

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

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## ABSTRACT

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute lymphoblastic leukemia (ALL) in children is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published 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 in a table in this review (Summary of Treatment Recommendations Made by the Expert Panel for Pediatric Acute Lymphoblastic Leukemia) and were reached unanimously by a panel of ALL experts. The priority areas of needed future research in pediatric ALL are unrelated marrow or blood donor versus unrelated cord blood donor allogeneic SCT; alternative, nonfamily allogeneic donor versus autologous SCT; better methods for identifying high-relapse-risk patients; assessments of the effect of current chemotherapy regimens on early relapse; and use of pre-SCT detection of minimal residual disease to predict post-SCT outcomes.

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## KEY WORDS

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

## INTRODUCTION

The American Society for Blood and Marrow Transplantation in 1999 began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of blood and marrow transplantation 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 con-

duct each review. Two reviews have been published in *Biology of Blood and Marrow Transplantation*: one on diffuse large cell B-cell non-Hodgkin lymphoma in 2001 [1] and one on multiple myeloma in 2003 [2].

The following is the third review to result from this initiative. Its goals are to

1. Assemble and critically evaluate all of the evidence regarding the role of hematopoietic stem cell transplantation (SCT; in this review, *SCT* refers to the general term *hematopoietic stem cell transplantation*, including bone marrow transplantation [BMT], peripheral blood SCT [PBSCT], or both) in the therapy of

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	
I++	High quality meta analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	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	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

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pediatric (<21 years) acute lymphoblastic leukemia (ALL).

2. Make treatment recommendations based on the available evidence.
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 a systematic manner. Treatment recommendations were subsequently graded on the basis of 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 by 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 ( $\leq 10$  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 2 articles: one including studies of pediatric ALL and the other including studies of adult ALL. Articles were excluded from the pediatric ALL review if >50% of the study population was >16 years; these articles are included in the adult ALL review [3]. Abstracts and presentations at national or international meetings were also not included as evidence in this review because of their lack of formal peer review, the limited availability of details on study design and results, and because they are usually presented as preliminary—not final—analyses of clinical trial data.

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

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

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

Indication for SCT	Treatment Recommendation*	Highest Level of Evidence†	References‡	Comments
SCT vs. chemotherapy in first complete remission	B	2++	5-8	Demonstrated benefit only for matched related allogeneic SCT in very-high-risk (Ph+ only) ALL. Not recommended for standard or other high-risk (ie, induction failure, hypodiploidy, etc.) patients except in the context of clinical trial
SCT vs. chemotherapy in second complete remission	B	2++	11-14	Recommended only for matched related allogeneic transplantation vs. chemotherapy; however, the recommendation is tempered because of one prospective trial that did not demonstrate a benefit for transplantation when analyzed by the presence vs. absence of a related donor in an intent-to-treat analysis. Evidence is insufficient to support a recommendation for an unrelated allogeneic transplantation vs. chemotherapy
Autologous purged SCT	C	2+	26-29	Although a majority of patients with late relapses achieve extended leukemia-free survival (LFS) with an autologous purged SCT, the evidence is insufficient to determine that this is better than chemotherapy alone. For those with an early relapse, the outcomes with autologous purged SCT are even less promising.
Autologous, unpurged SCT	N/A	N/A	N/A	Data are unavailable on outcomes of unpurged autologous SCT.
Related allogeneic SCT	C	2+	41-48	A substantial proportion of patients achieve extended LFS.
Unrelated allogeneic SCT	C	2++	58-59	A substantial proportion of patients achieve extended LFS.
Related vs. unrelated allogeneic SCT	None	2+	65-67	Outcomes of related vs. unrelated donor allogeneic SCT have not been adequately studied, especially in patients who have had high-resolution typing. No recommendation can be made at this time.
Comparison of conditioning regimens	B	1+	69-71	TBI-containing regimens have better outcomes than non-TBI containing regimens.
Autologous vs. allogeneic SCT	None	2+	74-76	The outcomes of autologous vs. allogeneic SCT have not been adequately studied. No recommendation can be made at this time.

\*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.

### QUALITATIVE AND QUANTITATIVE GRADING OF THE EVIDENCE

The hierarchy of evidence, including a grading scheme for the quality and strength of the evidence and the 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,

**Table 4.** Comparison of Patient Characteristics and Outcomes from Articles Included in the Transplantation versus Chemotherapy Section

Reference	Quality and Strength of Evidence <sup>a</sup>	Patient Populations	No. of Patients by Treatment Regimen	Upper Limit (Median) of Age at Diagnosis (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS <sup>b</sup>	OS	Significance: OS <sup>b</sup>
<b>First complete remission</b>										
5	2++	MRC UKALL X and XI trials	Total 452 Allo BMT 101 <sup>c</sup> Chemo 351	15 (not stated) 15 (not stated)	17.8% 3.1%	60 BMT 96 overall	10-y EFS <sup>d</sup> 50.4% 39.7%	Not significant	10-y <sup>d</sup> 61.2% 54.0%	Not significant
7	2++	Multicenter Ph+ ALL high-risk protocols per center	Total 267 Auto 25 Matched Rel 38 Mismatched Rel 16 Matched UnRel 21 Allo undefined 20 Chemo 147	20 (8.1) <sup>e</sup>	12% 8% 44% 43% 25% 5%	87.6 <sup>e</sup>	5-y EFS 65%	P < .001	5-y 72%	P = .002
8	2++	AIEOP BMT trials; Chemo Trials 8503, 8703, 8803, 9103	Total 160 Rel allo 30 Chemo 130	15 (8.3) 15 (5.7)	10% 4%	48 overall	4-y DFS <sup>f</sup> 58.5% 47.7%	Not significant	Not stated-it	Not compared
9	2+	Nordic ALL population-based case-control study	Total 471 Rel Allo BMT 22 Matched Chemo 44 <sup>g</sup> Unmatched Chemo 405 <sup>g</sup>	15 (not stated) 15 (not stated) 15 (not stated)	13% 9% 1%	Not stated (minimum 24)	10-y DFS 73% 50% 59%	P = .02 for Allo vs. matched Chemo	Not stated	Not compared
10	2+	Single Canadian center Ph+ ALL	Total 21 Matched Unrel or Rel 11 Chemo 10	16 (7) 13 (9)	At 5 y 27% 20%	41 26	4-y EFS 53% 33%	Not stated	Not stated	Not stated
<b>Second complete remission</b>										
11	2++	IBMTR vs. POG 8303, 8304, 8710, 8862	Total 510 Rel Allo BMT 255 Chemo 255	18 (7) 18 (6)	At 5 y 27% 14%	Not stated	5-y LFS 40% 17%	P < .001	Not stated	Not compared

Table 4. Continued

Reference	Quality and Strength of Evidence <sup>a</sup>	Patient Populations	No. of Patients by Treatment Regimen	Upper Limit (Median) of Age at Diagnosis (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS <sup>b</sup>	OS	Significance: OS <sup>b</sup>
12	2++	MRC UKALL X trial: relapsed, re-treated pts	Total 432 Allo BMT 110 <sup>h</sup> Auto BMT 61 Chemo 261	14 (not stated) 14 (not stated) 14 (not stated)	17% 5% 5%	Not stated (minimum 24)	4-y EFS 42.6% 35.4% 28.2%	P = .05 for Allo vs. Chemo	Not stated	Not significant
13	2++	GITMO and AIEOP trials	Total 287 Rel allo BMT 57 Chemo 230	18 (not stated) Not stated	19.3% 2.6%	74	5-y DFS 41.1% 21.7%	P = .006 <sup>i</sup>	Not stated	Not compared
14	2++	MRC UKALL R1 trial	Total 206 Rel donor 67 No Rel donor 139	15 (not stated) 15 (not stated)	Not stated	72	8-y EFS 45% 37%	Not significant	Not stated	Not compared
15	2+	Population based Nordic ALL database	Total 225 Rel Allo BMT 75 Chemo 150	15 (not stated) 15 (not stated)	19% Not stated	Not stated (minimum 24)	EFS 40% 23%	P = .02	Not stated	Not compared
16	2+	ALL-REZ BFM trials <sup>j</sup>	Total 165 BMT 31 <sup>k</sup> Chemo 134	16 (7.8) 14 (4.4)	13% 4%	23 56	5-y EFS 36% 50%	P < .05	Not stated	Not compared
17	2+	ALL-REZ BFM trials, <sup>j</sup> matched case-control study	Total 162 Matched Unrel BMT 81 Chemo 81	18 (not stated) 18 (not stated)	30% 4%	49 95	5-y EFS 42% 17%	P < .001	Not stated	Not compared
18	2+	BMT pts from Leiden University; Chemo pts from DCLSG	Total 122 Rel Allo BMT 25 Chemo 97	Not stated Not stated	20% 0%	Not stated	5-y LFS 44% 24%	Not significant	Not stated	Not significant
19	2+	BFM Chemo/ auto BMT trials, <sup>j</sup> matched case-control study	Total 104 Auto BMT 52 Chemo 52	15 (4.3) 14 (4.7)	4% 2%	46 55	9-y EFS 26% 32%	Not significant	Not stated	Not compared
20	2+	AIEOP centers	Total 69 <sup>l</sup> Auto BMT 19 Rel Allo BMT 9 Chemo 41	Not stated Not stated Not stated	16% 33% 12%	Not stated (minimum 48)	5-y DFS 56.3% Not stated 12.6%	P = .026	Not stated	Not compared
21	2+	Single US center	Total 66 Rel Allo BMT 37 Chemo 29	17.6 (8.1) 17 (5.3)	Not stated	149 65	5-y DFS 62% 26%	P = .03	Not stated	Not compared

Table 4. Continued

Reference	Quality and Strength of Evidence <sup>a</sup>	Patient Populations	No. of Patients by Treatment Regimen	Upper Limit (Median) of Age at Diagnosis (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS <sup>b</sup>	OS	Significance: OS <sup>b</sup>
22	2+	CCG-1884	Total 62 BMT 19 <sup>m</sup> Chemo 43	21 (not stated) 21 (not stated)	21% 0%	Not stated	2-y EFS 37% 18%	P = .017	Not stated	Not compared
23	2-	Multicenter Spanish study	Total 61 Rel Allo BMT 21 Chemo 40	17 (not stated) 17 (not stated)	Not stated	49 30	Overall DFS 47% 9%	P < .025	BMT 34	Not compared
24	2-	Single US center	Total 45 Rel Allo BMT 24 Chemo 21	16 (8) 15 (7)	8% 0%	33 20	Overall DFS 38% 5%	P = .002	46% 10%	Not stated
25	2-	2 Italian centers	Total 36 Rel Allo BMT 17 Chemo 19	12 (6) 11 (6)	12% 0%	33 31	Overall DFS 58% 18%	P = .01	At 53 mo 48% At 37 mo 22%	P = .04

LFS indicates leukemia-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; MRC, Medical Research Council; UKALL, United Kingdom Acute Lymphoblastic Leukemia; Allo, allogeneic; BMT, bone marrow transplantation; Chemo, standard chemotherapy comparison group; ALL, acute lymphoblastic leukemia; Auto, autologous; Rel, related donor; Unrel, unrelated donor; AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; IBMTR, International Bone Marrow Transplant Registry; POG, Pediatric Oncology Group; GITMO, Gruppo Italiano Trapianto di Midollo Osseo; ALL-REZ, Relapsed Acute Lymphoblastic Leukemia; BFM, Berlin-Frankfurt-Munster Study Group; DCLSG, Denmark Childhood Leukemia Study Group; CCG, Children's Cancer Group; pts, patients.

