic leukemia" and "transplant" limited to human trials and English language. The MEDLINE subject heading terms for any article about ALL included acute lymphoblastic leukemia, acute lymphoid leukemia, and acute lymphocytic leukemia, regardless of which term was used in the published article. Therefore, the search by "acute lymphoblastic leukemia" generated all articles on ALL even if the article did not use this term to define ALL. The original search included publications from January 1, 1980, to August 18, 2002, was updated on February 18, 2003, and underwent a final update on January 3, 2005. In addition, articles were excluded if they were not peer-reviewed reports; were editorials, letters to the editor, case reports (≤10 patients), phase I (dose escalation or dose finding) studies, reviews, consensus conference reports, practice guidelines, or laboratory studies with no clinical correlates; or did not focus on an aspect of therapy with SCT for the treatment of ALL. The review of SCT for ALL is published as two articles: one including studies of pediatric ALL, and the other including studies of adult ALL. Articles are excluded from the adult ALL review if more than 50% of the study population was younger than 16 years; these articles were included in the pediatric ALL review [3]. Abstracts and presentations at national or international meetings were also not included as evidence in this review because the lack of formal peer review, the limited availability of details on study design and results, and the usual presentation as preliminary, not final analyses of clinical trial data.

QUALITATIVE AND QUANTITATIVE GRADING OF THE EVIDENCE

The hierarchy of evidence, including a grading scheme for the quality and strength of the evidence, and strength of each treatment recommendation, has been established and published as an editorial policy statement in *Biology of Blood and Marrow Transplantation* [4]. Tables 1 and 2 are reprinted from the policy statement and define criteria used to grade the studies included in the review and grade the treatment recommendations. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan, also were considered in evaluating the studies. All data in the text and tables were abstracted

Table 2. *Grading the Strength of the Treatment Recommendation*

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or 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+

RCT indicates randomized controlled trial.

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.

Table 3. *Summary of Treatment Recommendations Made by the Expert Panel for Adult Acute Lymphoblastic Leukemia*

Indication for SCT	Treatment Recommendation*	Highest Level of Evidence†	Reference No.‡	Comments
SCT vs. chemotherapy in first complete remission	B	1+	5-7	In first complete remission, SCT yields outcomes similar to chemotherapy and is not recommended as first choice therapy in standard-risk patients. For high-risk patients, there are no direct comparisons, but some data suggest an advantage for SCT.
SCT vs. chemotherapy in second complete remission	D	3	N/A	In second complete remission, SCT is recommended over chemotherapy as a sizable fraction of patients achieve extended leukemia-free survival compared with chemotherapy alone; however, there are no direct comparative data.
Autologous purged SCT	D	2−	24-27	Leukemia-free survival is in the same range seen with chemotherapy.
Autologous, unpurged SCT	D	2+	18-20	Leukemia-free survival is in the same range seen with chemotherapy.
Related allogeneic SCT	C	2++	30	Effective at producing extended leukemia-free survival in some patients. High-risk Ph+ ALL patients have very poor LFS (<10%) with chemotherapy; although there are no direct comparisons, there appears to be a survival advantage for related allogeneic SCT in Ph+ ALL patients in first or subsequent remissions.
Unrelated allogeneic SCT	C	2++	53	Produces extended leukemia-free survival in some patients. There is a possible benefit of unrelated allogeneic SCT over chemotherapy in Ph+ ALL patients, although there are no direct comparisons. Higher TRM may compromise the potential antitumor advantage of unrelated allogeneic SCT.
Related vs. unrelated allogeneic SCT	D	2+	56	Equivalent outcomes between related and unrelated allogeneic SCT in one study.
Comparison of conditioning regimens	N/A	N/A	N/A	There are not enough data to make a recommendation of the superiority of one conditioning regimen. There appears to be a benefit to TBI-containing regimens compared with non-TBI-containing regimens. There are not enough data evaluating nonmyeloablative conditioning regimens to determine the effect on TRM and leukemia-free survival.
Autologous vs. allogeneic SCT	B	1+	8,66,67	Preponderance of evidence favoring allogeneic over autologous SCT. There are insufficient data to determine if this effect is more apparent in risk subgroups, including Ph+ ALL.

LFS indicates leukemia-free survival.

*Definitions: See Table 2.

†Definitions: See Table 1.

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

from the original articles first by one author (T. H.), then double-checked for accuracy and clarity by another author (P. L. M.) and at least two additional reviewers (see acknowledgements). In some articles there were discrepancies within the data reported, i.e., the median follow-up reported in the abstract was not the same as in the results section, or data presented in a table did not agree with those in the text. In these cases, the data most consistent with the text of the article were presented in this review. The first author (T. H.) takes responsibility if errors remain. Clinical studies were summarized with enough detail to give a concise summary of study design, sample size, eligibility criteria, treatment schedule, duration of follow-up, and outcomes measured. Subjective statements regarding issues such as short versus adequate versus long follow-up, small versus large sample size, improper or inappropriate study design were not used so that the reader is not biased by the authors' opinions.

TREATMENT RECOMMENDATIONS

The strength of this review is the detail conveyed in the text and the study comparisons in the summary

tables at the end of each major section. Table 3 contains the summary of treatment recommendations made by the ALL expert panel. Subsequent sections of the review present the detailed descriptions of the strengths and weaknesses of the evidence and are specific to each treatment recommendation. Additional sections describe other limitations of this review, additional ongoing studies, areas of needed research, and future initiatives.

There were not enough data published as of January 3, 2005, to determine the impact of imatinib mesylate in patients with Philadelphia chromosome–positive (Ph+) ALL on the outcome of SCT or on the ability to achieve higher complete remission (CR) rates making more patients eligible for SCT. The use of imatinib mesylate before SCT, as part of the conditioning regimen and after SCT, has not been adequately studied to determine its effect on overall survival (OS) and leukemia-free survival (LFS).

TRANSPLANTATION VERSUS CHEMOTHERAPY IN ADULT ALL

Table 4 summarizes the grading criteria, study populations, patient characteristics, and outcomes from adult studies included in the transplantation versus chemotherapy section. Evidence in this section is taken from self-described studies of adult populations all of which included patients at least 13 years of age. Evidence is presented with the highest quality studies first; studies of equal quality are presented in descending order with the largest sample size first.

First CR

Fiere et al. [5] performed a prospective, multicenter study (Leucémie Aiguë Lymphoblastique de l'Adulte [LALA]-87 trial) between 1986 and 1991 in adult (≥15 years) patients with ALL comparing related allogeneic bone marrow transplantation (BMT), autologous BMT, and chemotherapy. At time of first CR (CR1), 436 patients and their siblings were human leukocyte antigen (HLA) typed and those aged 15 to 40 years with an available donor (n = 116) were treated with an allogeneic BMT (n = 98). The results of the related allogeneic BMT group are summarized in Sebban et al. [6] below. Patients younger than 40 years with no available related donor, and patients between 40 and 50 years old (n = 262) were randomized to receive either an autologous BMT (n = 95 randomized, actual BMT in 63 patients) or chemotherapy (n = 96). All patients older than 50 years were treated with chemotherapy (n = 58). Adjustment for time to transplantation bias was not performed; however, median time from CR1 to allogeneic BMT was 63 days and median time from CR1 to autologous BMT was 116 days.

At a median follow-up of 38 months, the autologous BMT and chemotherapy groups did not have a significant difference in either disease-free survival (DFS) (3-year DFS 39% versus 32%, respectively; $P = .8$; Figure 1) or OS (3-year OS 49% versus 42%, respectively; $P = .9$). By intent-to-treat analysis, the allogeneic BMT group had a 3-year DFS of 43% and a 3-year OS of 55%. The chemotherapy group (age > 50 years) had a 3-year DFS of 24% and a 3-year OS of 28%. Factors associated with poor outcome were age, Ph+ ALL, immunophenotype, white blood cell count (WBC) greater than 30,000/μL at diagnosis, and platelet count less than 100,000/μL at diagnosis.

Thomas et al. [7] performed a prospective multicenter partially randomized (LALA-94) trial from 1994 to 2002 in adult (≥15 years) patients with ALL comparing related allogeneic SCT, autologous SCT, and chemotherapy. A total of 1000 patients were enrolled and underwent induction (n = 922 eligible patients) and consolidation (n = 706) chemotherapy. Patients at standard risk (n = 430) received only chemotherapy and comprised all patients with T-lineage ALL achieving CR1 after one course of chemotherapy and with B-lineage ALL with no central nervous system (CNS) involvement, absence of Ph+, t(4;11), t(1;19), or other 11q23 rearrangements, WBC less than 30×10^9/L, $CD10^+/CD19^+$ immunophenotype, $CD20^+/CD19^+$ immunophenotype and the absence of myeloid markers, and achievement of CR1 after one course of chemotherapy. Patients at high risk with non-Ph+ and non-CNS ALL (n = 238) who achieved CR1 (n = 211) and did not have a sibling donor (n = 129) were randomized to receive autologous SCT followed by 2-year maintenance with methotrexate (MTX) and mercaptopurine (n = 70) versus chemotherapy (n = 59). Those with an HLA–matched sibling donor received a related allogeneic SCT (n = 82). Conditioning regimens for both autologous and allogeneic SCT were cyclophosphamide (Cy) plus total body irradiation (TBI) (1000 cGy in a single fraction or 1200 cGy in 6 fractions). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (CSA) ± MTX; all grafts were T-cell replete. At a median follow-up of 5.2 years, the 3-year DFS in the autologous SCT versus chemotherapy group was 39% versus 24% (P = not significant; Figure 2).

An additional 198 patients with Ph+ ALL who achieved CR1 (n = 140) were biologically randomized to receive a related allogeneic SCT if a suitable donor was available (n = 75) or an autologous SCT (n = 65) and the results are presented by Dombret et al [8]. A fourth group of 56 patients with CNS-positive ALL who achieved CR1 (n = 48) were biologically randomized to receive a related allogeneic SCT if a suitable donor was available (n = 18) or an autologous SCT (n = 30). This group's results were combined with the related allogeneic and autologous SCT/che-

Table 4. *Comparison of Patient Characteristics and Outcomes from Articles Included in the Transplantation Versus Chemotherapy in Adult Acute Lymphoblastic Leukemia in First Complete Remission Section*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients by Treatment Regimen	Median (range) Age at Time of Therapy	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
Auto SCT vs. Chemotherapy										
5	1+	LALA-87 trial*	Total 191 Auto BMT 95 Chemo 96	 25 (15-50) 28 (15-48)	Overall 4% 4%	38	3-y DFS 39% 32%	Not significant	3 y 49% 42%	Not significant
7	1+	LALA-94 trial	Total 129 Auto PBSCT 70 Chemo 59	33 (15-55)†	At 3 y 0% 7%	62†	3-y DFS 39% 24%	Not significant	3 y 44% 35%	Not stated
Related Allo SCT vs. Chemotherapy +/− Auto SCT										
7	1+	LALA-94 trial	Total 259 Rel donor 100 No Rel donor 159	33 (15-55)†	At 3 y 18% 7%	62†	3-y DFS 47% 34%	$P = .007$	3 y 51% Not stated	Not compared
6	2++	LALA-87 trial‡	Total 257 Rel Allo BMT 116 Chemo/Auto BMT 141	 26 (15-40) 24 (15-40)	Overall 16% 3%	62	5 y DFS 45% 31%	Not significant	5 y 48% 35%	Not significant
9-11	2++	IBMTR vs. two German cooperative group trials	Total 718 Rel Allo BMT 234 Chemo 484	Not stated (15-45) Not stated (15-45)	At 9 y 53% 5%	90	9-y LFS 34% 32%	Not significant	Not stated	Not compared
12	2++	IBMTR vs. JALSG trial ALL-87	Total 290 Rel Allo BMT 214 Chemo 76	 26 (15-51) 29 (15-55)	 ≤30 y 32% vs. 3% >30 y 57% vs. 13%	48 54	5-y LFS ≤30 y 53% vs. 30% >30 y 26% vs. 30%	$P = .02$ Not significant	Not stated	Not compared
13	2++	German ALL/AUL trial	Total 76 Rel Allo BMT 38 Chemo 38§	Not stated (15-45) Not stated (15-45)	Not stated	Not stated	3-y DFS 34% 34%	Not significant	Not stated	Not compared
14	2+	JALSG ALL-93 trial	Total 142 Rel donor 34 No Rel donor 108	Not stated (15-40) Not stated (15-40)	Not stated	63	Not stated	Not compared	6 y 46% 40%	Not significant
15	2+	Single Canadian center	Total 87 Rel donor 48 No Rel donor 39	 34 (16-54) 25 (16-52)	At 1 y 19% 5%	52	3-y EFS 40% 39%	Not significant	3 y 46% 58%	Not significant

Table 4. *Continued*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients by Treatment Regimen	Median (range) Age at Time of Therapy	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
16	2+	JALSG ALL-90 trial	Total 57 Rel Allo BMT 17 Chemo 40	Not stated (15-45) Not stated (14-45)	Not stated	62	Not stated	Not compared	6 y 41% 30%	Not significant
17	2–	Single Japanese center	Total 30 Rel Allo BMT 12 Chemo 18	Not stated Not stated	Overall 8% 0%	37	Overall DFS 36.5% 23.4%	Not significant	Overall 80.2% 33.3%	$P < .05$

ALL indicates acute lymphoblastic leukemia; Allo, allogeneic; AUL, acute unclassified leukemia; Auto, autologous; BMT, bone marrow transplantation; Chemo, standard chemotherapy comparison group; DFS, disease-free survival; EFS, event-free survival; IBMTR, International Bone Marrow Transplant Registry; JALSG, Japan Adult Leukemia Study Group; LALA, Leucémie Aiguë Lymphoblastique de l'Adulte (Adult Acute Lymphoblastic Leukemia); LFS, leukemia-free survival; OS, overall survival; PBSCT, peripheral blood stem cell transplant; Rel, related; SCT, stem cell transplantation.

*The updated results of this study were not peer reviewed (*Hematol Oncol Clin North Am* 2000; 14:1353–1366, however, the results with 10-year follow-up are not different from the interim analysis reported here.

†Includes all 922 patients enrolled in the trial.

‡The patient population reported in reference 6 overlaps with the patient population reported in reference 5.

§Reference 9 includes the same 484 patients with chemotherapy from which 38 matched control subjects were chosen for the reference 13 study.

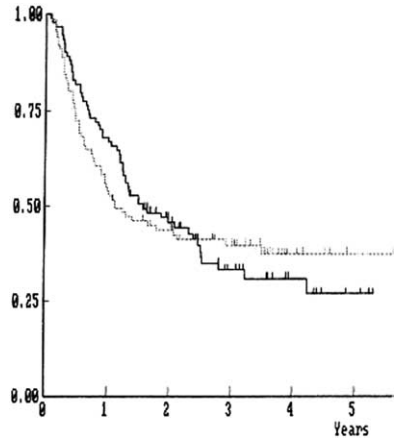

Figure 1. DFS according to the administration of autologous BMT or chemotherapy. BMT: total 96, dead 63; censored, 33. Chemotherapy: total, 95, dead 58; censored, 47. (P=.8). Reprinted with permission [5].

motherapy high-risk group described in the previous paragraph to perform a sibling donor versus no sibling donor comparison that demonstrated a significantly better 3-year DFS in the available sibling donor group (47% versus 34%; $P = .007$; Figure 3).

Sebban et al. [6] reported the results of the LALA-87 multicenter prospective trial conducted from 1986 to 1991 that compared related allogeneic BMT in patients with an HLA–matched donor (n = 116, of whom 92 actually underwent transplantation in CR1) with a control group of patients with no suitable sibling donor (n = 141, of whom 117 were actually randomized). The control group consisted of patients who were randomized to receive either an autologous BMT (n = 58) or chemotherapy (n = 59) (results of the randomized comparison are reported by Fiere et al. [5] above). There was no significant difference in median DFS (24 versus 22 months; $P = .1$)

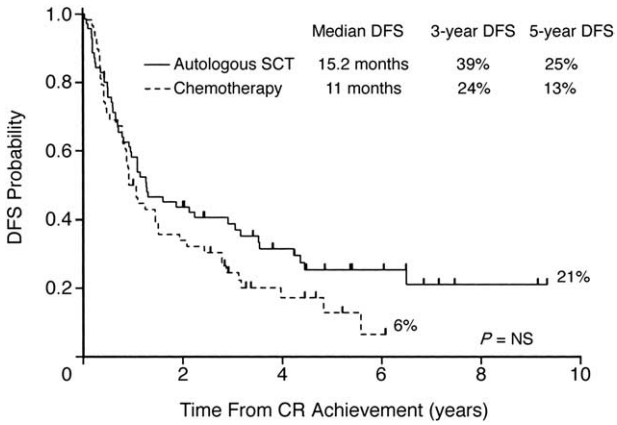

Figure 2. Disease-free survival (DFS) according to second randomization for patients in group 2 (70 patients in the autologous stem-cell transplantation [SCT] arm and 59 patients in the chemotherapy arm). CR, complete remission. Reprinted with permission [7].

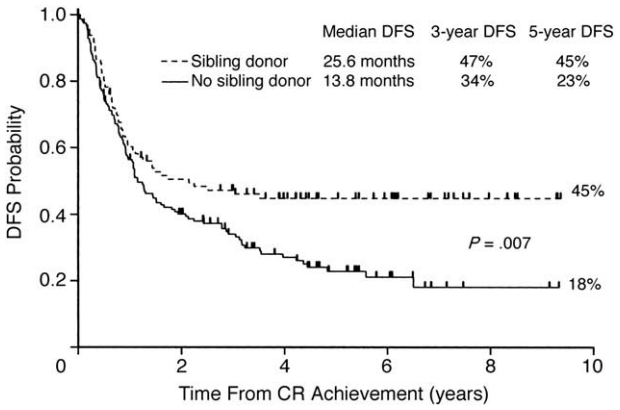

Figure 3. Disease-free survival (DFS) according to genetic randomization. For this analysis, patients from group 2 (211 patients) and those from group 4 (48 patients) were pooled. The group with a sibling donor comprised 100 patients, whereas that with no sibling donor included 159 patients. CR, complete remission. Reprinted with permission [7].

or OS (51 versus 30 months; $P = .08$) between the allogeneic BMT and chemotherapy groups, respectively.

In a subset of 96 patients with high-risk ALL, there was a significant benefit for the allogeneic BMT group (n = 41) compared with the chemotherapy group (n = 55) with respect to DFS (median 21 versus 9 months; $P = .01$) and OS (median 30 versus 15 months; $P = .03$; Figure 4). There was no difference in DFS or OS between the allogeneic BMT and chemotherapy groups in patients with standard-risk ALL. Patients with high-risk ALL had at least one of the following characteristics: (1) Ph+ ALL; (2) null leukemia or undifferentiated leukemia; or (3) common leukemia with at least one adverse prognostic factor (age > 35 years, WBC > 30×10^9/L, or >4 weeks to achieve CR1).

Zhang et al. [9-11] retrospectively compared related allogeneic BMT in adult patients with ALL from 98 hospitals worldwide reported to the International BMT Registry (IBMTR) (n = 234) with patients treated with chemotherapy from 44 hospitals in West Germany (n = 484). All patients were treated between 1980 and 1987, were in CR1, and were 15 to 45 years of age. Adjustments were made for time to transplantation bias and differences in disease characteristics. There were similar prognostic factors of treatment failure for both groups (immunophenotype, WBC at diagnosis, and time to achieve CR1). At a median follow-up of 7.5 years, the 9-year LFS was 32% in the chemotherapy group and 34% in the related allogeneic BMT group ($P > .2$). The probability of relapse at 9 years was 66% in the chemotherapy group and 30% for the transplantation group ($P < .0001$).

Oh et al. [12] performed a retrospective case control study of 76 patients treated with chemotherapy from trial ALL-87 of the Japan Adult Leukemia Study Group (JALSG) and 214 patients with related HLA–matched allogeneic BMT from the IBMTR. There is no overlap with the patients reported in Zhang et al. [9-11] above. All patients were diagnosed with ALL from 1988 to 1990, were 15 to 55 years old, and treated in CR1. Adjustments were made for time to transplantation bias and differences in baseline characteristics. The 5-year LFS in patients age 30 years or younger was 30% for the chemotherapy group and 53% for the BMT group ($P = .02$). However, there was no significant difference in LFS between the chemotherapy and BMT groups for patients older than 30 years (26% versus 30%; $P = .70$).

Messerer et al. [13] reported the German ALL/AUL study of 484 patients treated between 1980 and 1986 with chemotherapy and 41 patients treated between 1981 and 1988 with related HLA–matched allogeneic BMT in CR1 [13]. The 484 patients treated with chemotherapy in this study are the same 484 patients treated with chemotherapy from the Zhang et al. [9-11] study noted above. In the study by Messerer et al. [13], a retrospective matched case control analysis was performed by selecting 38 patients from each group. Case and control patients were matched on sex, age, WBC at diagnosis, immunophenotype, and time to reach CR1; analyses were made adjusting for time to transplantation bias. There was no difference in the 3-year DFS between the two groups (34% versus 34%).

Takeuchi et al. [14] presented the results of the prospective multicenter JALSG-ALL-93 study conducted from 1993 to 1997 in patients in CR1 who were younger than 40 years comparing those with HLA–matched sibling donors (related allogeneic BMT group, n = 34) to those without (chemotherapy

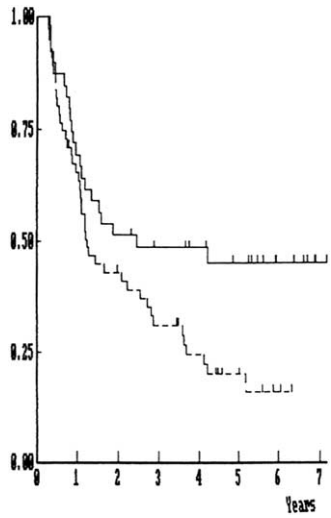

Figure 4. Overall survival of patients with high-risk leukemia according to allocation arm. (Solid line BMT; dashed line control). Reprinted with permission [6].

group, n = 108). Patients in the chemotherapy group received chemotherapy (n = 81), unrelated BMT (n = 17), autologous peripheral blood SCT (PBSCT) (n = 8), or autologous BMT (n = 2). The 6-year OS was not significantly different between the related allogeneic BMT and chemotherapy groups (46% versus 40%; $P = .58$). OS was also not significantly different when comparing actual treatment received (BMT [n = 41] versus chemotherapy [n = 91], excluding 10 patients with autologous BMT/PBSCT).

Gupta et al. [15] reported a single Canadian center experience from 1992 to 2001 offering all adult (≥16 years) patients with ALL in CR1 a matched related allogeneic BMT if a sibling donor was available (n = 48, 35 were HLA–identical, 4 were a 1-antigen mismatch, and 9 were unrelated donors), otherwise 2-year maintenance and intensification was given with chemotherapy only (n = 39, no patients received an autologous BMT; 6 patients received an unrelated donor BMT). Conditioning regimen was Cy and TBI (1200 cGy in 6 fractions); GVHD prophylaxis consisted of CSA and MTX ± methylprednisolone (MP). At a median follow-up of 52 months and using an intent-to-treat approach, there was no significant difference in 3-year OS or event-free survival (EFS) between the donor and no donor groups. After excluding the 17 patients with Ph+ ALL, there was also no significant difference in EFS or OS between the donor and no donor groups.

Ueda et al. [16] described the results of the prospective, multicenter JALSG-ALL-90 study conducted from 1990 to 1993 in patients with ALL in CR1 younger than 45 years old comparing those who received HLA–matched related BMT (n = 17) to those who received chemotherapy (n = 40). Adjustments were made for time to transplantation bias. The 6-year OS was not significantly different between the related allogeneic BMT and chemotherapy groups (41% versus 30%; $P = .226$).

Tamura et al. [17] retrospectively evaluated patients with ALL who were younger than 45 years in CR1 who from 1982 to 1989 received HLA–matched related allogeneic BMT (n = 12) or chemotherapy in those without related donors (n = 18). OS was significantly higher for the related BMT group compared with the chemotherapy group (80.2% versus 33.3%; $P < .05$). DFS was not significantly different between the two groups (36.5% versus 23.4%; $P > .05$).

Second CR

There are no data comparing transplantation versus chemotherapy in adult patients with ALL in second CR (CR2). There are data for adults undergoing SCT in CR2 that will be presented in later sections as appropriate (i.e., comparing related and unrelated donor BMT in CR2).

AUTOLOGOUS BMT IN ADULT ALL

Table 5 summarizes the grading criteria, study populations, patient characteristics, and outcomes from adult studies included in the Autologous BMT section, including unpurged, purged, and purged and unpurged autologous BMT. Evidence in this section is taken from self-described studies of adult populations, all of which included patients at least 13 years of age. Evidence is presented with the highest quality studies first; studies of equal quality are presented in descending order with the largest sample size first.

Unpurged Autologous BMT

Powles et al. [18-20] evaluated 50 consecutive adult (≥15 years) patients with ALL in CR1 at a single United Kingdom center who received between 1984 and 1994 either an unpurged autologous BMT (n = 38) conditioned with melphalan (Mel) plus TBI or unmanipulated autologous PBSCT (n = 12) conditioned with Mel alone, followed by maintenance chemotherapy with daily 6-mercaptopurine and weekly MTX for 2 years. Maintenance chemotherapy could be initiated in 78.9% of BMT and 91.7% of PBSCT recipients. No patients with autologous BMT had HLA–identical sibling donors. After December 1992, autologous PBSCT was offered as the preferred therapy regardless of donor availability. In all, 47 patients (94%) received induction and early intensification therapy according to the United Kingdom ALL (UKALL) X regimen B protocol. Seven patients (18%) received marrow purged *in vitro* with Campath-1M. No patients experienced graft failure. Overall treatment-related mortality (TRM) was 16%. At a median follow-up of 40 months, the 4-year OS and DFS were 56.2% and 53.2%, respectively.

Lambertenghi Deliliers et al. [21] reported the results of 20 patients with ALL (85% were adult but specific age not stated) treated with an unpurged autologous BMT in CR1 (n = 7), CR2 (n = 8), or third CR (CR3) (n = 5) at a single Italian center between 1984 and 1992. Conditioning regimen was cytosine arabinoside (Ara-c), Cy, and TBI (1000 cGy in 5 fractions) for all patients. There were no cases of early death or death in CR. At a median follow-up of 59 months, the 5-year EFS was 57% for patients who underwent transplantation in CR1 versus 31% for patients who underwent transplantation in CR2 or CR3 (*P* not stated). Patients treated after one or more CNS relapses had a 5-year EFS of 53% compared with those treated after a hematologic relapse with a 5-year EFS of 14% (*P* not stated).

Carey et al. [22] performed 34 consecutive unpurged autologous BMTs from 1984 to 1988 in 15 adult (≥15 years) patients with ALL and 6 patients with high-grade non-Hodgkin's lymphoma. These patients had previously been treated with the same

Table 5. *Comparison of Patient Characteristics and Outcomes from the Articles in the Autologous Bone Marrow Transplantation in Adult Acute Lymphoblastic Leukemia Section*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients	Median (range) Age at Time of Transplant	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
Unpurged Autologous BMT										
18-20	2+	Single UK center*	CR1 50	26 (15-58)	16%	40	4-y DFS 53.2%	Not compared	4 y 56.2%	Not compared
21	2−	Single Italian center	Total 20 CR1 7 CR2/3 13	18 (10-39)	0%	59	5-y EFS 57% 31%	Not compared	Not stated	Not compared
22-23	2−	UK NE ALL III trial	CR1 15	31 (15-50)	0%	30	3-y DFS 48%	Not compared	Not stated	Not compared
Purged Autologous BMT										
24,25	2−	Single German center	CR≥2 or high-risk CR1 32	24 (13-52)	12.5%	143	12-y DFS 37.5%	Not compared	12 y 37.5%	Not compared
26	2−	Single UK center	CR1 27	18 (11-45)	7%	41	7-y DFS 32%	Not compared	Not stated	Not compared
27	2−	Single UK center*	CR≥1 23	Not stated	35%	120	10-y DFS 26%	Not compared	Not stated	Not compared
Purged + unpurged autologous BMT										
28,29	2+	Single US center	Total 89† CR1 10 CR2 27 CR≥3 25 Relapse 27	 28.1 (2-45) 18.3 (4-44) 12 (2-46) 19 (6-47)	Overall 30% 15% 16% 22%	42	2-y DFS 50% 21%‡ 21%‡ 0%	Not stated	Not stated	Not compared

ALL indicates acute lymphoblastic leukemia; BMT, bone marrow transplantation; CR1, first complete remission; CR2/3, second or third complete remission; CR≥1, first or greater complete remission; CR≥2, second or greater complete remission; CR≥3, third or greater complete remission; DFS, disease-free survival; EFS, event-free survival; LFS, leukemia-free survival; OS, overall survival; UK, United Kingdom.

*There is some overlap between reference 27 and 18.

†Fifty patients received purged and 39 patients received unpurged marrow, but results are presented for both groups together.

‡DFS was given for CR2 and CR≥3 groups combined.

induction therapy regimen: the UK NE ALL III trial and were in CR1 at time of BMT [23]. All patients received Mel and TBI as conditioning regimen with no TRM. At a median follow-up of 3 years, the DFS for the 13 patients in CR1 was 48%.

Purged Autologous BMT

Abdallah et al. [24] reported the long-term follow-up of 32 adult (≥13 years) patients with ALL treated with autologous purged BMT between 1984 and 1994 at a single German center. Marrow was purged with mafosfamide (n = 25) or by *in vitro* immunomagnetic bead purging with a panel of monoclonal antibodies (n = 7; anti-CD10, anti-CD19, anti-CD20, anti-HLA-DR). All patients received the same induction regimen according to the German Multicentre ALL (GM-ALL) trial [25]. At time of transplantation, all patients were either in CR2 or greater (CR≥2) or were considered high risk by having one of the following poor prognostic factors: older than 35 years; WBC greater than 30×10^9/L at diagnosis; null-ALL phenotype; or failure to achieve CR1 within 4 weeks of treatment. Of 32 patients, 12 were in continuous CR at a median follow-up of 143 months (range: 66-181 months) postautologous BMT; the DFS and OS rates were both 37.5%.

Gilmore et al. [26] presented the results of 27 patients with ALL (78% ≥ 16 years) treated in CR1 with a purged autologous BMT at a single United Kingdom center between 1983 and 1989. Patients received Cy and TBI (1500 cGy in 2 fractions, n = 21) or Ara-c, Cy, and TBI (1500 cGy in 2 fractions, n = 6) as the conditioning regimen. Harvested marrow was purged with anti-T- (anti-CD67) or anti-B- (anti-CD10 ± anti-CD19) cell monoclonal antibodies. At a median follow-up of 3.4 years, the DFS was 32%.

Mehta et al. [27] reported the long-term follow-up of 23 patients with ALL (52% ≥ 15 years) treated in CR1 (n = 11) or CR2 to fourth CR (n = 12) with a purged autologous BMT at a United Kingdom center from 1984 to 1986. Harvested marrow was purged *in vitro* with Campath-1 (anti-CD52) antibodies. All patients received Mel and TBI (850-1150 cGy in a single fraction) as the conditioning regimen. At a median follow-up of 10 years, the 10-year DFS was 26% and the 10-year probability of relapse was 51%.

Purged and Unpurged Autologous BMT

Doney et al. [28,29] retrospectively analyzed 89 consecutive patients with ALL (>50% > age 16 years) treated with an autologous BMT from 1979 to 1991 at a single US center. Marrow was purged with 4-hydroperoxycyclophosphamide (n = 2), purged with monoclonal antibodies (n = 48), or was unpurged (n = 39). Remission status at time of BMT was 10 CR1, 27 CR2, 25 greater than CR2, and 27 relapse. Median duration of CR1 was 15.9, 24, and 24.7 months for the CR2, >CR2, and relapse groups, respectively. Sites of extramedullary disease at relapse were CNS (n = 28), CNS and testes (n = 7), or other (n = 15). All patients received TBI-based conditioning regimens, with TBI doses ranging from 1000 to 1575 cGy. Median follow-up time was not stated. The 2-year DFS was 50% in the CR1, 21% in the CR≥2, and 0% in the relapse groups, respectively (*P* not stated). A lower relapse rate was associated with a lower WBC at diagnosis, BMT in CR1, and BMT given while not in relapse.