<sup>a</sup>Quality and strength of evidence definitions are listed in Table 1.

<sup>b</sup>Not significant:  $P > .05$ .

<sup>c</sup>The Allo BMT group includes 76 related Allo BMTs and 25 unrelated BMTs; the chemotherapy group includes 6 Auto BMTs.

<sup>d</sup>Based on the donor versus no-donor group comparisons, adjusted for time-to-transplantation bias and the prognostic factors, WBC at diagnosis, Ph chromosome status, and ploidy.

<sup>e</sup>Of 326 patients enrolled in the multicenter trial.

<sup>f</sup>The rates for DFS are for the unadjusted comparison. The model adjusting for prognostic factors did not specify estimates of DFS for the BMT versus chemotherapy groups.

<sup>g</sup>This study compared the BMT group with the chemotherapy group chosen as controls (matched Chemo group) and with the remaining chemotherapy-treated patients who were not chosen as matched controls (unmatched Chemo group).

<sup>h</sup>The Allo BMT group includes 83 related and 27 unrelated donors.

<sup>i</sup>The  $P$  value is based on the comparison of Allo BMT versus Chemo from the multivariate model for DFS.

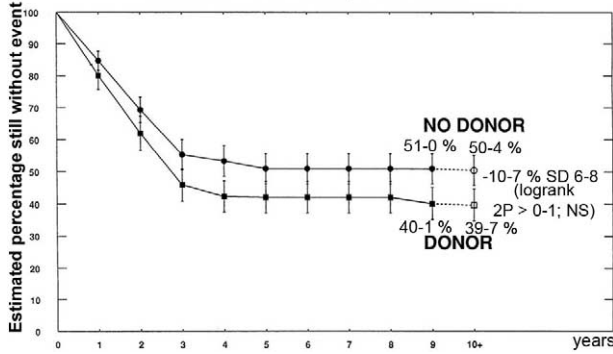
<sup>j</sup>There is some overlap among references 16, 17, and 19.

<sup>k</sup>The BMT group includes 17 related Allo and 14 Auto BMT patients.

<sup>l</sup>This study included only patients with an isolated CNS relapse.

<sup>m</sup>The BMT group includes 11 related Allo, 7 Auto, and 1 unrelated Allo BMT patients.

HIGH RISK ALL: EVENT-FREE SURVIVAL BY DONOR AVAILABILITY ADJUSTED FOR WCC, PH & PLOIDY



**Figure 1.** Descriptive EFS of HLA-typed patients with a sibling donor versus those with no donor. ■, sibling donor; ●, no sibling donor. The EFS is adjusted for time to transplantation, WBC count, Ph chromosome status, and ploidy. Vertical lines indicate one SE above or below each plotted point. Reprinted with permission.<sup>5</sup>

and treatment plan, also was considered in evaluating the studies. All data in the text and tables were first abstracted by one author (T.H.) from the original articles; they were then double-checked for accuracy and clarity by another author (P.L.M.) and at least 2 additional reviewers (see “Acknowledgments”). In some articles, there were discrepancies within the data reported; ie, the median follow-up reported in the abstract was not the same as that 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, and improper or inappropriate study design were not used so that the reader is not biased by the authors’ opinions.

**TREATMENT RECOMMENDATIONS**

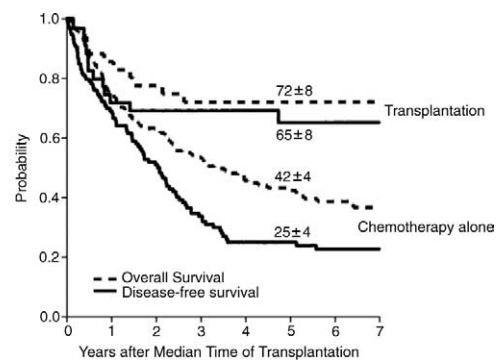
The strength of this review is the detail conveyed in the text and the study comparisons in the summary tables at the end of each major section. Table 3 contains the summary of treatment recommendations made by the ALL expert panel. Subsequent sections of the review present the detailed descriptions 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.

**TRANSPLANTATION VERSUS CHEMOTHERAPY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA**

Table 4 summarizes the grading criteria, study populations, patient characteristics, and outcomes from pediatric studies included in the transplantation-versus-chemotherapy section. Evidence in this section is taken from self-described studies of pediatric populations, all of which included patients <21 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.

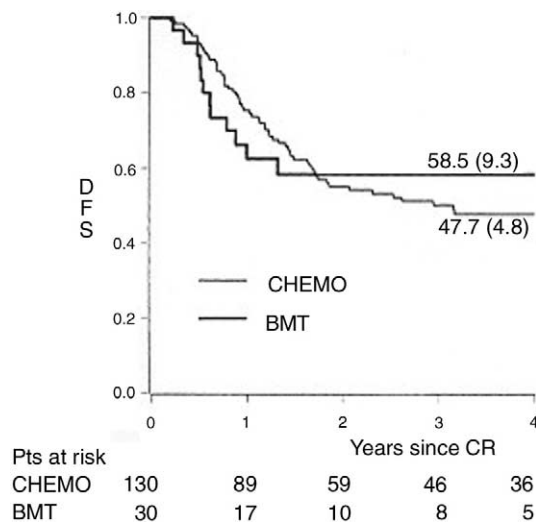
**First Complete Remission**

Wheeler et al. [5-6] presented the results of a subgroup of very-high-risk pediatric (<16 years at the time of treatment) patients with ALL from the Medical Research Council (MRC) United Kingdom Acute Lymphoblastic Leukemia (UKALL) X and XI trials (n = 473 very-high-risk patients of 3676 total trial patients) treated from 1985 to 1997. Very-high-risk ALL was defined by a hazard score incorporating age, sex, and white blood cell count (WBC) at diagnosis or as Philadelphia chromosome-positive (Ph<sup>+</sup>) ALL, near-haploid ALL, or >4 weeks needed to achieve first complete remission (CR1). The 473 patients were identified as very high risk and eligible for BMT; however, only 452 achieved the stable CR1 required to proceed to BMT. Ninety-two children had no siblings, whereas 62 were not typed by choice and 12 had no information regarding typing. The remaining 286 (60%) children underwent human leu-



PATIENTS AT RISK								
Chemotherapy alone	198	84	57	36	24	22	18	14
Transplantation from matched related donor	18	28	25	26	23	17	9	6

**Figure 2.** Estimates of disease-free and overall survival (±SE) in 267 patients treated with transplantation of bone marrow from HLA-matched related donors or chemotherapy only. The curves have been adjusted for waiting time to transplantation, so that the 0 on the time axis corresponds to the median time from diagnosis to transplantation (6 months). Patients were assigned to this treatment group in a time-dependent fashion. Five-year estimates are shown. P values are from the Mantel-Byar test. P = .002 for the comparison of the 2 treatments with respect to overall survival; P < .001 for the comparison with respect to disease-free survival. Reprinted with permission.<sup>7</sup>



**Figure 3.** Kaplan-Meier estimates of the DFS curves in the groups of children who underwent allogeneic bone marrow transplantation (BMT) and of matched controls who underwent chemotherapy (CHEMO). Reprinted with permission.<sup>8</sup>

kocyte antigen (HLA) typing, of whom 99 (35%) had an HLA-matched sibling donor and 76 (27%) received a related allogeneic BMT. Additionally, 25 patients received a matched unrelated donor (URD) BMT and were analyzed with the related allogeneic BMT group; 6 patients received an autologous BMT and were analyzed with the chemotherapy group. Related donor transplantations were performed at 22 centers; autologous BMT, at 18 centers; and URD transplantations, at 3 centers.

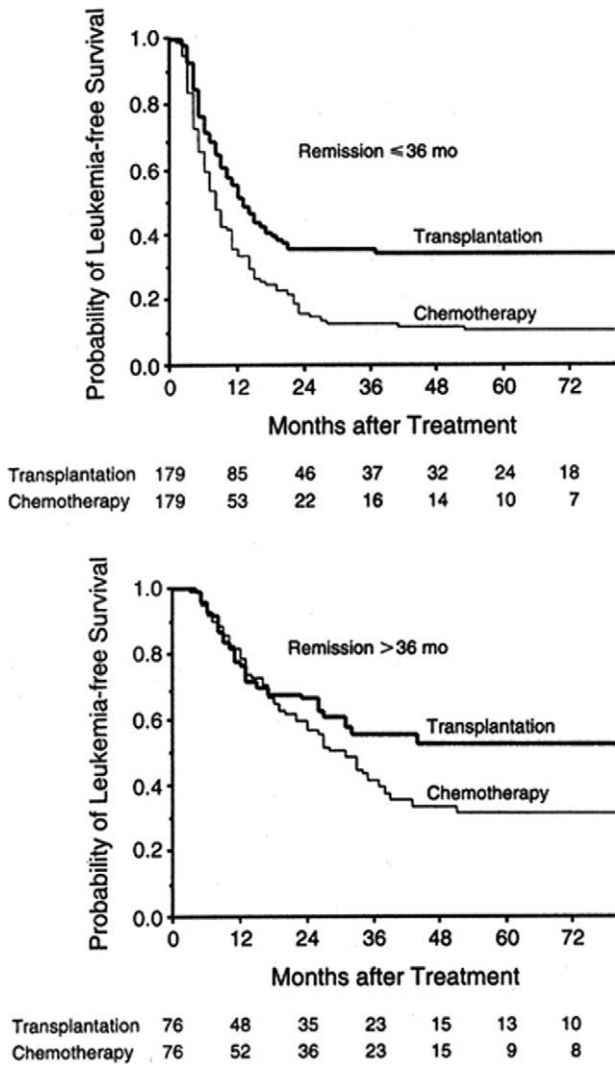
At a median follow-up of 8 years, the unadjusted 10-year event-free survival (EFS) was 46.8% for the BMT group and 38.3% for the chemotherapy group—a difference of 8.5% (95% confidence interval [CI], -3.5% to 20.5%). After adjustment for time-to-transplantation bias and prognostic factors (WBC at diagnosis, Ph chromosome status, and ploidy), the 10-year EFS was 45.3% for the BMT group and 39.3% for the chemotherapy group—a difference of 6% (95% CI, -10.5% to 22.5%). Patients were also compared on the basis of a “biologic randomization”: among the 286 patients who were typed, those with matched sibling donors were compared with those without matched sibling donors. The adjusted model yielded a 10-year EFS of 50.4% for the no-donor group and 39.7% for the donor group—a difference of 10.7% (95% CI, -2.6% to 24%; Figure 1). None of these comparisons reached statistical significance.

Arico et al. [7] analyzed the results of a retrospective multicenter cohort study of 326 pediatric (<20 years at diagnosis) patients with Ph<sup>+</sup> ALL who were treated between 1986 and 1996 by 10 cooperative groups or large single institutions in Europe and the United States. All were categorized as high-risk ALL patients because of the presence of the Ph chromo-

some by cytogenetic or molecular criteria. Of the 326 patients, 82% (n = 267) achieved a CR with induction chemotherapy; the remaining patients died of treatment-related mortality (TRM; n = 3) or resistant leukemia (n = 56). Children in the CR group (n = 267) were stratified into 3 prognostic cohorts: worst (WBC >100 000/ $\mu$ L; n = 80), intermediate (n = 92), and best (WBC <50 000/ $\mu$ L and age <10 years; n = 95). One hundred patients underwent autologous (n = 25), matched related donor (n = 38), mismatched related donor (n = 16), or matched URD (n = 21) BMT. The median time from diagnosis to BMT for all transplant patients was 6.6 months. BMT conditioning and graft-versus-host disease (GVHD) prophylaxis regimens were not stated. The overall TRM for the BMT group was 27%. Examination of the 3 prognostic cohorts in all CR1 patients (BMT + chemotherapy group) produced significantly different rates of disease-free survival (DFS) at 5 years: 20%, 30% and 49%, respectively ( $P < .001$ ). HLA-matched related donor BMT demonstrated significantly better results than chemotherapy alone in all 3 prognostic cohorts (DFS,  $P < .001$ ; overall survival [OS],  $P = .002$ ; Figure 2). Multivariate analysis adjusting for WBC, age, sex, and time to transplantation found no significant difference among the chemotherapy, autologous BMT, matched URD BMT, or mismatched related donor BMT groups; however, patients in the matched related donor BMT group had significantly improved DFS (relative risk [RR] = -0.3;  $P < .001$ ) and OS (RR = -0.4;  $P = .002$ ) compared with the chemotherapy group.

Uderzo et al. [8] reported the results of a matched case-control study of high-risk pediatric (<16 years at the time of treatment) patients with ALL treated in CR1 on Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP) trials at 13 Italian centers from 1986 to 1994 comparing related HLA-matched allogeneic BMT with chemotherapy. High-risk patients were defined as having (1) any cytogenetic abnormalities [t(9;22), t(4;11), or other], (2) Berlin-Frankfurt-Munster (BFM) risk index >1.7, (3) T-cell immunophenotype and WBC >100 000/ $\mu$ L or day 7 steroid resistance, or (4) failure to achieve CR by day 42 of induction therapy. Thirty BMT patients were matched to 130 controls (median 4 controls per case selected from 397 chemotherapy-treated patients) on induction protocol, age at diagnosis, WBC at diagnosis, immunophenotype, and duration of CR1.

At a median follow-up of 4 years, the 4-year unadjusted DFS was not significantly different: 58.5% in the BMT group and 47.7% in the chemotherapy group (Figure 3). The multivariate analysis adjusting for the 5 matching criteria and time-to-transplantation bias yielded a hazard ratio for DFS at 2 years after achievement of CR1 of 0.35 (95% CI, 0.06-1.91;  $P > .05$ ), which is a nonsignificant advantage for BMT



**Figure 4.** Actuarial probability of leukemia-free survival in matched cohorts of children receiving chemotherapy or undergoing transplantation, according to the duration of the first remission. Reprinted with permission.<sup>11</sup>

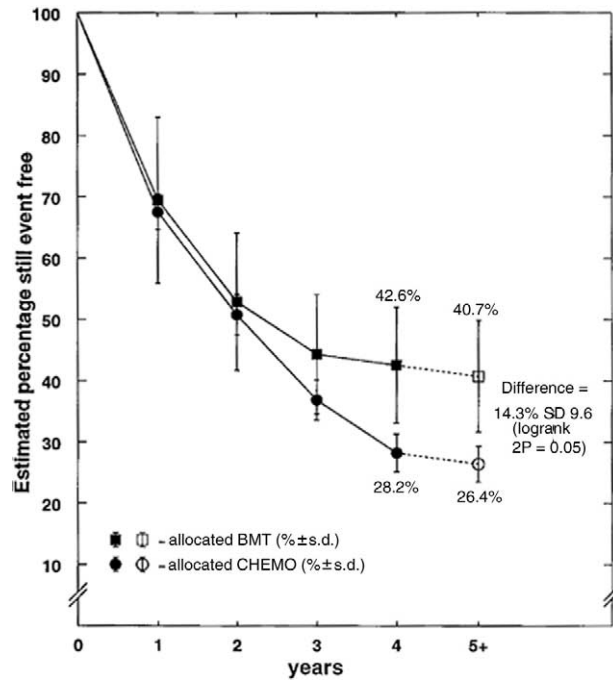
versus chemotherapy. Stratification by sex (not a matching criterion) did not affect these results.

Saarinen et al. [9] performed a matched case-control study of very-high-risk pediatric (<16 years at diagnosis) patients with ALL selected from a population-based registry of all children with ALL diagnosed between 1981 and 1991 from 5 Nordic countries. *High risk* was defined as having a WBC >50 000/ $\mu$ L, central nervous system (CNS) involvement at diagnosis, T-cell immunophenotype, mediastinal mass, or cytogenetic abnormalities. Twenty-two patients received an HLA-compatible related donor allogeneic BMT in CR1 and were compared with 2 matched controls per case treated on standard chemotherapy protocols (n = 44; matched control group) as well as with the remaining children in the registry cohort (n = 405; unmatched control group). Donors included HLA-matched siblings (n = 17), HLA-mismatched siblings

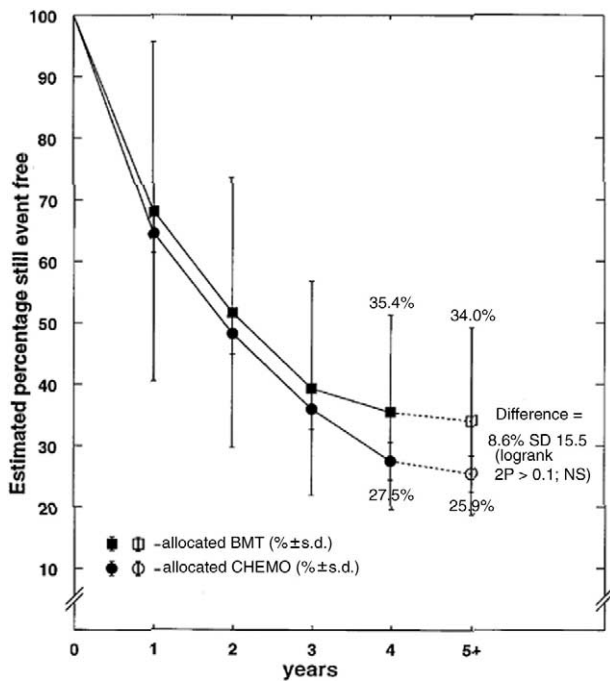
(n = 3), and HLA-mismatched parents (n = 2). Matched controls had to achieve and maintain a CR for a period equal to or longer than the case patient's time between CR1 and BMT to control for time-to-transplantation bias. Controls were matched for WBC at diagnosis, age at diagnosis, sex, time period of diagnosis (July 1981 to June 1984 versus July 1984 to June 1986 versus July 1986 to December 1991), and immunophenotype. Matched control patients could not be selected from the same center or the same country for each case.

The 10-year DFS was significantly higher in the BMT group compared with the matched control group (73% versus 50%;  $P = .02$ ); there was a higher, but nonsignificant, DFS in the BMT group than in the unmatched control group (73% versus 59%;  $P = .12$ ). The median follow-up time was not stated in the article, but the range was 2 to 12.5 years. Significantly more matched controls relapsed compared with the BMT group (41% versus 9%;  $P < .01$ ). Death in remission was highest in the BMT group (13% BMT versus 9% matched and 1% unmatched control groups).

Sharathkumar et al. [10] performed a retrospective cohort study of 21 pediatric (<17 years) patients with Ph<sup>+</sup> ALL diagnosed at or referred to a single Canadian center between 1985 and 2001. All patients received BFM-based induction therapy protocols; those whose induction therapy failed received teniposide



**Figure 5.** Effect of allogeneic BMT compared with chemotherapy on EFS from the time of relapse. Descriptive curves were obtained from a Mantel-Byar analysis stratified for duration of first remission, site of relapse, and age. Because of the small number of events beyond 4 years, the dotted lines indicate the cumulative results beyond this time. Reprinted with permission.<sup>12</sup>



**Figure 6.** Effect of autologous BMT compared with chemotherapy on EFS from time of relapse. Descriptive curves were obtained from a Mantel-Byar analysis stratified for duration of first remission, site of relapse, and age. Because of the small number of events beyond 4 years, the dotted lines indicate the cumulative results beyond this time. Reprinted with permission.<sup>12</sup>

(VM-26) and cytosine arabinoside (Ara-C) for reinduction. Eleven patients underwent an HLA-matched related (n = 4) or unrelated (n = 7) allogeneic BMT in CR1. Ten patients received consolidation chemotherapy (n = 6) or consolidation chemotherapy plus salvage allogeneic BMT in second CR (CR2; n = 4). Conditioning regimens consisted of cyclophosphamide (Cy) or etoposide (VP) plus total body irradiation (TBI; 1200 cGy in 6 fractions); GVHD prophylaxis consisted of cyclosporine (CSA) and methotrexate (MTX). At a median follow-up of 3.4 years in the BMT in CR1 group and 2.2 years in the chemotherapy/BMT in CR2 group, the 4-year EFS was 53% versus 33%, respectively (P value not stated).

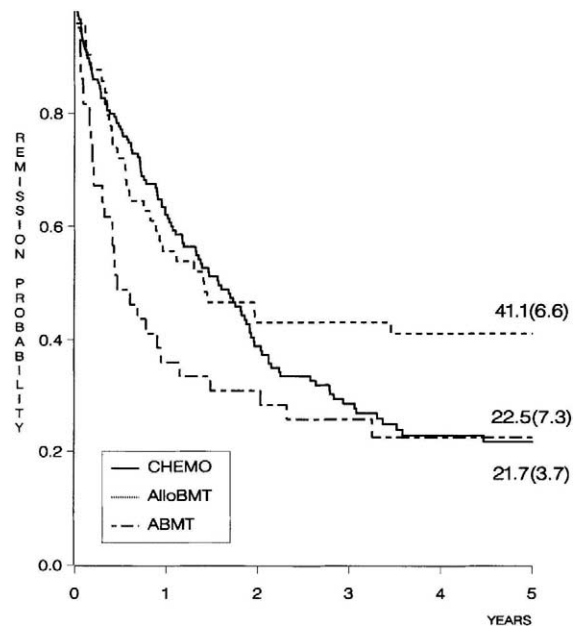
**Second or Greater Complete Remission**

Barrett et al. [11] reported a retrospective matched case-control study of pediatric (<19 years at the time of treatment) ALL patients in CR2 that compared 376 related HLA-matched allogeneic BMT patients (underwent transplantation between 1983 and 1991) reported to the International Bone Marrow Transplant Registry with 540 patients treated on 4 Pediatric Oncology Group chemotherapy trials between 1983 and 1991. From these 2 groups, 255 matched pairs were chosen with identical inclusion and exclusion criteria. The pairs were matched on prognostic factors (age at CR2, WBC at diagnosis, duration of CR1, and immu-

nophenotype), and the study accounted for time-to-transplantation bias (the chemotherapy group patient had to survive in CR at least as long as the time between CR2 and BMT in the matched BMT patient).

Leukemia-free survival (LFS) at 5 years was significantly higher in the BMT group compared with the chemotherapy group (40% versus 17%; P < .001). This result was similar to that in the unmatched comparison of the BMT and chemotherapy cohorts (36% versus 16%; P < .001). The risk of relapse was significantly lower in the BMT group compared with the chemotherapy group (45% versus 80%; P < .001); however, the TRM within 5 years was significantly lower in the chemotherapy group (14% versus 27%; P < .001). The 5-year LFS was higher in the BMT group for both the early relapse group (CR1 <36 months; 35% versus 10%) and the late relapse group (CR1 >36 months; 53% versus 32%; Figure 4). The LFS results did not vary when compared across different subgroups of prognostic factors: the BMT group fared better than the chemotherapy group in all subgroup comparisons, including the duration of CR1.