RELATED DONOR ALLOGENEIC BMT IN ADULT ALL

Table 6 summarizes the grading criteria, study populations, patient characteristics, and outcomes from adult studies included in the Related Donor Allogeneic BMT section. Evidence in this section is taken from self-described studies of adult populations, all of which included patients at least 13 years of age. Evidence is presented with the highest quality studies first; studies of equal quality are presented in descending order with the largest sample size first.

Ringden et al. [30], as part of a larger study examining acute leukemia outcomes, compared the results of 826 adult (≥16 years) patients with ALL treated with HLA–identical related allogeneic BMT to 345 adult (≥16 years) patients with ALL treated with HLA–identical related allogeneic PBSCT reported to the European Group of Blood and Marrow Transplant (EBMT) registry between 1994 and 2000. Of the BMT recipients, 62% were in CR1 at time of transplantation, 18% were in CR2, and 20% had more advanced disease. The corresponding numbers for the PBSCT recipients were CR1 55%, CR2 20%, and more advanced 25%. In all, 9% of the BMT and 17% of the PBSCT donor grafts were T-cell depleted. TBI-based conditioning regimens were used in 82% of the BMT and 69% of the PBSCT groups. Engraftment was significantly faster in the PBSCT group (mean time to neutrophil recovery: 14 versus 19 days; $P < .0001$). By multivariate analysis, there was no significant difference between the BMT and PBSCT groups with regard to acute or chronic GVHD, TRM, LFS, or OS. The only significant multivariate risk factors for improved LFS and OS were disease status at transplantation (CR1 > CR2 > advanced disease) and MTX-containing immunosuppression for GVHD prophylaxis.

Passweg et al. [31] assessed the impact of immunophenotype on risk of relapse and GVHD. Recipients of 1132 BMTs from HLA–matched siblings in CR1 (n = 605) or CR2 (527) for T-lineage (n = 416) or cALLa+ B precursor (B-lineage) (n = 716) ALL reported to the IBMTR between 1982 and 1992 by 165 centers were studied. Median duration of CR1

Table 6. *Comparison of Patient Characteristics and Outcomes from the Articles in the Related Donor Allogeneic Stem Cell Transplantation Section*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients	Median (range) Age at Time of Transplant	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
30	2++	EBMT registry[a]	Total 1171		Overall		Overall LFS	Not significant	Overall	Not significant
			BMT 826	28 (16-60)[b]	23%[c]	25[b]	59%[c]		63%[c]	
			PBSCT 345	31 (16-62)[b]	23%[c]	14[b]	46%[c]		57%[c]	
31	2+	IBMTR[d]	Total 1132	20 (1-49)[e]	Not stated	Not stated	Not stated[f]	$P < .05$[f]	Not stated	Not compared
			T lineage 416	23 (1-52)[e]						
			B lineage 716							
32	2+	EBMT registry[a]	Total 790	21 (1-43)	3 y		3-y LFS	$P = .004$	Not stated	Not compared
			BMT < 1986 248	23 (1-51)	39%	93	45%			
			BMT ≥ 1986 542		25%	38	54%			
33	2+	EBMT registry[a]	Total 772[g]		2 y		2-y LFS			
			CR1 430	24 (1-52)						
			cGVHD 110		13%	Not stated	77%	$P = .0005$		
			No cGVHD 236		13%		60%			
			CR>2/Rlps1 342	14 (1-48)						
			cGVHD 62		35%		44%	Not significant	Not stated	Not compared
			No cGVHD 204		12%		54%			
34	2+	Single US center	Total 605							
			Donor/patient sex F/F 121	33 (1-72)[h]	Not stated	Not stated	Not stated	$P = .07$[i]	Not stated	$P = .09$[i]
			M/F 93	32 (1-64)[h]						
			F/M 186	32 (1-70)[h]						
			M/M 205	33 (1-68)[h]						
35	2+	IBMTR twins vs. sibs[d]	Total 264		3 y		3-y LFS	Not significant	Not stated	Not compared
			Identical twins 24	17 (1-30)	10%	65	57%			
			Matched sibs 240	17 (1-36)	21%	60	58%			
36	2+	IBMTR Ph+ ALL	Total 67	28 (5-49)	2 y	36	2-y LFS	Not compared	Not stated	Not compared
			CR1 33		42%		38%			
			CR2/Rlps 22		40%		42%			
			PIF 12		42%		25%			
37	2+	2 US centers	CR1 53	24 (<1-45)	Overall 26%	66	5-y DFS 61%	Not compared	5 y 61%	Not compared
38	2+	10 French centers	CR1 42	25.9 (3-41)[b]	Overall 38%	66	7-y EFS 40%	Not compared	7-y 45%	Not compared
39	2+	IBMTR	PIF 38	32 (1-50)	3 y 44%	41	3-y LFS 23%	Not compared	Not stated	Not compared
40	2+	Single US center[j]	CR1 34	27.8 (1-45)	Overall 29%	24	3-y DFS 64%	Not compared	Overall 65%	Not compared
41	2+	Single US center	CR1 55[k]	24 (0-48)	Overall 22%	72	10-y EFS 64%	Not compared	10-y 66%	Not compared
42	2+	Single Korean center Ph+ ALL	Total 23	36 (15-44)	2 y 27.8%	24	2-y DFS 43.5%	Not compared	Not stated	Not compared
			CR1 14							
			CR2 9							
43	2−	IBMTR	Total 634	Not stated (16-not stated)	Not stated	21	Not stated[l]	Not compared	Not stated	Not compared
			CR1 243							
			CR2 391	Not stated (not stated)						

Table 6. *Continued*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients	Median (range) Age at Time of Transplant	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
44	2−	Single US center	Total 43	Not stated (9-51)	Overall 26%	106	Not stated[m]	Not compared	Not stated[m]	Not compared
45	2−	Single Canadian center	Total 40 BuCy 29 BuCyVP 11	 23 (2-49) 16 (1-39)	2 y 24% 27%	33	3-y DFS 39.9% 45.5%	Not significant	Not stated	Not compared
46	2−	Single US center	CR1 39	23 (16-41)[n]	Overall 23%	18	Overall DFS 63%	Not compared	Not stated	Not compared
47	2−	Single UK center	CR1 32	23 (7-41)	3 mo 22%	50	Overall DFS 50%	Not compared	Not stated	Not compared
48	2−	Single Spanish center	Total 30 CR1/2 17 CR≥3 13	 17 (5-36) 16 (6-33)	1 y 18% 15%	48	5-y DFS 69.5% 15.4%	$P < .01$	Not stated	Not compared
49	2−	Single Hong Kong center	CR≥1 or Rlps≥1 29	31 (15-43)	Day 100 10%	38	3-y DFS 40%	Not compared	Not stated	Not compared
50	2−	Single Australian center	Total 27 CR1 13 Rlps≥1, CR≥2 14	 20 (15-42) 21 (14-52)	Overall 32.5%[o] 42.5%[o]	Not stated	Overall DFS 86% 28%	Not compared	Overall 48% 21%	$P = .06$
51	2−	Single Italian center	Total 24 CR1/2 17 Rlps 7	23 (6-49)	Overall 17.6% 14.3%	 92 66	Overall EFS 59% 14%	Not compared	Not stated	Not compared
52	2−	Single US center Ph+ ALL	CR1 23[p]	30 (6-44)	Day 100 26%	40	3-y DFS 65%	Not compared	Not stated	Not compared

ALL indicates acute lymphoblastic leukemia; BMT, bone marrow transplantation; Bu, busulfan; cGVHD, chronic graft-versus-host disease; CR1, first complete remission; CR2, second complete remission; CR1/2, first or second complete remission; CR≥1; first or greater complete remission, CR≥2, second or greater complete remission; CR≥3, third or greater complete remission; Cy, cyclophosphamide; DFS, disease-free survival; EBMT, European Group for Blood and Marrow Transplant; EFS, event-free survival; F, female; IBMTR, International Bone Marrow Transplant Registry; LFS, leukemia-free survival; M, male; OS, overall survival; PBSCT, peripheral blood stem cell transplantation; Ph^+, Philadelphia Chromosome positive; PIF, primary induction failure; Rlps, relapse; Rlps1, first relapse; Rlps≥1, first or greater relapse; sibs, siblings; VP, VP-16/etoposide; UK, United Kingdom.

[a]There is some overlap between references 30, 32, and 33.

[b]Mean instead of median was given in article.

[c]In CR1 patients only, in CR2 patients TRM was 29% (BMT) and 25% (PBSCT), in advanced disease patients. TRM was 55% (BMT) and 45% (PBST).

[d]There is some overlap between the patients included in reference 31 and 35.

[e]Data are given for the 273 T-lineage and 332 B-lineage ALL patients who underwent transplantation in CR1. The results for the 143 T-lineage and 384 B-lineage ALL patients who underwent transplantation in CR2 were similar.

[f]Multivariate analysis of relapse risk showed a significant risk reduction in those who developed GVHD in both T-lineage ALL (RR = 0.34; $P = .005$) and B ALL (RR = 0.44; $P = .002$) transplanted in CR1 and in T-lineage ALL (RR = 0.54; $P = .05$) and B-ALL (RR = 0.61; $P = .01$) transplanted in CR2; LFS, EFS, DFS, OS, TRM, and median follow-up time were not stated in the article.

[g]Patients had to be alive at 3 months post-BMT without relapse to be included in this group.

[h]Includes patients with ALL, AML, CML, HD, NHL, MDS, MM, and other hematologic malignancies.

[i]Based on the hazard ratio of risk of relapse or survival. EFS/DFS/OS were not stated for any groups.

[j]There is some overlap with reference 37.

[k]Includes 39 adult (≥18 y) and 16 pediatric (<18 y) patients.

[l]Relapse risk is stated comparing methotrexate-treated vs. cyclosporine or T-cell depletion-treated patients; DFS/RFS were not stated.

[m]OS and RFS curves are presented but the rate at any given time point was not stated.

[n]With the exception of one infant included in the study population.

[o]Rate is given for both the AML (n = 42) and ALL (n = 27) patients together.

[p]Four patients were also included in reference 40.

was 12 versus 28 months for the patients with T- versus B-lineage ALL in CR2 ($P = .0001$). Sites of prior relapse were not stated. There was no difference in the incidence or severity of acute or chronic GVHD between the T- and B-lineage ALL groups when stratified by CR1 versus CR2. There was a significantly lower risk of relapse in patients who did versus did not develop GVHD, which was seen in both the T- and B-lineage groups stratified by CR1 versus CR2 (T-ALL in CR1 relative risk [RR] = 0.34, $P = .005$; B-ALL in CR1 RR = 0.44, $P = .002$; T-ALL in CR2 RR = 0.54, $P = .05$; B-ALL in CR2 RR = 0.61, $P = .01$).

Frassoni et al. [32] assessed the impact of year of BMT on TRM, LFS, and relapse rate in 790 adult and pediatric patients with ALL treated with an HLA–matched related allogeneic BMT in CR1 and reported to the EBMT registry between 1979 and 1991. Patients treated before 1986 (n = 248, median age 21 years) were compared with those treated in 1986 or later (n = 542, median age 23 years). Patients treated since 1986 had a significantly shorter follow-up time ($P < .001$), fewer TBI-containing conditioning regimens ($P = .001$), more patients receiving CSA and MTX for GVHD prophylaxis compared with either agent alone ($P < .0001$), a shorter interval from diagnosis to BMT ($P = .0004$), and a lower incidence of chronic GVHD ($P = .003$). There was a marginally higher median age at BMT in the 1986 and later group (23 versus 21; $P = .07$). TRM at 3 years was significantly lower in patients who underwent transplantation since 1986 compared with earlier (25% versus 39%; $P < .0001$); correspondingly, LFS increased from 45% before 1986 to 54% since 1986 ($P = .004$). The relapse incidence did not change over time. Significant multivariate prognostic factors for higher TRM were older age (measured as a continuous variable in all analyses; $P < .0001$), female donor to male recipient ($P = .008$), and year of BMT (measured as a continuous variable in all analyses; $P < .0001$). Significant multivariate prognostic factors for improved LFS were year of BMT after 1986 ($P < .0001$) and younger age at BMT ($P < .0001$).

Ringden et al. [33] assessed the impact of acute and chronic GVHD on relapse rate, TRM, and LFS in 772 adult and pediatric patients with ALL treated with an HLA–matched sibling allogeneic BMT in CR1 (n = 430, median age 24 years) or CR≥2/first relapse (n = 342, median age 14 years) between 1987 and 1993 and reported to the EBMT by 89 centers. Sites of prior relapse and duration of CR1 were not stated. All patients received CSA and MTX for GVHD prophylaxis. There was a significant decrease in relapse rate and LFS with a corresponding significant increase in TRM for both groups with increasing grade of acute GVHD. For patients who underwent transplantation in CR1, the relapse rate was significantly lower ($P < .0001$) and the 2-year LFS was significantly better in patients who developed chronic GVHD compared with those who did not. In the more advanced disease group, there was no significant difference in the relapse rate or 2-year LFS but a significantly higher TRM rate in the patients who developed chronic GVHD compared with those who did not.

Randolph et al. [34] compared the risk of relapse by donor-recipient sex in 3238 patients with hematologic malignancies treated with an HLA–matched related donor at a single US center from 1969 to 2001. Adult (median age 33 years) patients with ALL (n = 605) who received a female/female (n = 121), male/female (n = 93), female/male (n = 186), or male/male (n = 205) donor/recipient related allogeneic SCT were included if they expressed at least one class I HLA allele from the following: HLA-A1, A2, A3, B7, B8, B40, or B60. These alleles were chosen because they are the most common in the North American population and present at least one of the defined H-Y antigens. It is not stated how many patients were HLA typed by serologic versus molecular methods. Conditioning regimens and GVHD prophylaxis regimens were not stated for patients with ALL, but were TBI-containing in 74% and CSA and MTX in 45% of all patients, respectively. In patients with ALL, male SCT patients with female donors had a trend toward a lower risk of relapse compared with other donor/recipient sex categories (hazard ratio = 0.77, adjusted for patient and donor age, GVHD prophylaxis, disease status, conditioning regimen, and patient/donor cytomegalovirus status; $P = .07$). Male SCT recipients with female donors also had a trend toward an increased risk of death compared with other categories (hazard ratio = 1.18, controlling for the same factors as risk of relapse. $P = .09$).

Gale et al. [35] performed a matched case control study of 24 identical twin BMTs for ALL in CR1 treated between 1978 and 1990 reported to the IBMTR by 66 centers with 240 HLA–matched sibling donor BMTs for ALL in CR1 selected from 581 BMTs reported by 163 centers to the IBMTR during the same time period. Donor-recipient sex matching and GVHD prophylaxis significantly differed between the groups but could not be matched on. Factors including age at BMT, WBC at diagnosis, immunophenotype, and time to CR1 were compared by univariate analysis for significant differences to determine factors used for matching; only age at BMT was significant and used to match case and control subjects. BMT recipients from identical twins had a higher 3-year relapse rate (36% versus 26%; $P = .1$) and lower 3-year TRM (10% versus 21%; $P = .1$) compared with the matched sibling BMT group. There was no difference in 3-year LFS between the two groups (57% versus 58%; $P > .2$).

Barrett et al. [36] analyzed the outcomes of 67 patients with Ph+ ALL (81% ≥ 16 years old) treated with an HLA–matched sibling BMT and reported to the IBMTR between 1978 and 1990. Ph+ was the only karyotypic abnormality in 45 patients (67%), whereas 22 patients (33%) had the Ph+ with other karyotypic abnormalities. Conditioning and GVHD prophylaxis regimens varied by reporting center; however, 72% of patients received a TBI-containing conditioning regimen. At a median follow-up of 36 months, 33 patients who underwent transplantation in CR1 had a 2-year LFS of 38% versus 41% in 22 patients with relapse and 25% in 12 patients with primary induction failure.