Wheeler et al. [12] retrospectively examined the outcomes of 432 children diagnosed with ALL between 1985 and 1990 who received induction therapy in the MRC UKALL X trial and who subsequently relapsed (before October 1993), achieved a CR2 after reinduction therapy (not randomized or standardized), and received maintenance chemotherapy or BMT. Related donor SCT was performed at 22 centers,



**Figure 7.** DFS rates (SE) in groups of patients who underwent an allogeneic BMT (AlloBMT; 57 patients), autologous BMT (ABMT; 36 patients), or chemotherapy (CHEMO; 230 patients) in second remission after a medullary relapse. Reprinted with permission.<sup>13</sup>

autologous BMT at 18 centers, and URD SCT at 3 centers. Comparisons were made between allogeneic BMT (n = 110; including 83 with related donors and 27 with URDs), chemotherapy (n = 261), and autologous BMT (n = 61). EFS at 4 years adjusted for prognostic factors (CR1 duration and site of relapse) and time-to-transplantation bias showed marginal significance in favor of allogeneic transplantation over chemotherapy (42.6% versus 28.2%;  $P = .05$ ; Figure 5). EFS at 4 years adjusted for prognostic factors (CR1 duration and site of relapse) and time-to-transplantation bias showed no difference between chemotherapy and autologous BMT (27.5% versus 35.4%, respectively;  $P > .10$ ; Figure 6).

Uderzo et al. [13] performed a retrospective case-control study of related HLA-matched allogeneic BMT (n = 57) versus maintenance chemotherapy (n = 230) in pediatric (<18 years at the time of BMT) patients with ALL treated in CR2 selected from 27 AIEOP or Gruppo Italiano Trapianto di Midollo Osseo centers. All patients had relapsed between 1980 and 1989. No matching on prognostic variables was conducted to evaluate the relationship and effect of prognostic factors in the multivariate model. The 5-year DFS adjusted for time-to-transplantation bias was higher in the allogeneic BMT than the chemotherapy group (41.4%  $\pm$  6.6% versus 21.7%  $\pm$  3.7%; no  $P$  value stated; Figure 7). Multivariate analysis of prognostic factors found only duration of CR1 to be significantly related to outcome. For patients with an early relapse (CR1 duration  $\leq$  30 months), allogeneic BMT had a significantly improved outcome compared with chemotherapy (RR = 0.45;  $P = .002$ ; 3-year adjusted DFS, 33.4% versus 16.1%). For patients with a late relapse (CR1 duration > 30 months), there was no difference in the failure rate between the allogeneic BMT and chemotherapy groups (RR = 0.94;  $P = .92$ ; 3-year adjusted DFS, 54.7% versus 39.6%).

Harrison et al. [14] performed a prospective non-randomized trial (MRC UKALL R1) from 1991 to 1995 comparing the outcomes of pediatric (<15 years at diagnosis) patients with ALL in CR2 who had related HLA-matched donors (n = 67) with those who did not have donors (n = 139). Most patients had previously been treated on the MRC UKALL X and XI trials, but none had received a BMT in CR1. Unadjusted EFS at 5 years was not significantly different between the patients who did and did not have related donors (45% versus 45%;  $P > .10$ ). After adjustment for prognostic factors, EFS at 8 years resulted in an 8% difference between the donor and no-donor groups and favored the donor group (45% versus 37%;  $P > .10$ ). According to the actual treatment received, EFS at 5 years was 46% for related allogeneic BMT (n = 63), 54% for unrelated allogeneic BMT (n = 41), and 43% for chemotherapy (n = 110) or autologous BMT (n = 15). Adjusting for

time-to-transplantation bias and prognostic factors, the odds ratio for any event in the related/unrelated allogeneic BMT group compared with the chemotherapy/autologous BMT group was 0.94 (95% CI, 0.64-1.39;  $P > .10$ ).

Schroeder et al. [15] retrospectively selected all related allogeneic BMT pediatric (<16 years at diagnosis) patients treated for ALL in CR2 (n = 75) from the Nordic population-based registry diagnosed between 1981 and 1992 and compared them with 150 controls randomly selected from the same registry in the same time period who received maintenance chemotherapy in CR2. Controls were matched on time period of diagnosis, immunophenotype, site of relapse, initial risk group, sex, and relapse <6 or  $\geq$ 6 months after completing therapy, and adjustment was made for time-to-transplantation bias. EFS was significantly better for the BMT group (40% versus 23%;  $P = .02$ ). The BMT group also had significantly improved EFS for patients who had early (<6 months from completion of therapy) marrow relapse (32% versus 11%;  $P = .01$ ) and marginal significance toward improved EFS for patients who had late marrow relapse (42% versus 29%;  $P = .05$ ).

Borgmann et al. [16] reported the results of all children ( $\leq$ 19 years at the time of relapse) with ALL in CR2 after an isolated (one site; n = 159) or combined (>one site; n = 6) extramedullary relapse treated prospectively on Relapsed ALL (ALL-REZ [Rezidiven]) BFM multicenter trials (the number of centers was not stated) between 1983 and 1993 by using allogeneic BMT (n = 17), autologous BMT (n = 14), or chemotherapy (n = 134). There was no statistically significant difference between the autologous and allogeneic BMT groups; therefore, the results are presented as a combined BMT group. Unadjusted EFS at 5 years was higher for the chemotherapy group compared with the BMT group (47% versus 36%;  $P > .05$ ). After adjustment for time-to-transplantation bias, there was a significantly higher EFS in the chemotherapy group (50% versus 36%;  $P < .05$ ). No multivariate analyses or adjustments were made for other prognostic factors.

Borgmann et al. [17] performed a matched-pair analysis of pediatric ( $\leq$ 18 years) patients with relapsed ALL treated in the multicenter (the number of centers was not stated) ALL-REZ BFM trial from 1983 to 1994 (there is some overlap with Borgman et al. [16], presented in the previous paragraph). Of 95 patients treated in CR2 with an URD BMT and 1188 patients treated in CR2 with chemotherapy and radiation therapy, 81 pairs were chosen that matched identically for site of relapse and immunophenotype and as closely as possible on CR1 duration, age, diagnosis date, and WBC at relapse. All patients were intermediate risk or high risk. Intermediate risk was defined as: (1) T or B lineage with an isolated extramedullary (IE) relapse

occurring very early (<18 months from diagnosis) or early ( $\geq 18$  months from diagnosis but <6 months from therapy cessation), (2) B lineage with combined bone marrow (BM) relapse occurring early or late (>6 months from therapy cessation), or (3) B lineage with isolated BMT relapse occurring late. High risk was defined as: (1) T lineage with isolated BM or combined BM relapse occurring at any time, (2) B lineage with combined BM relapse occurring very early, or (3) B lineage with isolated BM relapse occurring very early or early. The HLA-matching status of the URD BMT group was matched (64%), unknown (20%), 1-antigen class I or II mismatch (12%), and 2-antigen class I mismatch (4%). Conditioning regimens varied; however, 70% received Cy or VP + TBI, and 95% of all patients had TBI-containing regimens. T-cell depletion was used in 84% of URD BMTs. Most URD BMT patients received CSA + MTX + methylprednisolone as additional GVHD prophylaxis. At a median follow-up of 4.1 years from CR2 in the URD BMT group and 7.9 years from CR2 in the chemotherapy group, the 5-year EFS was significantly better in the URD BMT group (42% versus 17%;  $P < .001$ ). After stratification by risk, there was no significant difference in 5-year EFS between the URD BMT and chemotherapy groups in the intermediate-risk group (49% versus 39%, respectively;  $P = .105$ ); however, there was a significantly better 5-year EFS in the URD BMT group (44% versus 0%;  $P < .0001$ ).

Hoogerbrugge et al. [18] conducted a retrospective case-control study comparing children (upper age limit not stated) with ALL in CR2 treated at a single Dutch center between 1982 and 1991 with a related HLA-matched allogeneic BMT ( $n = 25$ ) or maintenance chemotherapy ( $n = 97$ ). Cases were matched with controls on site of relapse and duration of CR1, and adjustment was made for time-to-transplantation bias. All patients were initially treated with intensive chemotherapy regimens (3 or more drugs for induction therapy). There was a nonsignificant LFS advantage in favor of the BMT group (4-year LFS, 44% versus 24%; hazard ratio, 0.76;  $P = .43$ ). After stratification by site of relapse, there was no difference in LFS between the BMT and chemotherapy groups for treatment of isolated BM relapses ( $n = 70$ ; LFS hazard ratio, 0.98;  $P = .95$ ). There was also no statistically significant difference in LFS between the BMT and chemotherapy groups for the treatment of an isolated CNS relapse ( $n = 52$ ; LFS hazard ratio, 0.40;  $P = .23$ ).

Borgmann et al. [19] retrospectively compared pediatric patients with ALL in CR2 after an IE ( $n = 16$ ), isolated BM ( $n = 76$ ), or combined ( $n = 12$ ) relapse who received autologous BMT or chemotherapy as therapy in BFM multicenter trials between 1983 and 1994. Fifty-two matched pairs were chosen from BFM trial patients who received chemotherapy ( $n = 682$ ) or

autologous BMT ( $n = 66$ ). The pairs were matched on prognostic factors (age at diagnosis, sex, immunophenotype, site of relapse, and duration of CR1) and adjusted for time-to-transplantation bias. EFS at 9 years was not significantly different between the chemotherapy and BMT patient groups (32% versus 26%, respectively;  $P > .10$ ). No significant difference in EFS was found between the chemotherapy and BMT groups when stratified by early ( $\leq 36$  months) versus late (>36 months) relapse.

Messina et al. [20] compared treatment with autologous BMT ( $n = 19$ ) versus chemotherapy ( $n = 41$ ) at 10 AIEOP centers for pediatric (upper age limit not stated) patients with ALL in CR2 after an early isolated CNS relapse. Early relapse was defined as duration of CR1  $\leq 33$  months. All ALL patients treated for isolated CNS relapse at 10 AIEOP centers from 1986 to 1992 were included in this study, except for 9 related allogeneic BMT patients who were noted in the report to be too small a group for comparison. Multivariate analysis adjusting for time-to-transplantation bias and prognostic factors (duration of CR1, age, WBC at diagnosis, immunophenotype, and sex) found a significantly improved 5-year DFS in the autologous BMT group (56.3% versus 12.6%;  $P < .01$ ). Only treatment (autologous BMT versus chemotherapy) and WBC at diagnosis (>50 000 versus <50 000/ $\mu\text{L}$ ) were significantly associated with DFS in the multivariate model.

Boulad et al. [21] prospectively evaluated pediatric (<18 years at diagnosis) patients with ALL in CR2 after a medullary relapse (between 1979 and 1992) who received a related HLA-matched allogeneic BMT ( $n = 37$ ) or chemotherapy ( $n = 29$ ) at a single US center. Time-to-transplantation bias was adjusted for in the analyses of survival (all patients included had to survive in CR2 for a minimum of 3 months). DFS at 5 years adjusted only for time-to-transplantation bias was significantly higher in the BMT group (62% versus 26%;  $P = .03$ ). Adjusting for the confounding factors of age at diagnosis, leukocyte count at diagnosis, duration of CR1, and prior treatment intensity yielded a hazard ratio of 2.84 (95% CI, 1.78-3.91;  $P < .01$ ) for the chemotherapy group when compared with the BMT group. When stratified into high- versus average-/low-risk groups by Children's Cancer Group criteria, DFS for the BMT group remained significantly better than that for the chemotherapy group for both risk categories.

Feig et al. [22] prospectively enrolled 96 pediatric (<21 years at diagnosis) patients with ALL on a multicenter (number of centers not stated) protocol (Children's Cancer Group 1884) who experienced a medullary relapse while on or within 1 year of completing induction therapy (the range of years patients were enrolled was not stated). Sixty-two of these children subsequently achieved CR2 and were treated with

**Table 5.** Comparison of Patient Characteristics and Outcomes from Articles Included in the Autologous SCT Section

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median) Age at Time of Transplantations (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS§	OS	Significance: OS§
<b>Purged autologous BMT</b>										
26	2+	Italian multicenter BMT trials AIEOP protocols 55, 82, 87, and 88	Total 154 CR2 98 CR >2 56	21 (10)	9.7%	66	8-y EFS 34.6% 10.6%	Not significant	Not stated	Not compared
27	2+	Spanish multicenter study	Total 55 Early Rlps 32 Late Rlps 23	17 (8)	5%	76	6-y EFS 37% 56%	P = .036	Not stated	Not compared
28	2+	Single US center	51	18 (9) at diagnosis	9.8%	31	3-y EFS 53%	Not compared	3-y OS 63%	Not compared
29	2+	Single US center (no overlap with reference 28, above)	Total 44 CRI <24 mo CRI 24 to <36 mo CRI >36 mo	14 (4)	23%	28.5	5-y EFS 0% 33% 65%	P = .0002	Not stated	Not compared
30	2-	Italian AIEOP multicenter BMT trials	Total 75 IE Rlps 19 BM Rlps 56	19 (9)	9%	Not stated	5-y DFS 68.4% 13.1%	P < .001	5-y OS 31.7%	Not compared
31	2-	Spanish multicenter study	Total 27 CRI 6 CR2 13 CR3 8	16 (6)	5.3%†	15†	Overall DFS† CRI 71% CR2 46%	Not stated	Not stated	Not compared
32	2-	Single Swedish center	25	17 (8.6)	0%	50	Overall DFS 65%	Not compared	Not stated	Not compared
33	2-	Single US center	24	21 (9.5)	8.3%	41	2-y DFS 42%	Not compared	2-y OS 54%	Not compared
34	2-	4 French centers	Total 24 CR ≥2 19 Rlps/PIF 5	37 (13) 13 (5)	6 mo 26% 0%	14 28	Not stated	Not compared	Not stated	Not compared
35	2-	Single US center	23	18 (8.9)	4.3%	15.5	1-y DFS 29%	Not compared	1-y OS 49%	Not compared
36	2-	German BFM front line, BFM relapse protocols	22	17 (4.7)	9%	Not stated	4-y EFS 18%	Not compared	Not stated	Not compared
37	2-	AIEOP BMT trials 8702 and 8802, 8703, and 8803	12	15 (5.6) at diagnosis	8.3%	24	2-y EFS 80%	Not compared	Not stated	Not compared

Table 5. Continued

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median) Age at Time of Transplantations (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS†	OS	Significance: OS‡
38	2-	Standard or intermediate-risk AIEOP ALL-91 or ALL-95 protocols	11 PBST	16 (9)	0%	29	2-y EFS 89%	Not compared	Not stated	Not compared
<b>Purged vs. unpurged autologous BMT (the study below consists of &lt;70% pediatric patients)</b>										
39	2-	3 Spanish centers	Total 75 Purged 52 Unpurged 23	Not stated Not stated	9.6% 13%	11	3 y DFS 46.78% 25.55%	Not significant	Not stated	Not compared

LFS indicates leukemia-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; BMT, bone marrow transplantation; AIEOP, Associazione Italiana di Ematologica ed Oncologica Pediatrica; CR2, second complete remission; CR >2, greater than second complete remission; Rlps, relapse; CR1, first complete remission; IE, isolated extramedullary; BM, bone marrow; CR3, Third complete remission; CR ≥2, second or greater complete remission; PIF, primary induction failure; BFM, Berlin-Frankfurt-Munster Study Group; ALL, acute lymphoblastic leukemia; PBST, peripheral blood stem cell transplantation.

\*Quality and strength of evidence definitions are listed in Table 1.

†Results are for CR1 and CR2 patients only.

‡Not significant:  $P > .05$ .

BMT (11 related allogeneic, 1 unrelated allogeneic, and 7 autologous BMT) or chemotherapy (n = 33). Ten chemotherapy-treated patients relapsed before the mean time to transplantation and were excluded from the analysis. EFS at 2 years adjusted for time-to-transplantation bias was significantly higher in the BMT group compared with the chemotherapy group (37% versus 18%;  $P = .017$ ). Adjusting for the intensity of prior chemotherapy regimens and the duration of previous remission maintained the improved EFS of BMT over chemotherapy (RR = 2.59;  $P = .01$ ).

Torres et al. [23] reported 76 pediatric (<17 years at diagnosis) patients with ALL in CR2 after BM relapse treated in 1 of 4 Spanish centers from 1980 to 1988 with a related HLA-matched allogeneic BMT (n = 21) or, if no donor was available, chemotherapy (n = 55). Adjustment was made for time-to-transplantation bias, but there was no adjustment for or multivariate analysis of prognostic factors. DFS was significantly higher in the BMT group (47.1% versus 9%;  $P < .025$ ).

Johnson et al. [24] described the outcomes of 45 pediatric (<17 years) patients with ALL treated in CR2 with either a related allogeneic BMT (n = 24) or conventional maintenance chemotherapy (n = 21; children with no allogeneic donor were given treatment on Children's Cancer Group protocols) at a single US center between 1976 and 1980. All patients had an isolated or combined BM relapse while receiving maintenance chemotherapy and were able to achieve a CR2. The median duration of CR1 was 13 months in the chemotherapy group and 26 months in the BMT group. The conditioning regimen was Cy + TBI, and GVHD prophylaxis consisted of MTX alone. At a median follow-up of 33 months, the BMT group had a better OS (46% versus 10%;  $P$  not stated) and DFS (38% versus 5%;  $P = .002$ ) than the chemotherapy group.

Bacigalupo et al. [25] compared 17 children (<13 years at the time of treatment) with ALL in CR2 who were treated prospectively and received a related HLA-matched allogeneic BMT at one Italian center with 19 children who received standard consolidation and maintenance chemotherapy regimens at a second Italian center (the range of years patients were treated was not stated). Patients in the BMT group had a significantly higher rate of DFS (58% versus 18%;  $P = .01$ ) and OS (48% versus 22%;  $P = .04$ ) compared with the chemotherapy group. No multivariate analyses or adjustments were made for prognostic factors.

### Autologous Stem Cell Transplantation

Table 5 summarizes the grading criteria, study populations, patient characteristics, and outcomes from pediatric studies included in the autologous SCT section. Evidence in this section is taken from self-

described studies of pediatric populations, all of which included patients <21 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 SCT.* There are no data published for which at least half the study population was treated with unpurged autologous SCT. The studies summarized in the next section include a minority proportion of unpurged autologous SCT patients; however, most of the study populations received purged grafts.

*Purged autologous SCT.* Messina et al. [26] performed a retrospective cohort study of the AIEOP BMT registry between 1984 and 1994. This study examined the outcomes of 154 pediatric ( $\leq 21$  years at BMT) patients with ALL from 10 Italian pediatric BMT centers in CR  $\geq 2$  registered for autologous BMT by AIEOP. Criteria for autologous BMT were (1) a relapse within 30 months of diagnosis or high-risk group at diagnosis or multiple relapses, (2) lack of any suitable matched donor, and (3) morphologic remission before transplantation. Ninety-eight CR2 patients underwent autologous BMT, 65 had an isolated or combined BM relapse ( $n = 46$  and  $n = 19$ , respectively), and 33 had an IE relapse. Mafosfamide or vincristine + prednisolone were used for *in vitro* purging in 45 of 65 isolated or combined BM relapse patients and 21 of 33 IE relapse patients; 32 received unpurged grafts. The median duration of CR1 for this group was 25 months, and median follow-up was 66 months. Fifty-six patients underwent autologous BMT, 38 after 2 or more isolated and/or combined BM relapses and 18 after 2 or more IE relapses (CR  $> 2$ ). *In vitro* purging was used in 25 of 38 BM and 8 of 18 IE relapse patients. The median duration of CR1 for this group was 30 months, and the median follow-up was 66 months. BMT conditioning regimens consisted of busulfan (Bu) + Cy ( $n = 42$ ), vincristine + Cy + TBI ( $n = 42$ ), other TBI-containing regimens ( $n = 39$ ), or other chemotherapy-based regimens ( $n = 31$ ).

Of 154 patients, 15 (9.7%) children died of TRM: 8 (8.4%) in the CR2 group and 7 (12%) in the CR  $> 2$  group. The 8-year EFS for patients who underwent transplantation in CR2 and CR  $> 2$  were 34.6% and 10.6%, respectively ( $P = .11$ ). The 8-year EFS for the BM relapse group and the IE group was 15.2% and 49.9%, respectively ( $P = .0011$ ). Within the CR2 group, the 8-year EFS was significantly influenced by site of relapse: 18.2% BM versus 68.5% IE ( $P < .0001$ ). The CR  $> 2$  group was not significantly influenced by relapse site, purging, TBI conditioning regimen, or duration of CR1.

Maldonado et al. [27] performed a 3-center Spanish study of 55 pediatric (<18 years at BMT) patients with ALL from 1987 to 1994. All patients were in

CR2 when they received their monoclonal antibody (mAb)-purged BM by using complement ( $n = 48$ ) or magnetic beads ( $n = 7$ ); common ALL (c-ALL) and B-lineage ALL immunophenotypes were purged with anti-CD9, anti-CD10, anti-CD19, and anti-CD20 ( $n =$  not stated), and T-lineage ALL was purged with anti-CD2, anti-CD3, anti-CD4, anti-CD6, and anti-CD8 ( $n =$  not stated). Treatment before transplantation referral differed by center. The median duration of CR1 was 27 months. Of 32 children with an early relapse ( $\leq 30$  months from diagnosis), 14 patients had an IE relapse; of the late relapse group, 18 had an isolated BM relapse, and 5 had a combined BM relapse. Conditioning regimens were Cy + Ara-C + TBI ( $n = 23$ ), VP + Cy + TBI ( $n = 5$ ), Cy + TBI ( $n = 21$ ), or Bu + Cy + VP ( $n = 6$ ). Three patients (5%) died of TRM. At a median follow-up of 76 months, the 6-year EFS was 45%: 56.5% for the late relapse group and 37% for the early relapse group. None of the following factors was significant for 6-year EFS in the multivariate analysis: relapse site (IE, 43%; BM with or without another site, 46%), CR1 duration ( $\leq 30$  months, 37%;  $> 30$  months, 56%), conditioning regimen (Cy + TBI, 28%; Cy + TBI + Ara-C or VP, 60%), or interval between relapse and autologous BMT ( $< 6$  months, 47%;  $> 6$  months, 47%).