A subset analysis compared the 33 patients with CR1 and Ph+ ALL with 33 matched control patients selected from 106 patients with Philadelphia chromosome–negative ALL reported to the IBMTR during the same time period and who underwent transplantation in CR1. Control patients were matched on age at diagnosis, WBC at diagnosis, and time from diagnosis to transplantation; other patient characteristics were not significantly different between case and control subjects. Patients with Ph+ ALL tended to have earlier relapses (34% versus 23% at 2 years) and lower 2-year LFS (38% versus 49%) compared with the Philadelphia chromosome–negative ALL matched control patients; however, these differences were not statistically significant.

Chao et al. [37] presented the results of 53 patients with high-risk ALL (95% > 16 years old) treated in CR1 with an HLA–matched sibling BMT at two US centers. High risk was defined as having one of the following factors: WBC 25,000/μL or higher at diagnosis; cytogenetic abnormalities (t(4;11), t(8;14), or t(9;22)); age 30 years or older; extramedullary disease; and longer than 4 weeks to achieve CR1. Conditioning regimens were Ara-c, Cy, and TBI (1000 cGy in a single dose, n = 17), Cy and TBI (1320 cGy fractionated, n = 17), or etoposide (VP) and TBI (1320 cGy fractionated, n = 19). GVHD prophylaxis regimens consisted of MTX and prednisone, CSA and prednisone, or CSA, MTX, and prednisone. At a median follow-up of 5.5 years, the 5-year OS and DFS were both 61%. A multivariate analysis of prognostic factors indicated an improved DFS with male sex (P = .016), younger age (P = .003), and shorter time to CR (P = .014).

Deconinck et al. [38] reported the results of 42 patients with ALL (88% > 15 years old) treated with an HLA–matched sibling allogeneic BMT in CR1 at 10 French centers from 1987 to 1991. All patients received Ara-c, Mel, and TBI (1000 cGy as single dose in 14 patients or 1200 cGy in 6 fractions in 28 patients) as conditioning regimen. GVHD prophylaxis consisted of CSA and MTX (n = 39), CSA and MP (n = 2), or T-cell depletion (n = 1). At a median follow-up of 66 months, the 7-year OS and EFS rates were 45% and 40%, respectively.

Biggs et al. [39] analyzed 38 patients with ALL (8% < 10 years old, 45% ≤ 19 years old) treated with an HLA–matched sibling allogeneic BMT after failing to achieve CR1 with two or more courses of induction chemotherapy and reported to the IBMTR by 49 centers between 1982 and 1989. Conditioning regimens were TBI-based in 83% of patients. GVHD prophylaxis regimens varied by center. At a median follow-up of 41 months, the 3-year LFS was 23% (95% confidence interval, 12%-40%). LFS was significantly higher in patients <30 years compared with ≥30 at time of BMT (37% versus 9%; P < .02). The 3-year probability of TRM was significantly lower in patients <30 years compared with ≥30 at time of BMT (13% versus 80%; P < .004).

Snyder et al. [40] described the outcomes of 34 patients with ALL (79% > 20 years old) treated with an HLA–matched related allogeneic BMT between 1986 and 1992 at a single US center. All patients received VP and TBI (1320 cGy in 11 fractions) for conditioning, and CSA and MP (n = 15) or CSA, MP, and MTX (n = 19) for GVHD prophylaxis. At a median follow-up of 24 months, the 3-year DFS was 64%. The 3-year DFS was improved in patients younger than 20 years versus 20 years or older at time of BMT (100% versus 54%; P = .05).

Jamieson et al. [41] reported the results of a retrospective analysis of 85 pediatric and adult patients with ALL treated in CR1 or CR2 with an HLA–matched sibling allogeneic BMT at a single US center between 1987 and 2002. The majority of patients (71%) treated in CR1 (n = 55) were adults and their results are presented here. The majority of patients (83%) with CR2 (n = 30) were younger than 18 years and were presented in the pediatric ALL review [3]. All patients received VP and TBI (1350 cGy in 11 fractions). GVHD prophylaxis consisted of CSA and prednisone; CSA, MTX, and prednisone; or CSA and MTX. At a median follow-up of 6 years, the 10-year EFS was 64% and the 10-year OS was 66%.

Lee et al. [42] reported the results of 23 adult (≥15 years) patients with Ph+ ALL treated with an HLA–matched related allogeneic BMT at a single Korean center between 1996 and 2001. Patients underwent transplantation in CR1 (n = 14) or CR2 (n = 9). Median CR1 duration and sites of prior relapse were not stated for the patients with CR2. Conditioning regimen consisted of Cy and TBI (1329 cGy) for patients with CR1 and Ara-c, Mel, and TBI (1200 cGy) for patients with CR2. GVHD prophylaxis consisted of CSA and MTX. At a median follow-up of 24 months, the 2-year DFS was 43.5%. Eight patients had bone marrow samples taken before and after BMT and analyzed by reverse-transcription polymerase chain reaction for *BCR-ABL*. The kinetics of *BCR-*

ABL correlated with development of chronic GVHD and remission status.

Horowitz et al. [43] reported on 634 adult and pediatric patients with ALL treated in CR1 (n = 243, 100% > 16 years at time of BMT) or CR2 (n = 391, adults and children but no ages are stated) with an HLA–matched sibling BMT from 1978 to 1986 and reported to the IBMTR. Median duration of CR1 and sites of prior relapse were not stated. At a median follow-up of 21 months, the 5-year relapse rate for adults in CR1 who received MTX ± MP for GVHD prophylaxis was 10% compared with 50% for adults receiving no MTX ($P < .0003$). For adult and pediatric patients who underwent transplantation in CR2, the 5-year relapse rate in MTX-containing GVHD prophylaxis was 43% versus 65% in CSA-based regimens or T-cell depletion ($P < .0001$).

Kumar et al. [44] retrospectively reviewed 43 patients with ALL (median age > 25 years) treated with an HLA–matched (n = 37) or 1-antigen mismatched (n = 6) related BMT at a single US center between 1982 and 1999. Twenty-two patients were treated in CR1; all others had advanced (not specified) disease. The median CR1 duration and sites of prior relapse were not stated for the patients with advanced disease. Conditioning regimen consisted of Cy and TBI (1320 cGy, n = 28); VP, Cy, and TBI (1320 cGy, n = 13); or other (not specified, n = 2). GVHD prophylaxis consisted of CSA and MTX (n = 28); MTX alone (n = 6); CSA and prednisone (n = 4); CSA, MTX, and prednisone (n = 3); or other (n = 2). The 15 patients whose day+21 absolute lymphocyte count was 175×10^6/L or less had a significantly lower relapse-free survival and OS than the 28 patients whose absolute lymphocyte count was more than 175×10^6/L ($P = .0028$ and .0275, respectively). Survival rates were not stated in the article. Multivariate analysis determined that the day+21 absolute lymphocyte count $<175 \times 10^6$/L (RR 4.5; $P = .022$) and no chronic GVHD (RR 12.1; $P = .0006$) were significant independent risk factors for relapse.

von Bueltzingsloewen et al. [45] compared two non-TBI-containing conditioning regimens in 40 consecutive patients with ALL (73% > 15 years old) treated with a related allogeneic BMT from 1987 to 1991 at a single Canadian center. Remission status at time of BMT was 23 CR1, 11 CR2, 4 CR3, and 2 CR4. Median duration of CR1 and sites of prior relapse were not stated. Thirty-four patients had an HLA–matched, 4 patients had a single antigen mismatch, 1 patient a 2-antigen mismatch, and 1 a syngeneic donor. Conditioning regimens consisted of busulfan (Bu) and Cy (n = 29) or Bu, Cy, and VP (n = 11). GVHD prophylaxis consisted of CSA and MTX (n = 36); MTX and MP (n = 1); CSA, MTX, and MP (n = 1); MTX alone (n = 1); or nothing (n = 1 syngeneic). At a median follow-up of 33 months, the 3-year DFS was not significantly different between the conditioning regimen groups (39.9% Bu and Cy versus 45.5% Bu, Cy, and VP; $P = .72$).

Blume et al. [46] evaluated 39 patients with ALL (38 patients were ≥ 16 years old, 1 infant was also included) treated in CR1 with an HLA–identical related allogeneic BMT at a single US center between 1979 and 1985. Conditioning regimens were Ara-c, Cy, and TBI (1000 cGy, single fraction) (n = 18) and Cy and TBI (1320 cGy, fractionated) (n = 21). For GVHD prophylaxis, 28 patients received MTX and prednisone and 11 patients received CSA and prednisone. One patient received a second related allogeneic BMT for leukemia recurrence. At a median follow-up of 18 months, the DFS was 63%.

McCarthy et al. [47] reported 32 consecutive patients with ALL (72% > 16 years old) in CR1 treated with a HLA–matched related donor BMT at a single United Kingdom center from 1978 to 1987. Conditioning regimens consisted of vincristine, prednisolone, Cy, and TBI (950-1050 cGy in a single fraction, n = 20); vincristine, prednisolone, Ara-c, teniposide (VM26), daunorubicin, and TBI (1050 cGy in a single fraction, n = 4); vincristine, prednisolone, Ara-c, VM26, and TBI (1300 cGy in two fractions, n = 5); or not stated (n = 3). GVHD prophylaxis consisted of CSA alone (n = 21); T-cell depletion with Campath-1 and CSA (n = 6); T-cell depletion with Campath-1 alone (n = 4); or MTX alone (n = 1). Risk factors for BMT in CR1 included older than 16 years at diagnosis, WBC greater than 25×10^9/L, null or B-lineage disease, chromosomal translocations, or CNS disease. Patients had 1 (n = 21), 2 (n = 11), or 3 (n = 1) risk factors. Day 100 TRM was 22%. At a median follow-up of 50 months, DFS was 50%.

De la Camara et al. [48] studied 30 consecutive adult and pediatric patients with high-risk ALL (63% ≥ 15 years old) treated with an HLA–matched sibling BMT (including one identical twin) from 1983 to 1990 at a single Spanish center. High risk was defined as relapsed ALL (CR≥2 or first relapse) or the presence of one of more of the following in patients with CR1: 15 years or older at time of diagnosis; WBC greater than or equal to 100×10^9/L; longer than 7 weeks to achieve CR1; L3 or B mature immunophenotype; t(9;22) or t(8;14); or CNS disease. Cy and TBI was used as conditioning regimen in 87% of patients; CSA and MTX was used as GVHD prophylaxis in 67%. At a median follow-up of 4 years, the 5-year DFS was significantly higher in the CR1 and CR2 groups (n = 17) versus the greater than CR2 group (n = 13) (69.5% versus 15.4%; $P < .01$).

Au et al. [49] reported 29 consecutive adult (>15 years) patients with ALL treated with HLA–identical related allogeneic BMT in CR1 (n = 12) or first or greater relapse (Rel≥1)/CR≥2 (n = 17, CR2 n = 9, not in CR n = 8) between 1990 and 1997. Condition-

ing regimens included Cy and TBI (1200 cGy, n = 15); VP, Cy, and TBI (1200 cGy, n = 12); Bu and Cy (n = 1); and Cy, carmustine (BCNU), and VP (n = 1). CSA and MTX was used for GVHD prophylaxis. At a median follow-up of 38 months, the 3-year DFS was 40%.

Atkinson et al. [50] compared 41 adult (≥14 years) patients (acute myeloid leukemia [AML] n = 28, ALL n = 13) treated with an HLA–matched sibling donor allogeneic BMT in CR1 with 28 adult patients (AML n = 14, ALL n = 14) treated with an HLA–matched sibling donor in CR≥2 or Rel≥1 at a single Australian center between 1981 and 1985. An additional 6 patients had primary refractory disease and one patient was treated as initial therapy. All patients received Cy and TBI (1200-1400 cGy) as the conditioning regimen and CSA (n = 59) or MTX (n = 17) as GVHD prophylaxis. Posttransplantation therapy was given for leukemia recurrence and consisted of conventional chemotherapy (n = 13) or a second transplantation (n = 4) using the same donor and GVHD prophylaxis regimen but using Cy and Mel as the conditioning regimen. The 42-month OS was 48% for the ALL CR1 group versus 21% for the ALL Rel≥1/CR≥2 group ($P = .06$). The DFS, censoring all deaths caused by transplantation-related complications, was 86% for the ALL CR1 group versus 28% for the ALL Rel≥1/CR≥2 group (*P* not stated). At 12 months posttransplantation, the median Karnofsky performance score was 100% (range: 70%-100%) in the group that underwent transplantation in CR1 and 100% (range: 60%-100%) in those who underwent transplantation in Rel≥1/CR≥2.

Aversa et al. [51] studied an alternative conditioning regimen in 24 adult and pediatric patients with ALL (67% > 18 years old) treated with an HLA–matched related allogeneic BMT in CR1 (n = 7), CR2 (n = 10), or relapse (n = 7) from 1989 to 1993 at a single Italian center. Five patients had a history of extramedullary disease. The median duration of CR1 was 8 months. The conditioning regimen consisted of thiotepa, Cy, and TBI (1440 cGy) and antithymocyte globulin (ATG) in all patients. GVHD prophylaxis consisted only of *ex vivo* T-cell depletion by soybean agglutination and (sheep red blood cell) E-rosetting. There were no cases of graft failure or acute or chronic GVHD. Seventeen patients underwent transplantation in CR1 or CR2 with an EFS of 59% at a median follow-up of 7.7 years. Seven patients underwent transplantation in Rel≥1 with an EFS of 14% at a median follow-up of 5.5 years.

Snyder et al. [52] reported the results of 23 patients with Ph+ ALL (1 patient < 18 years old) treated with an HLA–matched sibling allogeneic BMT in CR1 between 1984 and 1997 at a single US center. Patients received VP and TBI (1320 cGy in 11 fractions) (n = 21); VP, Cy, and TBI (n = 1); or Cy and TBI (n = 1) as conditioning regimen. GVHD prophylaxis consisted of CSA, MTX, and MP (n = 12); CSA and MP (n = 8); or CSA and MTX (n = 3). At a median follow-up of 40 months, the 3-year DFS was 65%.

UNRELATED DONOR ALLOGENEIC BMT IN ADULT ALL

Table 7 summarizes the grading criteria, study populations, patient characteristics, and outcomes from adult studies included in the Unrelated Donor Allogeneic BMT section. Evidence in this section is taken from self-described studies of adult populations, all of which included patients at least 13 years of age. Evidence is presented with the highest quality studies first; studies of equal quality are presented in descending order with the largest sample size first.

Cornelissen et al. [53] reported the results of 127 adult (≥16 years) patients with ALL who received a matched (n = 78) or single antigen mismatched (n = 49) unrelated BMT through the National Marrow Donor Program between 1988 and 1999 at 46 centers. All patients were at poor risk defined as the presence of t(9;22) (n = 97), t(4;11) (n = 25), or t(1;19) (n = 5). Patients underwent transplantation in CR1 (n = 64), CR2 or CR3 (n = 16), or after primary induction or in relapse (PIF/Rel, n = 47). Conditioning regimens were TBI-based in 115 patients and chemotherapy alone in 12 patients. Thirty-three patients received T-cell depleted grafts. Primary graft failure occurred in 6% of patients. By multivariate analysis, risk factors for worse DFS were BMT in PIF/Rel (RR = 2.85; $P < .0001$), longer interval from diagnosis to BMT (RR = 1.33; $P = .008$), and HLA–mismatched donor (RR = 1.76; $P = .02$). The presence of t(9;22) demonstrated a significant DFS advantage (RR = 0.49; $P = .006$).