Billett et al. [28] performed a prospectively designed phase II study of autologous BMT in 51 pediatric (<18 years at diagnosis) patients with ALL at a single US center between 1980 and 1991. All patients lacked a suitable donor for allogeneic BMT and were in CR  $\geq 2$ , with CR1 lasting  $> 24$  months (median, 38 months). Five patients had previous IE disease, and 22 had previous combined BM and extramedullary disease. Twenty patients with CR1  $< 24$  months were excluded and are presented in Sallan et al. [29] below. All received BM that was purged *in vitro* with both anti-CD9 and -CD10 mAbs ( $n = 46$ ) or a single mAb ( $n = 5$ ) and received varied conditioning regimen combinations including Ara-C, VM-26, Cy, and TBI, as well as radiation therapy to extramedullary sites. Five (9.8%) patients died of TRM, and 18 (35.3%) patients relapsed within a median time of 8 months. At a median follow-up of 31 months, the 3-year EFS and LFS were 53% and 58%, respectively, and the OS rate was 63%, 55%, and 47% at 3, 4, and 7 years, respectively. The factors examined for association with EFS and LFS in the multivariate analysis were the longest duration of CR before autologous BMT, the duration of CR before autologous BMT, cell dose per kilogram, prior therapy, year of diagnosis, reinduction regimen, and Ara-C dose before BMT. The duration of the longest CR before autologous BMT ( $P = .07$ ) and the CR duration before BMT ( $P = .07$ ) showed marginal significance in predicting

EFS. The only significant predictor of LFS was cell dose per kilogram ( $P = .025$ ). The duration of the longest CR ( $P = .06$ ) showed marginal significance.

Sallan et al. [29] presented the results of 44 pediatric (<18 years at the time of BMT) patients with relapsed ( $n = 43$ ) or refractory ( $n = 1$ ) ALL treated with a purged autologous BMT at a single US center from 1980 to 1988. BMT was performed in CR1 ( $n = 1$ ), CR2 ( $n = 27$ ), CR3 ( $n = 15$ ), or CR4 ( $n = 1$ ). Patients with T-lineage ALL, HLA-compatible donors, and inability to achieve CR with chemotherapy alone were excluded. The median duration of CR1 was 29 months. The sites of first relapse were isolated BM ( $n = 27$ ), IE ( $n = 10$ ), or combined BM ( $n = 6$ ). BM was purged with anti-CD10 ( $n = 12$ ), anti-CD9 ( $n = 1$ ), or both ( $n = 31$ ) mAbs. The conditioning regimen consisted of Cy + Ara-C + VM-26 + TBI (850 cGy in a single dose to 1400 cGy in 8 fractions) with or without asparaginase. At a median follow-up of 28.5 months, the 5-year EFS was 29%. Five-year EFS significantly varied by CR1 duration: 0% for <24 months versus 33% for 24 to <36 months versus 65% for  $\geq 36$  months ( $P = .0002$ ).

Colleselli et al. [30] performed a retrospective cohort study of 9 Italian centers that reported data to the AIEOP BMT Registry between 1984 and 1992. The study included 75 pediatric (<20 years at BMT) patients with ALL who underwent an autologous BMT in CR2 after a single IE relapse ( $n = 19$ ) or a single BM relapse with or without another site ( $n = 56$ ). BMT conditioning regimens varied by center; 43 (57%) received TBI-based regimens. BM was unpurged ( $n = 18$ ) or was purged with mafosfamide ( $n = 43$ ) or vincristine + methylprednisolone ( $n = 14$ ). Seven (9%) patients died of TRM; 44 (58.6%) relapsed after autologous BMT. Twenty-four (32%) of 75 patients were in continuous complete remission at a median of 30 months. The median follow-up of survivors was not stated. The 5-year OS and DFS were 31.7% and 27.8%, respectively. The study examined the site of relapse, duration of CR1, duration of CR2 after autologous BMT, purging of BM, and TBI as a conditioning regimen, but only relapse site statistically influenced DFS (68.4% IE versus 13.1% BM;  $P < .001$ ).

Canals et al. [31] reported the results of a Spanish retrospective multicenter (number of centers not stated) cohort study of 27 pediatric (<17 years at BMT) patients with ALL who received purged autologous BMT between 1991 and 1994. Patient BM was harvested and immunomagnetically purged *ex vivo* at the same laboratory; B-lineage ALL BM ( $n = 31$ ) was purged with anti-CD10, -CD19, and -CD20 mAbs, and T-lineage ALL BM ( $n = 6$ ) was purged with anti-CD4, -CD5, -CD6, -CD8, and -CD28 mAbs. Twenty-seven (73%) patients were autografted in CR1 ( $n = 6$ ), CR2 ( $n = 13$ ), or CR >2 ( $n = 8$ ). For the CR2 group, the duration of CR1 was <24 months

( $n = 9$ ) or >24 months ( $n = 4$ ); the CR1 duration for the CR >2 group was not stated. The site of first relapse was not stated. Conditioning regimens were TBI based with different chemotherapy combinations. All patients autografted in CR  $\geq 3$  relapsed early (not defined in article) after autologous BMT. One (5.3%) patient died of TRM; 7 (36.8%) relapsed within a median of 3 months, and 11 (57.8%) remained in CR. At a median follow-up of 15 months, DFS was 71% and 46% for the CR1 and CR2 groups, respectively.

Lonnerholm et al. [32] reported the results of a Swedish single-center study of 25 consecutive pediatric (<17 years at BMT) patients with ALL with purged autologous BMT between 1985 and 1991. Two high-risk CR1 patients and 23 CR  $\geq 2$  patients received autologous BMT. The median time from diagnosis to first relapse was 2.8 years; the duration of CR1 was not stated in the article. Relapse sites included isolated BM ( $n = 14$ ), IE ( $n = 7$ ), or combined BM ( $n = 2$ ). Harvested marrow was purged by cytolytic mAbs plus rabbit complement; pre-B-lineage ALL was purged with anti-CD10 with or without anti-CD9 antibodies ( $n = 23$ ), and T lineage was purged with anti-CD7 antibodies ( $n = 2$ ). The conditioning regimen consisted of Cy + vincristine + Ara-C + daunorubicin + teniposide + prednisolone + TBI (single fraction, 750 cGy) for all patients. No patients died of TRM. The 2 patients who underwent transplantation in CR1 were in continuous complete remission 5.3 and 3.4 years after autologous BMT. Sixteen (70%) of 23 children who underwent transplantation in CR  $\geq 2$  are in continuous complete remission at a median follow-up of 50 months. Overall DFS for the entire group is 65%.

Houtenbos et al. [33] performed a prospective US single-center cohort study of 24 pediatric (<21 years at BMT) patients with ALL who received purged autologous BMT between 1990 and 1996. Patients had no suitable related or unrelated allogeneic donor and had high-risk ALL in either CR1 ( $n = 5$ ) or CR  $\geq 2$  ( $n = 19$ ) when they underwent transplantation. High-risk ALL in CR1 was defined as age <1 year, diagnostic WBC >250 000/ $\mu\text{L}$ , >6 weeks to attain CR1, or chromosomal abnormalities [t(4;11) or t(9;22)]. For the CR  $\geq 2$  group, the median CR1 duration was 34 months, and relapse sites were isolated BM ( $n = 11$ ), IE ( $n = 3$ ), or combination BM ( $n = 5$ ). All were conditioned with VP + Cy + TBI + verapamil, and their CR BM was purged *ex vivo* with verapamil + vincristine + VP. The patients were divided into 3 cohorts for posttransplantation therapy. Cohort 1 ( $n = 4$ ) received CSA alone, cohort 2 ( $n = 7$ ) received CSA +  $\alpha$ -interferon, and cohort 3 ( $n = 13$ ) received CSA, 6 alternating cycles of  $\alpha$ -interferon + chemotherapy, and 6 additional cycles of chemotherapy followed by granulocyte colony-stimulating factor (posttransplantation immune chemotherapy). Two (8.3%) patients died of TRM. At a median follow-up of 41

months, the 2-year DFS and OS were 42% and 54%, respectively. Patients receiving posttransplantation immune chemotherapy versus immunotherapy alone (CSA with or without  $\alpha$ -interferon) had significantly better EFS and OS probabilities ( $P = .008$  and  $P = .06$ , respectively). None of the prognostic factors examined, including the duration of CR1 and CR  $>1$ , relapse site, timing of relapse, or chemotherapy, was associated with DFS or OS.

Pico et al. [34] performed a prospective phase II study at 4 French centers between 1982 and 1985 of purged autologous BMT in 24 patients with ALL (88%  $\leq 18$  years at BMT) who lacked an HLA-matched allogeneic donor. Nineteen patients were in CR  $\geq 2$ , and 5 patients had primary refractory or relapsed disease. Sites of prior relapse were IE ( $n = 11$ ), isolated BM ( $n = 10$ ), or BM and other ( $n = 4$ ) [editorial note: numbers do not add up but are given as stated in the article]. All patients received carmustine + Ara-C + Cy + 6-thioguanine as their conditioning regimen. Twenty-one patients received marrow purged *in vitro* with either mafosfamide ( $n = 17$ ) or anti-cALLa (common acute lymphoblastic leukemia antigen) mAb and complement ( $n = 4$ ); 3 patients received unpurged BM. Fourteen (74%) of 19 CR  $\geq 2$  patients died of disease before 12 months after BMT ( $n = 9$ ) or of TRM ( $n = 5$ ), and 4 (80%) of 5 progressive disease patients died of disease before 12 months after BMT.

Ramsay et al. [35] reported the results of a single US center prospective phase II study of 23 pediatric ( $<17$  years at diagnosis) patients with ALL in CR  $\geq 2$  treated with purged autologous BMT between 1982 and 1984. Sites of prior relapse were isolated BM ( $n = 19$ ) or BM + extramedullary ( $n = 4$ ). BM was purged with mAbs (anti-CD24, anti-CD9, and anti-CD10) and rabbit complement. All patients received Cy + TBI as the conditioning regimen. The median CR1 durations for the CR2 and CR  $\geq 2$  groups were 8.7 and 16.7 months, respectively. One patient (4.3%) died of TRM. At a median follow-up of 15.5 months, the 1-year OS and DFS were 49% and 29%, respectively.

Schmid et al. [36] performed a phase II study of purged autologous BMT in 22 high-risk pediatric ( $<17$  years at diagnosis) patients with ALL at a single German center between 1987 and 1992. Remission status was CR2 ( $n = 13$ ), CR3 ( $n = 8$ ), or CR4 ( $n = 1$ ). Sites of relapse were isolated BM ( $n = 18$ ), IE ( $n = 3$ ), or combined BM ( $n = 1$ ); the median duration of CR1 was 31 months. Patients received VP + TBI for conditioning and were infused with mAb-purged BM; common ALL and B-cell ALL BM received anti-CD10, -CD19, and -CD24 ( $n = 18$ ), and T-cell BM received anti-CD2, -CD3, -CD5, and -CD7 ( $n = 4$ ). Two patients (9%) died of TRM. The median follow-up of surviving patients was not stated. The 4-year EFS was 18%, and the probability of relapse was 80%.

Rossetti et al. [37] reported the results of an Italian single-center study in which 12 pediatric ( $<15$  years at diagnosis) patients with early IE (10 CNS and 2 testicular) relapsed ALL underwent autologous BMT between 1987 and 1991. Early relapse was defined as relapse occurring during chemotherapy or within 6 months of chemotherapy cessation. This study examined the toxicity and efficacy of the conditioning regimen Ara-C + TBI (1440 cGy) before autologous BMT. All first-line treatments were administered according to AIEOP cooperative protocols (intermediate risk, 8702 and 8802; high risk, 8703 and 8803). Nine patients received mafosfamide-purged BM, and the last 3 patients received unpurged BM. One patient (8.3%) died of TRM. Three patients (25%) died due to BM relapse occurring 1.5, 4, and 5 months after autologous BMT. At a median follow-up of 24 months, EFS was 80%.

Balduzzi et al. [38] reported the results of a prospective Italian single-center study performed of purged autologous PBSCT for 11 of 12 consecutive pediatric ( $<18$  years at BMT) patients with B-lineage precursor ALL in CR2 after IE ( $n = 2$ ), isolated BM ( $n = 6$ ), or combined BM ( $n = 3$ ) late relapse (median, 37 months; range, 31-51 months after the onset of CR1) between 1997 and 1999. One patient did not mobilize enough peripheral blood stem cells, underwent an unmanipulated autologous BMT, and is not included in the analysis. All 11 patients received first-line therapy according to either the LLA-91 or LLA-95 AIEOP protocol and received the same conditioning regimen of VP + Cy + TBI. Peripheral blood stem cells were purged *in vitro* with mAbs (anti-CD11b and -19). No patients died of TRM. At a median follow-up of 29 months, the 2-year EFS was 89%. One patient (9%) relapsed and died after autologous PBSCT, but the remaining 10 were alive and in CR. The one patient who did not mobilize enough CD34<sup>+</sup> cells underwent unpurged autologous BMT and died of relapse.

### Purged and Unpurged Autologous Stem Cell Transplantation

The following study consisted of  $<70\%$  pediatric patients: Graña et al. [39-40] reported the results of patients with ALL (52% of purged and 57% of unpurged groups were  $<15$  years at the time of BMT) who received a purged ( $n = 52$ ) or unpurged ( $n = 23$ ) autologous BMT at 3 Spanish centers from 1987 to 1993. Remission states for purged BMT patients were 48.1% for CR1, 46.2% for CR2, and 5.7% for CR  $\geq 3$ . Remission states for unpurged BMT patients were 34.8% for CR1, 47.8% for CR2, and 17.3% for CR  $\geq 3$ . Prior sites of relapse and duration of CR1 were not stated in the article. If the leukemia immunophenotype was known at diagnosis, then the harvested marrow was purged with anti-T-cell (CD2, CD3,

**Table 6.** Comparison of Patient Characteristics and Outcomes from Articles Included in the Related Donor Allogeneic SCT Section

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median Age at Time of Transplantation (y))	Treatment-Related Mortality	Median Follow-Up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS‡	OS	Significance: OS‡
<b>Related donor</b>										
41	2+	IBMTR study	Total 690 CR1 <16 y 56 CR1 > 16 y 243 CR2 391	15 (13) 48 (24) 49 (15)	Overall 18% 37% 36%	21	5-y LFS 56% 39% 26%	$P < .02†$	Not stated	Not compared
42	2+	Survey of 14 US centers	Total 213	45.7 (10.7)	Not stated	Not stated	3-y DFS 38%	Not compared	Not stated	Not compared
43	2+	Multicenter trials of BFM Relapse Study Group	Total 169 CR2 136 CR3 33	15 (4) 13 (4)	13% 30%	63 44	6-y EFS 49% 48%	Not significant	Not stated	Not compared
44	2+	Single Swedish center	Total 112§ cGVHD 31   No cGVHD 69	17 (9)¶	Day 100 9%¶	84¶	Not stated	Not compared	5-y 76% 45%	$P = .009$
45	2+	Single US center	Total 59 CR2 31 CR3 12 CR4 or Rlps 16	18 (8) 18 (10) 18 (9)	5-y 23% 33% 13%	61 64 74	5-y EFS 64% 42% 23%	Not stated	Not stated	Not compared
46	2+	Multicenter study AIEOP protocols 87, 88, 91 and 95, and others	Total 40 CR1 13 CR2 27	18(9)	1 yr 8% 19%	36	3-y DFS 85% 56%	Not significant	Not stated	Not compared
47	2+	Single US center	CR2 30	42 (10)	Overall 13%	47	10-y EFS 61%	Not compared	10-y 62%	Not compared
48	2+	Multicenter study of SFGM	Total 21 CR1 15	4 (2.3)	Day 100 0%	47	4-y DFS 61.1% 61.9%	Not compared	4-y 68.6% 72.2%	Not compared
49	2–	Pediatric Oncology Group 32 US centers	Total 297 BMT 42	21 (not stated) at diagnosis	Overall 41%	Not stated	Not stated	Not compared	Not stated	Not compared
50	2–	2 US centers	Total 41 CR2 27 CR3 or Rlps 14	19 (8)	Overall 30% 50%	98	5-y EFS 59%	Not compared	Not stated	Not compared

Table 6. Continued

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median) Age at Time of Transplantation (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS	OS	Significance: OS
51	2–	Single US center	CR2 57	17 (not stated)	Day 100 25%	48+	5-y DFS 40%	Not compared	Not stated	Not compared
52	2–	Single US center	Total 52 CR1 9 CR2 34 CR ≥3 9	15 (8.5)	Not stated	96	3-y EFS 30% 36% 22%	Not compared	Not stated	Not compared
53	2–	Single French center FRALLE or other protocol	42	15 (not stated), mean 8.9	Day 100 26%	36	4-y EFS 53%	Not compared	Not stated	Not compared
54	2–	French multicenter study	32	16 (13.5)	Day 100 12.5%	30	5-y LFS 84.4%	Not compared	Not stated	Not compared
55	2–	Single US center	CR2 or 3 20	16 (6.5)	1-y 30%	58	Overall 58%	Not compared	Overall 58%	Not compared
<b>&lt;70% Pediatric patients</b>										
56#	2+	Single US center	Total 74 CR1 18 CR2 36 CR3/4 20	36 (24) 41 (14) 37 (12)	6-mo 39% 36% 40%	57 54 72	5-y EFS 42% 43% 25%/0%	Not compared	Not stated	Not compared
57#	2+	Single US center	Total 48 HLA match 16 HLA mismatch 32	48 (12) 46 (10)	Day 100 13% 28%	46	Overall LFS** 38%	Not stated**	6-y 38%	Not compared

LFS indicates leukemia-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; IBMTR, International Bone Marrow Transplant Registry; CR1, first complete remission; BFM, Berlin-Frankfurt-Munster Study Group; CR2, second complete remission; CR3, third complete remission; cGVHD, chronic graft-versus-host disease; CR4, fourth complete remission; Rlps, relapse; AIEOP, Associazione Italiani di Ematologica ed Oncologica Pediatrica; SFGM, Société Française de Greffe de Moelle; BMT, bone marrow transplantation; CR ≥3, third or greater complete remission; FRALLE, French Multicenter Acute Lymphoblastic Leukemia Study.

\*Quality and strength of evidence definitions are listed in Table 1.

† $P < .02$  comparing adult CR1 versus pediatric CR1 groups,  $P < .02$  comparing adult CR1 and adult + pediatric CR2 groups,  $P < .003$  comparing pediatric CR1 and adult + pediatric CR2 groups.

‡Not significant:  $P > .01$ .

§A total of 72% of all 169 AML and ALL patients received grafts from related donors; 28% were from unrelated donors; the numbers for related versus unrelated donors are not stated for only ALL patients.

||Patients had to survive to day 90 after SCT to be at risk for chronic GVHD; therefore, the numbers do not add up to 112.

¶Includes 57 AML and 112 ALL patients.

#<70% of patients met study criteria.

\*\*LFS was 38% for 6/6, 50% for 5/6, 36% for 4/6, and 30% for 3/6 HLA-matched donor BMTs;  $P = .89$ .

CD4, CD5, CD6, and CD8) or anti-B-cell (CD9, CD10, CD19, and CD20) mAbs; otherwise, the patient received unpurged marrow. Patients received Cy + TBI (1000-1400 cGy;  $n = 63$ ) or Bu + Cy ( $n = 12$ ) as the conditioning regimen. At a median follow-up of 11 months, the 3-year DFS was 46.8% and 25.6% in the purged and unpurged groups, respectively ( $P = .13$ ). On multivariate analysis, there was an improved DFS in the purged group for patients  $>15$  years ( $P = .04$ ),  $>1$  month to achieve CR1 ( $P = .02$ ), and BMT in CR1 ( $P = .016$ ).

## RELATED DONOR ALLOGENEIC STEM CELL TRANSPLANTATION

Table 6 summarizes the grading criteria, study populations, patient characteristics, and outcomes from pediatric studies included in the related allogeneic donor SCT section. Evidence in this section is taken from self-described studies of pediatric populations, all of which included patients less than 21 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.

Barrett et al. [41] conducted a study of pediatric ( $<16$  years at the time of BMT) and adult (age  $\geq 16$  years at the time of BMT) patients with ALL reported to the International Bone Marrow Transplant Registry by 107 centers between 1978 and 1986 who received an HLA-matched sibling allogeneic donor BMT in CR1 ( $n = 299$ ) or CR2 ( $n = 391$ ). Conditioning regimens varied by center; however, 70% received Cy + TBI, and 98% received a TBI-containing regimen. GVHD prophylaxis also varied by center. Sites of prior relapse and duration of CR1 were not stated in the article. The results of patients treated in CR1 were stratified by pediatric versus adult patients; however, the results of patients treated in CR2 were pooled (56% were  $<16$  years at the time of BMT). Adult ALL patients treated in CR1 ( $n = 243$ ) had a significantly lower 5-year LFS than that in pediatric ALL patients treated in CR1 ( $n = 56$ ; 39% versus 56%;  $P = .02$ ). Patients who underwent transplantation in CR2 had a significantly lower 5-year LFS (26%) than children ( $P < .0003$ ) and adults ( $P < .02$ ) who underwent transplantation in CR1. However, children and adults who underwent transplantation in CR1 had a similar 5-year probability of relapse (27% versus 30%;  $P =$  not significant). Multivariate analysis of significant risk factors for LFS in the adult CR1 group were GVHD prophylaxis and donor-recipient sex, and in the CR2 group, were age at the time of BMT ( $\geq 16$  versus  $<16$  years) and relapse occurring while receiving chemotherapy. There were too few patients in the pediatric CR1 group to perform a multivariate analysis of LFS risk.

Weyman et al. [42] performed a retrospective survey of 14 US centers assessing 213 patients with ALL (70% were  $<16$  years at the time of BMT) treated between 1981 and 1989 with a related allogeneic BMT (82% were HLA-matched siblings and conditioned with Ara-C + TBI). Remission states were 12.1% for CR1, 57.5% for CR2, 15.5% for CR  $\geq 3$ , and 15% for relapse  $\geq 1$ . Sites of prior relapse and duration of CR1 were not stated in the article. The Ara-C cumulative dose was either 24 or 36 g/m<sup>2</sup>, and TBI was either fractionated (1000-1575 cGy;  $n = 197$ ) or delivered in a single dose (750-1000 cGy;  $n = 16$ ). The TRM and median follow-up time were not stated in the article. The 3-year DFS in all patients was 38%. DFS was higher in patients aged 0 to 11 years compared with  $\geq 11$  years (52% versus 25%;  $P$  value not stated) and in patients who underwent transplantation in CR1 versus CR  $\geq 2$  versus relapse (54% versus 41% versus 19%;  $P$  value not stated). Multivariate analysis of risk factors for shorter DFS yielded age (as a categorical variable;  $P = .0003$ ), WBC at diagnosis ( $P = .028$ ), disease status at BMT ( $P = .005$ ), and donor HLA matching ( $P = .001$ ) as statistically significant.