Gaderet et al. [54] compared the outcomes of PBSCT versus BMT in patients with ALL (n = 102) or AML (n = 111) treated with an unrelated allogeneic transplantation between 1994 and 1999 and reported to the EBMT Acute Leukemia Registry. Of the patients with ALL, 58% were older than 16 years at time of transplantation. Of the patients with ALL, 19 (19%) underwent transplantation in CR1, 54 (53%) in CR2 or CR3, and 29 (28%) in other disease stages. PBSCT recipients were matched with a historic group of BMT recipients on the following: disease status at transplantation, patient age, year of transplantation, and T-cell depletion. There was no information on WBC at diagnosis, immunophenotype, CR1 duration, or sites of prior relapse. At a median follow-up of 16 and 23 months in the PBSCT and BMT groups, respectively, the 2-year LFS was significantly lower in the patients with ALL treated with PBSCT versus

Table 7. *Comparison of Patient Characteristics and Outcomes from the Articles in the Unrelated Donor Allogeneic Stem Cell Transplantation Section*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients	Median (range) Age at Time of Transplant	Treatment-Related Mortality	Median Follow-Up (ms)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
53	2++	NMDP 46 worldwide centers	Total 127*		2 y	Overall	2-y DFS	*P* = .0001	2 y	Not stated
			CR1 64	31 (16-54)	54%	24	Not stated		40%	
			CR2/3 16	27 (17-51)	75%				17%	
			PIF/Rlps 47	36 (19-51)	64%				5%	
54	2−	EBMT ALWP	Total 102		Overall		2-y LFS	*P* = .04	2 y	*P* = .04
			PBSCT 36	18 (5-66)	61%	16	21%		24%	
			BMT 66	17 (1-50)	47%	23	32%		34%	
55	2−	Single US center Ph+ ALL	Ph+ 18	25 (1.7-51)	22%	17	2-y LFS 22%	Not compared	Not stated	Not compared

ALWPI, Acute Leukemia Working Party; BMT, bone marrow transplant; CR1, first complete remission; CR2/3, second or third complete remission; DFS, disease-free survival; EBMT, European Bone Marrow Transplant; EFS, event-free survival; LFS, leukemia-free survival; NMDP, National Marrow Donor Program; OS, overall survival; PBSCT, peripheral blood stem cell transplant; PIF, primary induction failure; Rlps, relapse.

*A total of 97 patients had Ph+ ALL.

BMT (21% versus 32%; $P = .04$). The 2-year OS was also significantly lower for the PBSCT group (34% versus 24%; $P = .04$). Multivariate analysis indicated PBSCT was a risk factor for decreased LFS and OS, and CR at transplantation was associated with an increased LFS and OS.

Sierra et al. [55] presented the outcomes of 18 patients with Ph+ ALL who underwent HLA–matched unrelated allogeneic BMT from 1988 to 1995 at a single US center. Of 18 patients, 3 (17%) were younger than 18 years at time of BMT. Disease status at time of BMT was CR1 (n = 7), CR2 (n = 1), relapse 1 (n = 3), or refractory disease (n = 7). All patients received Cy and TBI for conditioning and MTX and CSA or tacrolimus as GVHD prophylaxis. At a median follow-up of 17 months, 5 patients had recurrent disease and died of disease, whereas 4 died of treatment-related causes. LFS at 2 years was 49%.

RELATED AND UNRELATED DONOR ALLOGENEIC BMT IN ADULT ALL

Table 8 summarizes the grading criteria, study populations, patient characteristics, and outcomes from adult studies included in the Related and Unrelated Donor Allogeneic BMT section. Evidence in this section is taken from self-described studies of adult populations, all of which included patients at least 13 years of age. Evidence is presented with the highest quality studies first; studies of equal quality are presented in descending order with the largest sample size first.

Kiehl et al. [56] compared the outcomes of 221 consecutive adult (≥17 years) patients with ALL treated with an HLA–matched related (n = 103) versus unrelated (n = 118) donor BMT at 9 European centers from 1990 to 2002. Significantly more patients received a related versus unrelated allogeneic BMT in CR1 (60% versus 27%; $P < .001$). Overall, 33% of patients had Ph+ ALL. Conditioning regimens consisted of Cy and TBI ± other (n = 65 related, 95 unrelated); Bu and Cy ± other (n = 15 related, 18 unrelated); VP and TBI (n = 21 related, 0 unrelated); or other combinations (n = 3 related, 5 unrelated). GVHD prophylaxis consisted of CSA and MTX (n = 49 related, 69 unrelated); CSA and prednisone (n = 27 related, 6 unrelated); CSA, MTX, and prednisone (n = 1 related, 21 unrelated); or other combinations (n = 11 related, 22 unrelated). At a median follow-up of 7.1 months, there was no significant difference in the 5-year DFS between related versus unrelated donor allogeneic BMT in CR1 (42% versus 45%; P = not stated) (Figure 5). There was a significantly improved 5-year DFS for TBI- versus Bu-based conditioning regimens in all patients regardless of donor relation or disease status at time of BMT (30% versus 17%; $P = .041$).

Cahn et al. [57] investigated the feasibility of performing allogeneic BMT in 192 patients with acute leukemia in CR1 older than 40 years reported to the EBMT registry. There were 41 patients with ALL older than 40 years in CR1 who were compared to 467 adult patients with ALL in CR1 aged 16 to 40 years reported to the same registry. Patients in the two age groups were not significantly different on interval from diagnosis to BMT, sex, French-American-British classification, sex match of the donor/recipient, or conditioning regimen. The article does not state if the donors were related, so it is assumed this study includes patients with both related and unrelated allogeneic BMT. The probability of TRM was higher in the older age group (37% versus 28%; $P = .09$). The probability of relapse at 4 years was 38% for the older and 29% for the younger age groups ($P = .32$). The probability of 4-year OS was significantly lower in the older age group (36% versus 54%; $P = .03$). Six factors were selected for multivariate analysis: age, sex, sex matching, conditioning regimen, acute GVHD prophylaxis, and time from diagnosis to BMT; however, none of these were significant independent predictors of OS or LFS.

Doney et al. [58] retrospectively analyzed the outcomes of 182 adult (≥18 years) patients with ALL treated with an allogeneic BMT in CR1 (n = 41) CR≥2 (n = 46), or relapse (n = 95) at two US centers between 1990 and 1997. Allogeneic donors were HLA–matched related (n = 88), HLA–matched unrelated (n = 33), HLA–mismatched related (n = 26), or HLA–mismatched unrelated (n = 35). Conditioning regimens consisted of Cy and TBI (1200-1575 cGy, n = 169), chemotherapy only (n = 8), or chemotherapy (not Cy) and TBI (1320-1575 cGy, n = 5). GVHD prophylaxis consisted of CSA and MTX (n = 105), CSA and MP ± other (n = 30), CSA alone (n = 26), or other (n = 21). Median duration of CR1 and sites of prior relapse for the patients with CR≥2 and relapse were not stated. At a median follow-up of 36 months, the 5-year DFS was 21% for all patients. Patients who underwent transplantation in CR1 had a significantly ($P < .001$) better 5-year DFS (43%) than those who underwent transplantation in CR≥2 (23%) or in relapse (9%). Multivariate analysis of risk factors determined age older than 40 years (RR = 1.91; $P < .01$), transplantation in relapse (RR = 3.46; $P < .01$), and GVHD prophylaxis with CSA alone (RR = 1.96; $P < .01$) were significant independent predictors of lower DFS.

Esprou et al. [59] retrospectively analyzed 121 consecutive patients with Ph+ ALL (84% ≥ 18 years old) treated with an allogeneic SCT on one of 3 prospective French trials at 27 centers between 1992 and 2000. Patients underwent transplantation in CR1 (n = 76), CR≥2 (n = 10), or with refractory disease (n = 35). Allogeneic donors were HLA–matched related (n = 87), identical twin (n = 1), HLA–matched unrelated (n = 31), or HLA–mismatched related (n = 2). Conditioning regimens consisted of VP, Cy, and TBI (1200 cGy in 6 fractions, n = 48); Mel, Ara-c, and TBI (1200 cGy in 6 fractions, n = 21); or various other regimens (n = 52). GVHD prophylaxis consisted of CSA and MTX in all but 8 patients who received T-cell depleted grafts. At a median follow-up of 29 months, the 2-year OS was significantly better for patients who underwent transplantation in CR1 compared with all others (50% versus 17%; $P < .0001$).

Stirewalt et al. [60] performed a retrospective analysis of 90 consecutive patients with Ph+ ALL (50% > 33 years old) treated with an autologous (n = 8), matched related donor (n = 31), mismatched related donor (n = 14), or matched unrelated donor (n = 37) SCT at a single US center from 1989 to 2001. Conditioning regimens were Cy and TBI (1200-1575 cGy, n = 74); Cy, TBI, and ATG (1200-1575 cGy, n = 7); VP, Cy, and TBI (1200-1575 cGy, n = 5); VP, Cy, and BCNU (n = 2); VP, Cy, and TBI (600 cGy, n = 1); and fludarabine (Flu) and TBI (200 cGy, n = 1). GVHD prophylaxis in allogeneic cases consisted of CSA and MTX (n = 81) and CSA and mycophenolate mofetil (MMF) (n = 1). At a median follow-up of 50 months, the 5-year OS and DFS were both 30%. Multivariate analysis demonstrated a significantly higher risk of relapse in patients in relapse at time of SCT (compared with remission at time of SCT, RR = 3.9; $P < .001$), in mismatched related or matched unrelated donor SCT (compared with autologous/matched related donor SCT, RR = 2.9; $P = .005$), and patients aged 33 years or older (compared with < 33 years, RR = 1.7; $P = .042$).

Iida et al. [61] described the outcomes of 46 patients with Ph+ ALL (50% > 28 years old) treated in CR1 (n = 18), CR≥2 (n = 8), or with relapsed/primary refractory disease (n = 20) with an allogeneic SCT at 7 Japanese centers from 1981 to 2000. Allogeneic donors were HLA–matched related (n = 22), HLA–mismatched related (n = 8), or unrelated (n = 16, HLA–match status not indicated). Conditioning regimens consisted of Cy and TBI (1000-1500 cGy) ± other (n = 23); Mel and TBI (1000-1500 cGy) ± other (n = 20); and Bu and Cy (n = 3). GVHD prophylaxis regimens consisted of CSA and MTX (n = 33); tacrolimus and MTX (n = 9); and other (n = 4). The 5-year TRM was 26%. At a median follow-up of 53 months, the 5-year DFS was significantly higher for those who underwent transplantation in CR≥1 versus those who underwent transplantation with disease (38.5% versus 7.5%; $P = .02$).

Lee et al. [62] reported the results of 41 consecutive adult (>15 years) patients with precursor B-lineage ALL treated with an HLA–matched allogeneic BMT in CR1 (n = 35) or CR2 (n = 6) between 1994

Table 8. *Comparison of Patient Characteristics and Outcomes from the Articles in the Related and Unrelated Donor Allogeneic Stem Cell Transplantation Section*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients	Median (range) Age at Time of Transplant	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
Related vs. Unrelated Donor Allogeneic SCT										
56	2+	9 European centers	Total 221 MRD 103 MUD 118	 32 (17-62) 29 (17-57)	5 y 43% 50%	Not stated	5-y DFS 42%* 45%*	Not significant	Not stated	Not compared
Related and Unrelated Donor Allogeneic SCT										
57	2+	EBMT registry	Total 508 Age >40 y 41 Age 16-40 y 467	43 (41-51) 24 (14-40)	Overall 37% 28%	 19 32	Not stated	Not compared	Overall 36% 54%	$P = .03$
58	2+	2 US centers	Total 182† CR1 41 CR≥2 46 Rlps 95	29.4 (18-57.6)	Day 100 34%	Not stated	5-y DFS 43% 23% 9%	$P < .001$	5 y 21%	Not compared
59	2+	27 French centers Ph+ ALL	Total 121‡ CR1 76 Other 45	35 (1-53)	Overall 38%	29	Not stated	Not compared	2 y 50% 17%	$P < .0001$
60	2+	Single US center Ph+ ALL	Total 90 Auto/MRD 39§ MisMRD/MUD 51‖	33 (2-56)	Overall 30%	50	5-y DFS 30%	$P = .005$¶	5 y 30%	Not compared
61	2+	7 Japanese centers Ph+ ALL	Total 46 CR>1 26 Rlps/Refr 20	28.5 (4-51)	5 y 26%	53	5-y DFS 38.5% 7.5%	$P = .02$	5 y 23%	Not compared
62	2+	Single Korean center	Total 41# t(9;22) or t(4;11) 12 Other karyotype 29	27 (15-43)	Overall 7%	36	3-y DFS 27.8% 68.8%	$P = .001$	Not stated	Not compared
63	2+	12 German centers Ph+ ALL	Total 22	43.5 (17-57)	Overall 36%	11.9	1-y DFS 25.5%	Not compared	1 y 44.8%	Not compared
64	2−	4 International trials	Total 27	50 (18-63)	Day 100 19%	27	Not stated	Not compared	2 y 31%	Not compared
65	2−	13 German centers	Total 22 NST as first 11 NST as second 11	38 (21-58)	Overall 41%	16.5	Not stated	Not compared	Overall 27% 9%	Not significant

Auto indicates, autologous; CR1, first complete remission; CR>1, greater than first complete remission; CR≥2, second or greater, complete remission; DFS, disease-free survival; EBMT, European Bone Marrow Transplant; EFS, event-free survival; LFS, leukemia-free survival; MisMRD, mismatched related donor; MRD, matched related donor; MUD, matched unrelated donor; NST, nonmyeloablative stem cell transplant; OS, overall survival; Refr, refractory; Rlps, relapse.

*Comparing patients transplanted in CR1.

†Includes 88 HLA-matched related, 26 HLA-mismatched related, 33 HLA-matched unrelated, and 35 HLA-mismatched unrelated donor BMTs.

‡75 Patients overlap with reference 8.

§Includes 8 autologous and 31 HLA-matched related donor SCTs.

‖Includes 37 HLA-matched unrelated donor and 14 HLA-mismatched related donor SCTs.

¶The multivariate analysis comparing the Auto/MRD vs. MisMRD/MUD groups yielded a relative risk of 2.9, $P = .005$, controlling for remission status and year of SCT. The 5-year DFS for this comparison was not stated.

#The article did not state the donor relation.

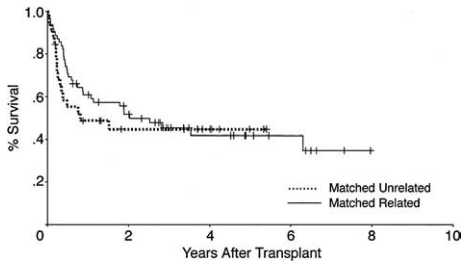

Figure 5. Kaplan-Meier estimation of disease-free survival in patients receiving transplantation from a matched related or unrelated donor in first complete remission. Reprinted with permission [56].

and 1999 at a single Korean center. No information was given regarding donor relation. Conditioning regimen consisted of Cy and TBI (1320 cGy fractionated); GVHD prophylaxis was CSA and MTX. Patients were classified as having an unfavorable karyotype if they had Ph+ ALL (n = 10) or t(4;11) (n = 2); all others, including patients with normal cytogenetics, were classified as having a favorable karyotype (n = 29). At a median follow-up of 36 months, the TRM was 7.3%. The 3-year DFS was significantly better for those with a favorable karyotype (68.8% versus 27.8%; $P = .001$). Multivariate analysis yielded unfavorable karyotype (RR = 11.6; 95% confidence interval 2.9-46.3; $P = .001$) and BMT in CR2 (RR = 6.9; 95% confidence interval 1.5-31.1; $P = .013$) as significant independent predictors of a lower DFS.

Wassman et al. [63] evaluated 22 adult (≥17 years) patients with Ph+ ALL treated with an allogeneic SCT after salvage therapy with imatinib mesylate. Patients underwent transplantation at 12 German centers from 2000 to 2001. Allogeneic donors were HLA–matched related (n = 9), HLA–mismatched related (n = 1), HLA–matched unrelated (n = 9), or HLA–mismatched unrelated (n = 3). Patients received imatinib mesylate as part of a phase II trial pre-SCT as a single daily oral dose of 600 mg, which was continued until severe toxicity or disease progression occurred; imatinib therapy was discontinued in all patients 1 to 14 days before starting the SCT conditioning regimen. Sixteen patients achieved a complete hematologic or molecular response within 4 weeks of initiation of imatinib therapy. Conditioning regimens consisted of Cy and TBI ± VP (dose of TBI not indicated, n = 11); Cy, TBI, and radioimmunotherapy (n = 2); Bu and Cy (n = 2); or other (n = 9). GVHD prophylaxis regimens were CSA, MTX, and ATG (n = 5); CSA and ATG (n = 3); CSA, ATG, and MMF (n = 2); CSA and MMF (n = 2); CSA and MTX (n = 2); or other combinations (n = 8). At a median follow-up of 11.9 months post-SCT, the 1-year DFS and OS for all patients were 25.5% and 44.8%, respectively.

Martino et al. [64] retrospectively reported the results of 27 adult (≥18 years) patients with ALL treated in CR1 (n = 4), CR≥2 (n = 10), Rel≥1 (n = 11), or with primary refractory disease (n = 2) with a reduced intensity conditioning regimen allogeneic SCT on one of 4 multicenter prospective studies accrued through 2001. Patients received a reduced intensity regimen as a result of age older than 55 years, prior autologous BMT, or severe comorbidity (pulmonary, cardiac, or other organ dysfunction contraindicating myeloablative conditioning). Allogeneic donors were HLA–matched related (n = 15), HLA–mismatched related (n = 4), HLA–matched unrelated (n = 4), and HLA–mismatched unrelated (n = 4). Reduced intensity conditioning regimens consisted of Flu (90-150 mg/m^2) and Mel (140 mg/m^2) (n = 21); Flu, Mel, and Ara-c (n = 3); Flu (90-150 mg/m^2), thiotepa (10 mg/kg), and Cy (n = 2); and Flu and TBI (single fraction 200 cGy, n = 1). GVHD prophylaxis consisted of CSA and MTX (n = 13); tacrolimus and MTX (n = 11); CSA and Campath (n = 2); and CSA and MMF (n = 1). Day 100 TRM was 18.5%; the incidence of grades II to IV acute GVHD was 48%. At a median follow-up of 26.7 months, the 2-year OS was 31% and the 2-year probability of disease progression was 49%.

Arnold et al. [65] described a prospective pilot study of nonmyeloablative conditioning for allogeneic SCT in 22 adult (≥21 years) patients with high-risk ALL conducted at 13 German centers (time period was not stated in the article). Allogeneic donors were HLA–matched related (n = 13), HLA–mismatched related (n = 1), or HLA–matched unrelated (n = 8). High-risk was defined by GM-ALL criteria: active disease (n = 16), Ph+ ALL in CR1 (n = 1), high WBC at diagnosis and in CR1 (n = 1), Ph+ ALL in CR2 (n = 1), T-lineage ALL in CR2 (n = 1), CR2 with relapse after prior SCT (n = 1), and graft failure after prior SCT (n = 1). A total of 11 patients received nonmyeloablative SCT as their first SCT; 11 patients received it as salvage after a failed prior autologous or allogeneic SCT. Sites of prior relapse and duration of CR1 were not stated. Conditioning regimen consisted of Flu and Bu ± ATG. GVHD prophylaxis consisted of CSA alone (n = 10); CSA and MMF (n = 7); CSA and MTX (n = 3); MTX alone (n = 1); and CSA and prednisolone (n = 1). At a median follow-up of 16.5 months, 9 patients (41%) died of GVHD or infection, 8 patients (36%) died of leukemia, and one died of graft failure. Donor lymphocyte infusions were given to 7 patients for residual/refractory disease post-SCT. Four patients were alive and in CR 5 to 30 months post-SCT.

AUTOLOGOUS VERSUS ALLOGENEIC BMT IN ADULT ALL

Table 9 summarizes the grading criteria, study populations, patient characteristics, and outcomes

from adult studies included in the Autologous versus Allogeneic BMT section. Evidence in this section is taken from self-described studies of adult populations, all of which included patients at least 13 years of age. Evidence is presented with the highest quality studies first; studies of equal quality are presented in descending order with the largest sample size first.

Hunault et al. [66] performed a prospective multicenter (21 institutions) phase III trial between 1994 and 1998 for adult (≥15 and <59 years) patients with ALL in CR1 with a biologic randomization between patients younger than 50 years with an HLA–identical sibling donor (n = 41) who received a related allogeneic SCT (n = 39) and patients older than 50 years (n = 9) or without an HLA–identical sibling donor (n = 106) who received an autologous PBSCT (n = 19) or BMT (n = 72). Patients were eligible for the trial if they had one or more of the following risk factors: age older than 35 years; B-lineage ALL; WBC greater than 30×10^9/L; cytogenetic abnormalities including t(4:11), t(9;22), t(1;19), or *BCR-ABL*+; or failure to achieve CR1 after one induction course. Both allogeneic and autologous SCT patients received VP, Cy, and TBI (1200 cGy in 6 fractions) as the conditioning regimen. GVHD prophylaxis regimens were not indicated. At a median follow-up of 5.1 years, the related donor group had a significantly improved 6-year DFS (72% versus 33%; $P = .0004$) and 6-year OS (75% versus 39%; $P = .0027$; Figure 6) compared with the no donor group. This comparison was restricted to the 106 patients younger than 50 years who were eligible for an allogeneic SCT and was performed on an intent-to-treat basis.

Attal et al. [67] performed a prospective phase III trial at 9 French centers between 1990 and 1992 with a biologic randomization: adult (>15 years) patients with ALL in CR1 with (n = 43) or without (n = 77) an HLA–identical sibling donor received a T-cell replete allogeneic (n = 41) or unpurged autologous (n = 64) BMT, respectively. BMT was performed in 83% of the no donor and 95% of the patients in the donor group; however, all analyses were performed on an intent-to-treat basis. In all, 12% of the donor group and 18% of the no donor group had Ph+ ALL. Patients with autologous BMT were further randomized to receive (n = 30) or not receive (n = 30) IL-2 for 5 cycles every other week after transplantation once the following post-BMT criteria were fulfilled: (1) CR; (2) WBC recovery; and (3) adequate kidney, liver, cardiac, and pulmonary function. The conditioning regimen for both autologous and allogeneic cases was Cy and TBI (1200 cGy, fractionated). GVHD prophylaxis for patients with allogeneic BMT was CSA and MTX. The 3-year DFS in the HLA–identical sibling group versus the no HLA–identical sibling group was 68% versus 26%; $P < .001$ (Figure 7). The corresponding TRM rates were 12% and 2%. In the autologous BMT group, there was no significant difference in the 3-year DFS (29% versus 27%; P = not significant) or 3-year OS (28% versus 36%; P not significant) in the patients who did or did not receive posttransplantation IL-2.

Dombret et al. [8] conducted a prospective phase III trial at 33 French and Belgian centers between 1994 and 2000 (LALA-94 trial) in patients (≥15 years old) with newly diagnosed untreated Ph+ or *BCR-ABL*+ with B-lineage ALL. A total of 154 patients were randomized to receive one of two induction therapy regimens, followed by a single consolidation/salvage regimen of intermediate-dose Ara-c and mitoxantrone. A total of 103 patients in CR after intermediate-dose Ara-c and mitoxantrone were eligible for a biologic randomization based on donor availability to either a matched related BMT (n = 46), matched unrelated BMT (n = 14), or autologous PBSCT (n = 43) at 3 months after consolidation. The conditioning regimen for autologous and related allogeneic BMT was Cy, VP, and TBI (1000cGy in 1 fraction or 1200 cGy in 6 fractions) but varied by center for unrelated donor BMT. GVHD prophylaxis regimens varied by center. Transplantation was actually performed in 44 (96%) of the matched related, 12 (86%) of the matched unrelated, and 24 (56%) of the autologous BMT groups; however, the results are based on an intent-to-treat approach. There was no difference in OS in the matched related versus unrelated BMT groups; therefore, the data were analyzed as donor (n = 60) versus no donor (n = 43) groups. The 3-year OS of the no donor group was significantly lower than the donor group (12% versus 37%; $P = .02$; Figure 8), even after adjustment for age, leukocyte count, and number of chemotherapy courses to achieve CR1. The 3-year relapse incidence was significantly higher in the no donor versus donor group (90% versus 50%; $P < .001$). The 2-year probability of death in CR was equivalent in the donor versus no donor groups (24% versus 24%; P = not significant).

Ringden et al. [68] compared 1416 autologous, 346 HLA–matched sibling allogeneic (who did not develop GVHD), and 23 identical twin BMT patients treated for ALL in CR1 between 1987 and 1999 and reported to the EBMT to determine if there was a graft-versus-leukemia effect in the absence of GVHD. Of patients, 17% were younger than 17 years at time of BMT; however, this is an aggregate of patients with AML and ALL. Autologous BMT recipients received purged (n = 759), unpurged (n = 1792), or unknown purged/unpurged (n = 2649) grafts. The majority of allogeneic BMT recipients received CSA and MTX (70%) for GVHD prophylaxis; another 14% received T-cell depleted grafts. Of all patients, 48% received TBI-containing conditioning regimens, another 16% received Bu and Cy, and 36% received other combi-

Table 9. *Comparison of Patient Characteristics and Outcomes from the Articles in the Autologous Versus Allogeneic Stem Cell Transplantation Section*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients	Median (range) Age at Time of Transplant	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
66	1+	GOELAL02 trial	Total 156	33 (15-59)	6 mo	61	6-y DFS	$P = .0004$*	6 y	$P = .0027$*
			Rel donor 41		15%		72%		75%	
			No Rel donor 115		3%		33%		39%	
67	1+	Multicenter French trial	Total 120	31 (15-55)	Overall		3-y DFS	$P < .001$	Not stated	Not compared
			Rel donor 43		12%	27	71%			
			No Rel donor 77		2%	25	30%			
8	1+	LALA-94 trial Ph+ ALL	Total 103	Not stated	2 y	54‡	Not stated	Not compared	3 y	$P = .02$
			Allo donor 60†		24%				37%	
			No donor 43		24%				12%	
68	2++	EBMT registry§	Total 1785		2 y	32	2 y	$P < .0001$#	Not stated	Not compared
			Auto 1416	34 (1-77)¶	9%		44%			
			Sib Allo 346‖	27 (1-66)¶	9%		61%			
			Identical twin 23	30 (1-70)¶	17%		54%			
69	2+	Single US center	Total 36	Not stated	Overall	Not stated	Overall DFS	$P = .0001$	Median OS (mos)	$P = .0001$
			Auto BMT 23		12%		21%		48	
			Allo BMT 13		8%		43%		12	
70	2−	Single Italian center	Total 79		Overall		10-y EFS	Not stated	Not stated	Not compared
			Auto 39	21 (10-53)	5%	158	37.1%			
			Allo 40	25 (8-54)	30%	99	46.9%			
71	2−	Single French center	Total 63		6 mo			$P < .06$		Not significant
			Auto BMT 34	29 (16-59)	3%	54	27%		26%	
			Allo BMT 29	24 (16-41)	24%	83	62%		61%	
72	2−	Single French center	Total 47		Overall		Overall DFS	Not stated	Overall	Not stated
			Auto 22	47 (31)	9%	25	40%		62%	
			Rel Allo 25	36 (22)	20%	42	71%		71%	
73	2−	Single US center	Total 36		Overall		Overall DFS	Not significant	Not stated	Not significant
			Auto BMT 22	28 (18-54)	18%	78	20%			
			Allo BMT 14	31 (19-50)	Not stated	Not stated	Not stated			
74	2−	Multicenter French trial	Total 34		Overall	Not stated	4-y EFS	Not compared	Not stated	Not compared
			Auto BMT 18	32 (16-49)	0%		17%			
			Allo BMT 16	29 (18-46)	38%		33%			
75,76	2−	4 German Centers Ph+ ALL	Total 24	28.5 (2-60)	Overall 25%	45	3-y DFS	Not compared	3-y	Not compared
			Auto 5	24 (6-48)	0%		Not stated		Not stated	
			Rel Allo 13	30 (4-60)	38%		46%#		50%**	
			Unrel Allo 6	16 (2-45)	17%		Not stated		Not stated	
77,78	2−	Single Spanish center	Total 23	30 (16-62)	Overall 11%	44	Not stated	Not compared	Not stated	Not compared
			Auto 9							
			Allo 14		29%					

Table 9. *Continued*

Reference	Quality and Strength of Evidence	Patient Populations	No. of Patients	Median (range) Age at Time of Transplant	Treatment-Related Mortality	Median Follow-Up (mos)	LFS/EFS/DFS	Significance LFS/EFS/DFS	OS	Significance OS
79	2–	Single UK center Ph+ ALL	Total 20†† Auto BMT 9 Allo BMT 11	 35 (9-55) 27 (3-37)	2 y 11% 27%	 17 26	3-y DFS 25.6% 21.8%	Not stated	Not stated	Not compared

ALL indicates acute lymphoblastic leukemia; Allo, allogencic; Auto, autologous; BMT, bone marrow transplantation; DFS, disease-free survival; EBMT, European Group for Blood and Marrow Transplant; EFS, event-free survival; LALA, Leucémie Aiguë Lymphoblastique de l'Adulte (Adult Acute Lymphoblastic Leukemia); LFS, leukemia-free survival; OS, overall survival; Rel, related; Sibl, sibling; Unrel, unrelated; UK, United Kingdom.

*The comparison of related donor vs. no donor groups was restricted to the 106 patients <50 years who were eligible to receive an allogeneic SCT if a donor was available.

†Includes 46 with matched related and 14 with matched unrelated donors; 93% of the Allo donor and 56% of the No donor groups actually underwent transplantation.

‡Median follow-up from time of initial randomization before induction therapy.

§There is some overlap between this study and references 30, 32, and 33.

‖Includes only HLA-matched sibling allo BMT patients who did not develop acute or chronic GVHD.

¶Median age includes AML and ALL patients. ALL patients are 39% of the total patient population.

#Comparing auto vs. sibling allo groups.

**DFS and OS is given for the 15 related+unrelated allogeneic BMT patients who were treated in CR1.

††A total of 5 patients overlap with reference 18.

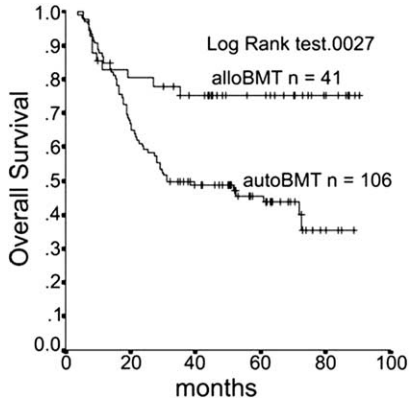

Figure 6. Overall survival according to alloBMT and autoBMT in an intent-to-treat analysis. Reprinted with permission [66].

nations. At a median follow-up of 32 months, the 2-year probability of relapse was 51% in the autologous, 33% in the siblings without GVHD, and 35% in the identical twin transplantation groups ($P < .0001$). The 2-year LFS was 44%, 61%, and 54%, respectively, in these groups ($P < .0001$).

Sotomayor et al. [69] performed a trial of a sequential therapy regimen in 85 consecutive unselected adult (≥17 years) patients with ALL at a single US center between 1983 and 1993. The sequential regimen consisted of one of two induction therapies, followed by intensification with Ara-c and daunorubicin. Patients in CR1 with an HLA–identical sibling donor received an allogeneic BMT (n = 13); those in CR1 with no suitable donor received either an autologous BMT purged *ex vivo* with 4-hydroperoxycyclophosphamide ± vincristine and MP (n = 23) or maintenance chemotherapy and late intensification (n = 17) for those patients ineligible for autologous or allogeneic BMT, because of patient refusal, early relapse, or

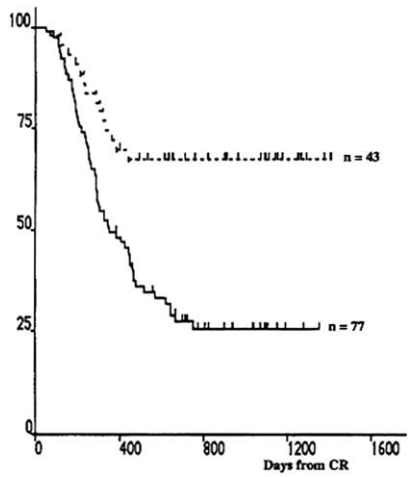

Figure 7. DFS was significantly superior ($P < .001$) for patients with an HLA-identical sibling (dashed line) than for patients without an HLA-identical sibling (solid line). Reprinted with permission [67].

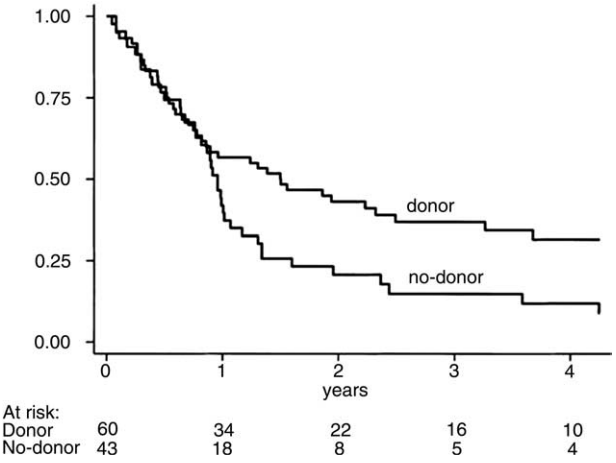

Figure 8. Kaplan-Meier landmark survival estimates (with a 90-day landmark period) for patients eligible for SCT according to the existence of an allogeneic donor (N = 103 patients) (relative risk in the no-donor group, 1.71; 95% confidenced interval, 1.09 to 2.68; $P = .02$ by the log-rank test). Reprinted with permission [8].

older age. Conditioning regimens were varied, but consisted mainly of Cy and TBI (n = 24) or Bu, Cy, and VP (n = 12); GVHD prophylaxis consisted of CSA or T-cell depletion. Median follow-up time of the surviving patients was not stated. The 4-year DFS was significantly better in the allogeneic BMT group compared with the autologous BMT group (43% versus 21%; $P = .0001$). Median OS was also significantly longer in the allogeneic BMT group (48 versus 12 months; $P = .0001$).

Annaloro et al. [70] presented the results of 79 patients with ALL (50% > 21 years old) who received an autologous (n = 39) or allogeneic (n = 40) BMT at a single Italian center from 1984 to 2002. Allogeneic donors were HLA–matched related (n = 36), HLA–matched unrelated (n = 3), or HLA–mismatched related (n = 1). In all, 17 autologous and 19 allogeneic BMT recipients were in CR1 at time of transplantation; the remaining patients had more advanced disease. Conditioning regimens consisted of Cy, Ara-c, and TBI (1000 cGy in 3 fractions, n = 76 autologous and related allogeneic BMT), and Cy and TBI (1320 cGy in 11 fractions, n = 3). GVHD prophylaxis consisted of CSA and MTX (n = 39), and CSA and MP (n = 1). Median duration of CR1 in the autologous BMT group was 13 months and in the allogeneic group was 14 months. At a median follow-up of 158 months in the autologous and 99 months in the allogeneic BMT groups, the 10-year EFS were 37.1% and 46.9%, respectively (*P* not stated).

Vey et al. [71] retrospectively analyzed 63 adult (>15 years) patients with ALL treated in CR1 with either autologous (n = 34, lacking an HLA–identical sibling donor) or allogeneic (n = 29, with an HLA–identical sibling donor) BMT between 1981 and 1991 at a single French center. All patients had at least one poor prognostic feature: age older than 30 years; WBC at diagnosis greater than 25×10^9/L; CNS involvement; B-lineage; t(4;11) or t(9;22); or time from diagnosis to CR1 longer than 4 weeks. Conditioning regimens included Cy and TBI; Mel and TBI; or Cy, Mel, and TBI. GVHD prophlyaxis in the allogeneic BMT group included MTX (n = 5), CSA (n = 9), or CSA and MTX (n = 15). In addition, 7 patients with allogeneic BMT received T-cell depleted grafts. Autologous BM was purged *in vitro* in 24 patients with anti-CD10, anti-DR, anti-CD5+ricin A chain, 4-hydroperoxycyclophosphamide, ASTA-Z, or VP. At a median follow-up of 5.5 years, the 6-year DFS was higher for the allogeneic compared with the autologous BMT group (62% versus 27%; $P < .06$).

Blaise et al. [72] performed a pilot trial of purged autologous (n = 22) and matched related allogeneic (n = 25) BMT in patients with high-risk ALL (78% of the autologous and 88% of the allogeneic group were ≥15 years old) in CR1 from 1981 to 1987 in a single French center. Patients without a matched sibling received an autologous BMT. Patients at high risk were defined as older than 15 years at diagnosis, 15 years or younger with a WBC greater than 100×10^9/L at diagnosis, or failure to achieve a CR within 1 month of induction therapy. All patients received TBI with Mel, Cy, or Mel and Cy as the conditioning regimen; GVHD prophylaxis was MTX or CSA or both (n = 17) or T-cell depletion (n = 8). At a median follow-up of 31 and 22 months in the autologous and allogeneic groups, there were no statistically significant differences in DFS or OS.

Soiffer et al. [73] treated 22 adult (>18 years) patients with B-lineage ALL with an autologous BMT purged *in vitro* with J5 and J2 monoclonal antibodies (CD10/CD9) plus rabbit complement. All patients received Cy and TBI (1200-1400 cGy, fractionated) as conditioning; the first 9 patients also received Ara-c. No patients with autologous BMT had HLA–identical sibling donors. All patients underwent transplantation in CR≥2 (n = 21) or had primary induction failures and achieved CR1 with subsequent chemotherapy (n = 1). These patients with autologous BMT were compared with a concurrent cohort of 14 adult patients with ALL treated in CR2 or CR3 with T-cell depleted (anti-CD6 monoclonal antibody plus complement) HLA–identical related allogeneic BMT. Patients with allogeneic BMT were treated with the same conditioning regimen as the autologous group and met similar eligibility criteria. There was no significant difference between the autologous and allogeneic BMT groups with respect to DFS or OS (survival and *P* not stated in original article). In the autologous BMT group, only age was a prognostic factor, where patients younger than 28 years at time of BMT had a longer DFS than those who were older than 28 years (45% versus 0%; *P* not stated).

Ifrah et al. [74] performed a prospective randomized trial of granulocyte macrophage colony–stimulating factor versus placebo after induction and intensification chemotherapy in 67 adult (≥15 years) patients with ALL between 1990 and 1992 at 16 French centers. After induction therapy, all patients who achieved a CR1, were younger than 45 years old and had an HLA–identical sibling donor (n = 18), underwent allogeneic BMT (n = 16); all others received one course of an intensification chemotherapy regimen followed by unpurged autologous BMT (n = 18). For patients with allogeneic BMT, conditioning regimens varied by center. For patients with autologous BMT, conditioning regimens were Cy and TBI (1200 cGy, n = 16) or Bu and Cy (n = 2). The 4-year EFS was 33% for the allogeneic and 17% for the autologous groups (statistical significance tests comparing autologous versus allogeneic BMT were not performed).

Kroger et al. [75,76] retrospectively assessed the outcomes of 24 patients with Ph+ ALL (79% ≥ 18 years old at time of BMT) treated with an autologous (n = 5) or allogeneic (n = 13 related, 6 unrelated donor) BMT between 1990 and 1997 at 4 German centers. Remission status at BMT was 19 CR1, 2 CR2, 1 PIF, and 2 relapse. Conditioning regimens consisted of VP, Cy, and TBI (n = 23) or VP, Cy, and Bu (n = 1); GVHD prophylaxis consisted of CSA and MTX ± ATG. At a median follow-up of 45 months in all patients, the DFS was 37.5%. Allogeneic BMT patients treated in CR1 (n = 15) had a 3-year DFS and OS of 46% and 50%, respectively.

Martino et al. [77,78] described the results of 22 consecutive adult (≥16 years) patients with ALL treated with an autologous (n = 9, 8 of which were purged) or an HLA–matched related allogeneic (n = 14) BMT at a single Spanish center from 1988 to 1997. Conditioning and GVHD prophylaxis regimens were not stated. All patients with autologous BMT and 9 patients with allogeneic BMT were in CR≥2 at time of BMT; 5 with allogeneic BMT were in second or greater relapse. At a median follow-up of 44 months, the median OS was 15.4 months for autologous and was not yet reached for patients with allogeneic BMT ($P = .2$).

Dunlop et al. [79] reported 19 patients (one patient was <18 years old) with Ph+ ALL who were treated with 20 transplantation procedures (9 autologous or 11 matched related allogeneic BMT) in CR1 (n = 12), CR2 (n = 3), or relapse (n = 5) between 1986 and 1995 at one United Kingdom center. Patients with autologous BMT received Mel ± TBI and patients with allogeneic BMT received TBI and Mel, Cy, or VP as conditioning regimen. GVHD prophylaxis was CSA ± MTX. No patients received purged or T-cell depleted grafts. Patients with autologous BMT received maintenance therapy with daily 6-mercaptopurine and weekly MTX for 2 years post-BMT. There was no significant difference in DFS between the autologous and allogeneic BMT groups. OS for the whole cohort was 37.5% at 3 years and was not specified for the two BMT groups.

FUTURE DIRECTIONS

Additional Ongoing Studies

Several studies have been published in abstract form, were recently completed, or are currently accruing patients but address critical issues that may affect the treatment recommendations made above. The Eastern Cooperative Oncology Group (ECOG), National Cancer Institute, and Medical Research Council have sponsored a randomized phase III international multicenter trial (UKALL XII/ECOG2993 study) of consolidation/maintenance chemotherapy versus SCT in adult (15-65 years) patients with ALL in CR1 [80-82]. Patients younger than 50 years are assigned to receive a related allogeneic SCT (an unrelated donor SCT is allowed for patients with Ph+ ALL) if a suitable donor is available, otherwise patients are randomized to receive an autologous SCT versus consolidation/maintenance chemotherapy. Patients age 50 to 65 years are randomized to consolidation chemotherapy versus autologous SCT. Patients with Ph+ ALL receive maintenance imatinib mesylate after autologous or allogeneic SCT.

The Cancer and Leukemia Group B has sponsored a phase II multicenter trial in adult (15-59 years) patients with Ph+ ALL. Patients receive a related donor allogeneic SCT if a suitable donor is available, otherwise receive an autologous SCT or chemotherapy if transplantation is not an option. Patients receive imatinib mesylate both before and after SCT.

Areas of Needed Research

After reviewing the evidence and highlighting the studies that are in progress, the panel recommends the following as the most important areas of needed research: monitoring of minimal residual disease and disease control before SCT; comparison of nonfamily (unrelated bone marrow or cord blood) donor versus autologous SCT; definition of high-risk groups, beyond Ph+ status, in CR1; evaluation of the impact of imatinib and other tyrosine kinase inhibitors on SCT for Ph+ ALL; analysis of the graft-versus-leukemia effect in reduced intensity versus myeloablative conditioning regimens; and outcomes data for SCT in older (>50 years) patients with ALL.

DISCUSSION

The authors strongly recommend methodology standardization, including study design, end point definitions, and reporting of study results. Multi-

center randomized phase III comparative trials with large enrollments and high statistical power are required to advance the field more constructively than single institution phase II trials with one treatment arm or retrospective multicenter or registry studies. In addition, publication of preliminary analyses should be reserved for studies in which the trial was terminated early because of excessive toxicity or significantly inferior or superior results. For most studies, 3 years of follow-up in surviving patients is needed to detect significant differences between treatment arms. The authors advocate prompt reporting of mature data in full-length article format. Abstracts do not adequately convey the full details of the study design or patient characteristics to meet evidence-based criteria for inclusion in systematic reviews, nor for making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial.

Much of today's therapies for cancer result from the clinical trial process. It is currently estimated that less than 5% of adults eligible to participate in cancer clinical trials actually enroll in a trial. The authors acknowledge the importance of removing barriers to participation in clinical trials, which may include patients' reluctance to be randomized, lack of patient access to clinical trials (e.g., geographic, transportation, cultural), financial constraints (no or incomplete insurance coverage for trial expenses), stringent trial eligibility criteria, and reluctance of community physicians to refer patients for clinical trial participation.

An additional challenge to the low rate of participation in clinical trials by adult patients with cancer is the relatively low incidence of adult ALL. According to the Surveillance, Epidemiology, and End Results Cancer Statistics Review [83], it is estimated that there will be approximately 1700 to 1800 new cases of adult ($\geq$20 years) ALL diagnosed in the United States in 2005. Thus, there is a small number of adult ALL cases that may be eligible for enrollment in a clinical trial examining any one of numerous therapeutic options.

LIMITATIONS OF THIS EVIDENCE-BASED LITERATURE REVIEW

There are limitations to any evidence-based review of the published literature. The criteria for this review included reliance on published data, specifically peer-reviewed articles published since 1980. Unpublished data, which were not included in this review, often represent negative findings and do not undergo peer review. We also excluded data published in abstract form because the data are usually not peer reviewed, are presented in an abbreviated format, and usually represent preliminary, not final data analyses. In addition, published literature may not address the management of all disease-specific clinical situations.

Limitations specific to this review topic include the variability in reporting patient characteristics pre-SCT, changing treatment modalities over time, and the paucity of randomized controlled trial data. The success of SCT is affected by prior sites of relapse, presence of extramedullary disease, and duration of CR1; many studies did not report this information in the published article making it difficult to compare SCT outcomes across studies. Chemotherapy regimens, particularly those used for salvage, and pre-SCT conditioning regimens and post-SCT supportive care have changed during the more than 20 years of trials included in this review. The effectiveness of salvage regimens impacts attainment of CR$\geq$2, which in turn impacts the effectiveness of SCT. Finally, randomized controlled trial data were lacking in many areas of this review leading to several treatment recommendations based on small prospective studies and/or large retrospective registry reports. For example, the expert panel could not make recommendations for or against the use of SCT for patients not in CR because available evidence was insufficient.

FUTURE INITIATIVES

This comprehensive systematic review of the available evidence for the role of cytotoxic therapy with SCT in the therapy of adult ALL is the fourth in a series of sequential articles sponsored by the ASBMT. Each review will summarize the evidence regarding the role of cytotoxic therapy with SCT in the treatment of a specific disease using defined methodology and grading criteria. The next review in the series will address the role of SCT in the therapy of pediatric acute myeloid leukemia.

ACKNOWLEDGMENTS

The ASBMT and Drs Hahn and McCarthy are indebted to the members of the ALL Review Panel and the Steering Committee, who voluntarily and enthusiastically participated in this endeavor. The authors acknowledge Dr C. Fred LeMaistre for pioneering and supporting this effort; Mr Alan Leahigh and Ms Dianne O'Rourke for their invaluable administrative assistance; Ms Hilary Roy, Mr David Roy, Ms Leslie Milk, Dr Afrin Wahab, and Ms Mary Rosen for serving as replication coders and abstractors, and Ms Dorothy Macchio for reviewing the manuscript.

Appendix A. *Glossary of Terms*

ALC	**Absolute lymphocyte count**
ALL	**Acute lymphoblastic leukemia**
ASBMT	**The American Society for Blood and Marrow Transplantation**
Ara-c	**Cytarabine; cytosine arabinoside**
ATG	**Anti-thymocyte globulin**
AUL	**Acute unclassified leukemia**
BMT	**Bone marrow transplantation**
Bu	**Busulfan**
CNS	**Central nervous system**
CR	**Complete remission**
CR1	**First complete remission**
CR>1	**Greater than first complete remission**
CR≥1	**First or greater complete remission**
CR2	**Second complete remission**
CR≥2	**Second or greater complete remission**
CR3	**Third complete remission**
CR≥3	**Third or greater complete remission**
CSA	**Cyclosporine**
Cy	**Cyclophosphamide**
DFS	**Disease-free survival**
EBMT	**European Group of Blood and Marrow Transplant**
EFS	**Event-free survival**
Flu	**Fludarabine**
GVHD	**Graft versus host disease**
HLA	**Human leukocyte antigen**
IBMTR	**The International Bone Marrow Transplant Registry**
JALSG	**Japan Adult Leukemia Study Group**
LALA	**Leućemie Aiguë Lymphoblastique de l'Adulte**
LFS	**Leukemia-free survival**
Mel	**Melphalan**
MMF	**Mycophenolate mofetil**
MP	**Methylprednisolone**
MTX	**Methotrexate**
NMDP	**National Marrow Donor Program**
OS	**Overall survival**
PBSCT	**Peripheral blood stem cell transplantation**
Ph+	**Philadelphia chromosome positive**
RCTs	**Randomized controlled trials**
RFS	**Relapse-free survival**
RR	**Relative risk**
SCT	**Hematopoietic stem cell transplantation**
TBI	**Total body irradiation**
TRM	**Treatment-related mortality**
UKALL	**United Kingdom Acute Lymphoblastic Leukemia**
VP	**Etoposide**
WBC	**White blood cell count**

Appendix B. *Outline of Article*

REFERENCES

1. Hahn T, Wolff SN, Czuczman MC, 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.

2. Hahn T, Wingard J, Anderson K, 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.
3. 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;11:823-861.
4. Jones R, Nieto Y, Rizzo JD, 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.
5. 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.
6. 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.
7. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol*. 2004;22:4075-4086.
8. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia–results of the prospective multicenter LALA-94 trial. *Blood*. 2002;100:2357-2366.
9. Zhang MJ, 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. The Acute Lymphoblastic Leukemia Working Committee. *Ann Intern Med*. 1995;123:428-431.
10. Horowitz MM, Messerer D, Hoelzer D, et al. Chemotherapy compared with bone marrow transplantation for adults with acute lymphoblastic leukemia in first remission. *Ann Intern Med*. 1991;115:13-18.
11. Messerer D, Neiss A, Horowitz MM, et al. Comparison of chemotherapy and bone marrow transplants using two independent clinical databases. *J Clin Epidemiol*. 1994;47:1119-1126.
12. Oh H, Gale RP, Zhang MJ, et al. Chemotherapy vs HLA-identical sibling bone marrow transplants for adults with acute lymphoblastic leukemia in first remission. *Bone Marrow Transplant*. 1998;22:253-257.
13. Messerer D, Neiss A, Aydemir U, et al. How can disease-free survival of adult ALL patients with or without transplants be compared? *Onkologie*. 1991;14:53-55.
14. Takeuchi J, Kyo T, Naito K, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. *Leukemia*. 2002;16:1259-1266.
15. Gupta V, Yi QL, Brandwein J, et al. The role of allogeneic bone marrow transplantation in adult patients below the age of 55 years with acute lymphoblastic leukemia in first complete remission: a donor vs no donor comparison. *Bone Marrow Transplant*. 2004;33:397-404.
16. Ueda T, Miyawaki S, Asou N, et al. Response-oriented individualized induction therapy with six drugs followed by four courses of intensive consolidation, 1 year maintenance and intensification therapy: the ALL90 study of the Japan Adult Leukemia Study Group. *Int J Hematol*. 1998;68:279-289.
17. Tamura S, Takemoto Y, Kanamaru A, et al. Comparison of the survivals between bone marrow transplantation and chemotherapy for acute leukemia in first remission–a Japanese single institution study. *Leuk Lymphoma*. 1992;8:361-364.
18. Powles R, Mehta J, Singhal S, et al. Autologous bone marrow or peripheral blood stem cell transplantation followed by maintenance chemotherapy for adult acute lymphoblastic leukemia in first remission: 50 cases from a single center. *Bone Marrow Transplant*. 1995;16:241-247.
19. Tiley C, Powles R, Treleaven J, et al. Feasibility and efficacy of maintenance chemotherapy following autologous bone marrow transplantation for first remission acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1993;12:449-455.
20. Mehta J, Powles R, Singhal S, et al. Melphalan-total body irradiation and autologous bone marrow transplantation for adult acute leukemia beyond first remission. *Bone Marrow Transplant* 1996;18(suppl 1):119-123.
21. Lambertenghi Deliliers G, Mozzana R, Annaloro C, et al. Long-term results of autologous bone marrow transplantation in adult acute lymphoblastic leukemia. *Leuk Lymphoma*. 1993;11:419-425.
22. Carey PJ, Proctor SJ, Taylor P, et al. Autologous bone marrow transplantation for high-grade lymphoid malignancy using melphalan/irradiation conditioning without marrow purging or cryopreservation. The Northern Regional Bone Marrow Transplant Group. *Blood*. 1991;77:1593-1598.
23. Proctor SJ, Taylor P, Thompson RB, et al. Acute lymphoblastic leukemia in the northern region of England–a study of 75 cases. *Q J Med*. 1985;57:761.
24. Abdallah A, Egerer G, Goldschmidt H, et al. Continuous complete remission in adult patients with acute lymphocytic leukemia at a median observation of 12 years after autologous bone marrow transplantation. *Br J Haematol*. 2001;112:1012-1015.
25. Hoelzer D, Thiel E, Loffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood*. 1988;71:123-131.
26. Gilmore MJ, Hamon MD, Prentice HG, et al. Failure of purged autologous bone marrow transplantation in high risk acute lymphoblastic leukemia in first complete remission. *Bone Marrow Transplant*. 1991;8:19-26.
27. Mehta J, Powles R, Treleaven J, et al. Autologous transplantation with CD52 monoclonal antibody-purged marrow for acute lymphoblastic leukemia: long-term follow-up. *Leuk Lymphoma*. 1997;25:479-486.
28. Doney K, Buckner CD, Fisher L, et al. Autologous bone marrow transplantation for acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1993;12:315-321.
29. Hill RS, Mazza P, Amos D, et al. Engraftment in 86 patients with lymphoid malignancy after autologous marrow transplantation. *Bone Marrow Transplant*. 1989;4:69-74.
30. Ringden O, Labopin M, Bacigalupo A, et al. Transplantation of peripheral blood stem cells as compared with bone marrow from HLA-identical siblings in adult patients with acute myeloid leukemia and acute lymphoblastic leukemia. *J Clin Oncol*. 2002;20:4655-4664.
31. Passweg JR, Tiberghien P, Cahn JY, et al. Graft-versus-leuke-

mia effects in T lineage and B lineage acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1998;21:153-158.
32. Frassoni F, Labopin M, Gluckman E, et al. Results of allogeneic bone marrow transplantation for acute leukemia have improved in Europe with time–a report of the acute leukemia working party of the European group for blood and marrow transplantation (EBMT). *Bone Marrow Transplant*. 1996;17:13-18.
33. Ringden O, Labopin M, Gluckman E, et al. Graft-versus-leukemia effect in allogeneic marrow transplant recipients with acute leukemia is maintained using cyclosporin A combined with methotrexate as prophylaxis. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 1996;18:921-929.
34. Randolph SSB, Gooley TA, Warren EH, et al. Female donors contribute to a selective graft-versus-leukemia effect in male recipients of HLA-matched, related hematopoietic stem cell transplants. *Blood*. 2004;103:347-352.
35. Gale RP, Horowitz MM, Ash RC, et al. Identical-twin bone marrow transplants for leukemia. *Ann Intern Med*. 1994;120: 646-652.
36. Barrett AJ, Horowitz MM, Ash RC, et al. Bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 1992;79:3067-3070.
37. Chao NJ, Forman SJ, Schmidt GM, et al. Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia during first complete remission. *Blood*. 1991;78:1923-1927.
38. Deconinck E, Cahn JY, Milpied N, et al. Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia in first remission: long-term results for 42 patients conditioned with an intensified regimen (TBI, high-dose Ara-C and melphalan). *Bone Marrow Transplant*. 1997;20:731-735.
39. Biggs JC, Horowitz MM, Gale RP, et al. Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. *Blood*. 1992;80:1090-1093.
40. Snyder DS, Chao NJ, Amylon MD, et al. Fractionated total body irradiation and high-dose etoposide as a preparatory regimen for bone marrow transplantation for 99 patients with acute leukemia in first complete remission. *Blood*. 1993;82: 2920-2928.
41. Jamieson CHM, Amylon MD, Wong RM, et al. Allogeneic hematopoietic cell transplantation for patients with high-risk acute lymphoblastic leukemia in first or second complete remission using fractionated total-body irradiation and high-dose etoposide: a 15-year experience. *Exp Hematol*. 2003;31:981-986.
42. Lee, S, Kim DW, Cho B, et al. Risk factors for adults with Philadelphia-chromosome-positive acute lymphoblastic leukemia in remission treated with allogeneic bone marrow transplantation: the potential of real-time quantitative reverse-transcription polymerase chain reaction. *Br J Haematol*. 2003;120: 145-153.
43. Horowitz MM, Gale RP, Barrett AJ, et al. Effect of methotrexate on relapse after bone-marrow transplantation for acute lymphoblastic leukemia. International Bone Marrow Transplant Registry. *Lancet*. 1989;1:535-537.
44. Kumar S, Chen MG, Gastineau DA, et al. Lymphocyte recovery after allogeneic bone marrow transplantation predicts risk of relapse in acute lymphoblastic leukemia. *Leukemia*. 2003;17: 1865-1870.
45. von Bueltzingsloewen A, Belanger R, Perreault C, et al. Allogeneic bone marrow transplantation following busulfan-cyclophosphamide with or without etoposide conditioning regimen for patients with acute lymphoblastic leukemia. *Br J Haematol*. 1993;85:706-713.
46. Blume KG, Forman SJ, Snyder DS, et al. Allogeneic bone marrow transplantation for acute lymphoblastic leukemia during first complete remission. *Transplantation*. 1987;43:389-392.
47. McCarthy DM, Barrett AJ, MacDonald D, et al. Bone marrow transplantation for adults and children with poor risk acute lymphoblastic leukemia in first complete remission. *Bone Marrow Transplant*. 1988;3:315-322.
48. De la Camara R, Figuera A, Steegmann JL, et al. Allogeneic bone marrow transplantation for high risk acute lymphoblastic leukemia. Results from a single institution. *Bone Marrow Transplant*. 1992;9:433-438.
49. Au WY, Lie AK, Ma SK, et al. Allogeneic bone marrow transplantation for adult acute lymphoblastic leukemia: a single-centre experience. *Hematol Oncol*. 1998;16:163-168.
50. Atkinson K, Biggs JC, Concannon A, et al. The impact of leukemia status at the time of HLA-identical sibling marrow transplantation on subsequent complication rate and survival of adults with acute leukemia. *Aust N Z J Med*. 1986;16:462-469.
51. Aversa F, Terenzi A, Carotti A, et al. Improved outcome with T-cell-depleted bone marrow transplantation for acute leukemia. *J Clin Oncol*. 1999;17:1545-1550.
52. Snyder DS, Nademanee AP, O'Donnell MR, et al. Long-term follow-up of 23 patients with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with allogeneic bone marrow transplant in first complete remission. *Leukemia*. 1999; 13:2053-2058.
53. Cornelissen JJ, Carston M, Kollman C, et al. Unrelated marrow transplantation for adult patients with poor-risk acute lymphoblastic leukemia: strong graft-versus-leukemia effect and risk factors determining outcome. *Blood*. 2001;97:1572-1577.
54. Gaderet L, Labopin M, Gorin NC, et al. Patients with acute lymphoblastic leukemia allografted with a matched unrelated donor may have a lower survival with a peripheral blood stem cell graft compared to bone marrow. *Bone Marrow Transplant*. 2003;31:23-29.
55. Sierra J, Radich J, Hansen JA, et al. Marrow transplants from unrelated donors for treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 1997;90:1410-1414.
56. 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.
57. Cahn JY, Labopin M, Schattenberg A, et al. Allogeneic bone marrow transplantation for acute leukemia in patients over the age of 40 years. Acute Leukemia Working Party of the European Group for Bone Marrow Transplantation (EBMT). *Leukemia*. 1997;11:416-419.
58. Doney K, Hägglund H, Leisenring W, et al. Predictive factors for outcome of allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2003;9:472-481.
59. Esprou H, Boiron JM, Cayuela JM, et al. A potential graft-versus-leukemia effect after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: results from the French Bone Marrow Transplantation Society. *Bone Marrow Transplant*. 2003;31:909-918.
60. Stirewalt DL, Guthrie KA, Beppu L, et al. Predictors of relapse

and overall survival in Philadelphia chromosome-positive acute lymphoblastic leukemia after transplantation. *Biol Blood Marrow Transplant*. 2003;9:206-212.
61. Iida H, Sao H, Kitaori K, et al. Twenty years' experience in allogeneic hematopoietic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia in the Nagoya Blood and Marrow Transplantation Group. *Int J Hematol*. 2004;79:79-84.
62. Lee S, Kim DW, Kim YJ, et al. Influence of karyotype on outcome of allogeneic bone marrow transplantation for adults with precursor B-lineage acute lymphoblastic leukemia in first or second remission. *Br J Haematol*. 2002;117:109-118.
63. Wassmann B, Pfeifer H, Scheuring U, et al. Therapy with imatinib mesylate (Glivec) preceding allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL). *Leukemia*. 2002;16: 2358-2365.
64. Martino R, Giralt S, Caballero MD, et al. Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study. *Haematologica*. 2003;88:555-560.
65. Arnold R, Massenkeil G, Bornhäuser M, et al. Nonmyeloablative stem cell transplantation in adults with high-risk ALL may be effective in early but not in advanced disease. *Leukemia*. 2002;16:2423-2428.
66. Hunault M, Harousseau JL, 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.
67. 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.
68. Ringden O, Labopin M, Gorin NC, et al. Is there a graft-versus-leukemia effect in the absence of graft-versus-host disease in patients undergoing bone marrow transplantation for acute leukemia? *Br J Haematol*. 2000;111:1130-1137.
69. Sotomayor EM, Piantadosi S, Miller CB, et al. Long-term follow-up of intensive ara-C-based chemotherapy followed by bone marrow transplantation for adult acute lymphoblastic leukemia: impact of induction Ara-C dose and post-remission therapy. *Leukemia Res*. 2002;26:461-471.
70. Annaloro C, Curioni ACE, Molteni M, et al. Hematopoietic stem cell transplantation in adult acute lymphoblastic leukemia: a single-center analysis. *Leuk Lymphoma*. 2004;45:1175-1180.
71. Vey N, Blaise D, Stoppa AM, et al. Bone marrow transplantation in 63 adult patients with acute lymphoblastic leukemia in first complete remission. *Bone Marrow Transplant*. 1994;14:383-388.
72. Blaise D, Gaspard MH, Stoppa AM, et al. Allogeneic or autologous bone marrow transplantation for acute lymphoblastic leukemia in first complete remission. *Bone Marrow Transplant*. 1990;5:7-12.
73. Soiffer RJ, Roy DC, Gonin R, et al. Monoclonal antibody-purged autologous bone marrow transplantation in adults with acute lymphoblastic leukemia at high risk of relapse. *Bone Marrow Transplant*. 1993;12:243-251.
74. Ifrah N, Witz F, Jouet JP, et al. Intensive short term therapy with granulocyte-macrophage-colony stimulating factor support, similar to therapy for acute myeloblastic leukemia, does not improve overall results for adults with acute lymphoblastic leukemia. GOELAMS Group. *Cancer*. 1999;86:1496-1505.
75. Kroger N, Kruger W, Wacker-Backhaus G, et al. Intensified conditioning regimen in bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1998;22:1029-1033.
76. Stockschlader M, Hegewisch-Becker S, Kruger W, et al. Bone marrow transplantation for Philadelphia-chromosome-positive acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1995; 16:663-667.
77. Martino R, Bellido M, Brunet S, et al. Intensive salvage chemotherapy for primary refractory or first relapsed adult acute lymphoblastic leukemia: results of a prospective trial. *Haematologica*. 1999;84:505-510.
78. Martino R, Bellido M, Brunet S, et al. Allogeneic or autologous stem cell transplantation following salvage chemotherapy for adults with refractory or relapsed acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1998;21:1023-1027.
79. Dunlop LC, Powles R, Singhal S, et al. Bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1996;17:365-369.
80. Goldstone AH, Lazarus HJ, Richards SM, et al. The outcome of 551 1st CR transplants in adult ALL from the UKALL XII/ECOG 2993 study [abstract]. *Blood*. 2004;104:178a.
81. Lazarus HM, Richards SM, Chopra R, et al. Adult patients with acute lymphoblastic leukemia (ALL) and central nervous system (CNS) leukemia at diagnosis may attain durab le complete remissions (CR). Results from the International ALL Trial (MRC UKALL-XII/ECOG E2993) [abstract]. *Blood*. 2004;104: 204b.
82. Goldstone AH, Chopra R, Buck G, et al. The outcome of 267 Philadelphia positive adults in the International UKALL12/ ECOG E2993 study. Final analysis and the role of allogeneic transplant in those under 50 years [abstract]. *Blood*. 2003;102:80a.
83. Ries LAG, Eisner MP, Kosary CL, et al. Surveillance, Epidemiology and End Results Cancer Statistics Review, 1975-2002, National Cancer Institute, Bethesda, MD. Available at: http://seer.cancer.gov/csr/1975_2002/. Accessed June 6, 2005.