Borgmann et al. [43] retrospectively identified 169 pediatric ( $<19$  years at the time of BMT) patients with relapsed ALL enrolled in 4 consecutive multicenter trials of the BFM Relapse Study Group between 1983 and 1985 who received a BMT from a related donor. Patients underwent transplantation in CR2 ( $n = 136$ ) or CR3 ( $n = 33$ ); the median duration of CR1 was 26 versus 32 months, respectively ( $P < .001$ ). Matched related BMT was recommended for all patients with first or subsequent BM relapse except for patients who relapsed  $>4$  years after CR1. Sites of first relapse for the CR2 group were isolated BM ( $n = 100$ ) or combined BM ( $n = 36$ ); immunologic subtypes were B precursor ( $n = 119$ ), T cell ( $n = 12$ ), or unclassified ( $n = 5$ ). Sites of second relapse for the CR3 group were isolated BM ( $n = 26$ ) or combined BM ( $n = 7$ ); immunologic subtypes were B cell ( $n = 28$ ), T cell ( $n = 4$ ), and unclassified ( $n = 1$ ). The conditioning regimen was VP  $\pm$  Cy + TBI (1200 cGy) in 93% of the CR2 and 82% of the CR3 groups; the remaining patients received various chemotherapy-based combinations. GVHD prophylaxis was not stated. TRM for the CR2 versus CR3 groups was 13% versus 30%. At a median follow-up of 63 months, EFS at 6 years for the CR2 group was 49% and varied by duration of CR1. The 6-year EFS for the CR3 group was 48% at a median follow-up of 44 months and was not significantly different from the CR2 group.

Gustafsson Jernberg et al. [44] retrospectively studied the effect of chronic GVHD on relapse and survival in 169 acute myeloid leukemia (AML;  $n = 57$ ) and ALL ( $n = 112$ ) pediatric ( $<18$  years at BMT) patients from a single Swedish center treated with a related ( $n = 122$ ) or unrelated ( $n = 57$ ) SCT from

1980 to 2000. Patients with ALL underwent transplantation in CR1 (n = 26), CR2 (n = 61), or CR  $\geq$ 3 (n = 16) or when they were not in remission (n = 9). The duration of CR1 and prior sites of relapse were not stated. Conditioning regimens consisted of Cy + TBI (750-1000 cGy in a single fraction; n = 124), Cy + TBI (fractionated 1200-1440 cGy; n = 26), or Bu + Cy (n = 19). GVHD prophylaxis consisted of CSA alone, MTX alone, or CSA + MTX; in addition, patients with unrelated or mismatched grafts received antithymocyte globulin (ATG), Orthoclone (Ortho Biotech Products, LP, Ravitan, NJ) anti-CD3 antibody (OKT3; n = 49), or *in vitro* T-cell depletion (n = 10). The 5-year probability of chronic GVHD was 34%; the median time to occurrence was 181 days after SCT. Chronic GVHD reduced the probability of relapse from 53% to 30% in ALL patients (*P* value not stated). At a median follow-up of 7 years, the OS was significantly improved in patients with ALL who had developed chronic GVHD compared with those who had not (76% versus 45%; *P* = .009).

Brochstein et al. [45] performed a prospective feasibility trial of 97 pediatric (<20 years at BMT) patients with ALL (n = 59) or AML (n = 38) treated with an HLA-matched sibling allogeneic BMT at a single US center between 1979 and 1985. ALL patients were in CR2 (n = 31), CR3 (n = 12), CR4 (n = 2), or relapse (n = 14) at the time of BMT. The median duration of CR1 was 18.8 months in the CR2 group, 22 months in the CR3 group, and 13 months in the CR4/relapse group. Sites of prior relapse were not stated. The conditioning regimen was Cy + TBI (1320-1440 cGy); GVHD prophylaxis was either MTX or CSA alone. At a median follow-up of 61, 64, and 74 months, the 5-year EFS was 64%, 42%, and 23% in the CR2, CR3, and CR4/relapse groups, respectively (*P* value not stated).

Zecca et al. [46] performed a prospective multicenter phase II study of thiotepe + Cy + TBI as a conditioning regimen in 40 consecutive pediatric (<19 years at the time of BMT) patients with ALL in CR1 or CR2 who received an HLA-identical sibling BMT from 1992 and 1997 at 6 AIEOP BMT centers. Thirteen high-risk patients underwent BMT in CR1; the median time from CR to BMT was 4.3 months. Indications for BMT in CR1 varied between centers, but overlapping criteria included unfavorable cytogenetics, resistance to corticosteroids (>1000 blasts per microliter in peripheral blood after 7 days of prednisone), high WBC count at diagnosis, T-cell immunophenotype, and lack of remission at the end of the induction phase. Out of the 27 patients who underwent transplantation in CR2, relapse sites were isolated BM (n = 20), combined BM (n = 4), and IE (n = 3); the median time from diagnosis to first relapse was 28 months. The preparatory regimen was thiotepe + Cy + TBI (990 cGy in 3 fractions [n = 4] or 1200 cGy in 6

fractions [n = 36]). GVHD prophylaxis consisted of CSA alone for all patients. Overall TRM was 15%: 8% in the CR1 group versus 19% in the CR2 group (*P* not stated). At a median follow-up of 36 months, the 3-year DFS was 65%: 85% in the CR1 group versus 56% in the CR2 group (*P* = not significant). There was no observed significance on patient outcome for the variables sex, age at diagnosis, age at BMT, WBC count at diagnosis, immunophenotype, interval from CR to transplantation, or GVHD.

Jamieson et al. [47] 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. Most (71%) patients treated in CR1 (n = 55) were adults, and their results are presented in the adult ALL review [3]. Most (83%) CR2 patients (n = 30) were <18 years and are presented here. All patients received VP + TBI (1350 cGy in 11 fractions). GVHD prophylaxis consisted of CSA + prednisone, CSA + MTX + prednisone, or CSA + MTX. At a median follow-up of 3.9 years, the 10-year EFS was 61%, and the 10-year OS was 62%.

von Bueltzingsloewen et al. [48] present the results of a retrospective multicenter study (the number of centers was not stated) of the Société Française de Greffe de Moelle of 21 pediatric (<4 years at BMT) patients with ALL who underwent transplantation with a matched related BMT between 1982 and 1992. Conditioning regimens were Bu-containing, non-TBI-based regimens that varied by center and date of BMT: Bu  $\pm$  Ara-C  $\pm$  Cy  $\pm$  VP  $\pm$  melphalan. Overlapping criteria for BMT in CR1 were as follows: (1) age  $\leq$  12 months at diagnosis; (2) non-T-cell ALL and WBC  $\geq$  100 000/ $\mu$ L; (3) t(4;11); (4) t(9;22); (5) poor response to initial therapy with corticosteroids according to European Organization for the Research and Treatment of Cancer criteria; or (6) induction failure to first-line therapy. At time of BMT, patients were in CR1 (n = 15), CR2 or relapse (n = 5), or primary induction failure (n = 1). Sites of relapse were isolated BM (n = 4) or IE (n = 1). The median duration of CR1 was 7 months. GVHD prophylaxis consisted of MTX + CSA (n = 14), CSA alone (n = 4), or MTX alone (n = 2). The median time from last CR to BMT was 80 days. No patient died of TRM. The 4-year DFS was 61.1% for all patients and 61.9% for those who underwent transplantation in CR1. At a median follow-up of 47 months, OS was 68.6% and 72.2% for the entire group and those who underwent transplantation in CR1, respectively.

Buchanan et al. [49] performed a prospective multicenter randomized trial of 297 pediatric (<21 years at diagnosis) patients with ALL from 1983 to 1986 according to Pediatric Oncology Group protocol 8303 at 32 US centers. Patients received remission induction, consolidation, and maintenance chemo-

therapy and were in first BM relapse within 6 months of initial therapy. Patients were then randomized to receive or not receive repeated reinduction. Those with matched sibling donors could be treated with allogeneic BMT instead of continued chemotherapy. Forty-two patients (16% of the Pediatric Oncology Group 8303 study population) received marrow from a matched sibling (n = 34), mismatched related donor (n = 3), or *ex vivo* purged autologous marrow (n = 5). The median duration of CR1 was not indicated for the BMT group. Conditioning regimens and GVHD prophylaxis varied among the 16 participating centers. Overall TRM in the BMT group was 41%; median LFS and OS were not stated. From the matched sibling group, 15 died of TRM, 10 died of relapsed ALL, and 9 were alive and disease free 8 to 11 years after transplantation. Two mismatched related BMT patients died of TRM, and the third is disease-free. Of the BMT patients with autologous purged marrow, 4 relapsed, and one is disease free. OS and LFS were not stated in the article.

Gordon et al. [50] performed a retrospective study of 65 ALL (n = 41), AML (n = 22), or myelodysplastic syndrome (n = 2) pediatric (<20 years at BMT) patients who underwent related or unrelated BMT at 2 US centers between 1981 and 1994. Patients underwent transplantation for ALL in CR2 (n = 27), CR3 (n = 6), or relapse (n = 8). Good-risk patients were considered ALL in CR2 (n = 27). High-risk patients were considered ALL in CR3 (n = 6) or relapse (n = 8). The median duration of CR1 for good-risk (CR2) patients was 24 months, and relapse sites were combined BM (n = 23), IE and BM (n = 2), or IE (n = 2). Sites of prior relapse and duration of CR1 were not stated for the high-risk (CR3/relapse) group. The conditioning regimen for all patients consisted of Ara-C and TBI (1200 cGy). Donors were matched sibling (n = 24; 1 syngeneic donor), class I antigen-mismatched sibling or parent (n = 2), or matched unrelated (n = 1). GVHD prophylaxis consisted of nothing or prednisone (n = 23, as part of a GVHD prophylaxis efficacy study), MTX ± prednisone (n = 26), CSA ± MTX (n = 8), or ATG + CSA + MTX ± prednisone (n = 8). TRM was 30% for ALL patients who underwent transplantation in CR2; TRM was not stratified by disease (AML/myelodysplastic syndrome versus ALL) in the high-risk group but was 32% for all high-risk patients. At a median follow-up of 95 months, the 2-, 5-, and 10-year EFS for ALL patients in CR2 was 59%, 59%, and 51%, respectively.

Sanders et al. [51] performed a retrospective analysis of 57 pediatric (<18 years at BMT) patients with ALL who received a BMT in CR2 from HLA-identical siblings at a single US center between 1973 and 1985. The duration of CR1 was <1 year (n = 11), 1 to 3 years (n = 31), and >3 years (n = 15); 35 patients

presented with extramedullary relapse (combined BM versus IE not specified). The conditioning regimen for all patients was intrathecal MTX + Cy + TBI (920-1575 cGy). GVHD prophylaxis was MTX (n = 55) or CSA (n = 2). Day 100 TRM was 25%. At a median follow-up of >4 years, the 5-year EFS was 40%.

Shah et al. [52] retrospectively evaluated 52 pediatric (<16 years at BMT) patients with ALL treated in CR1 (n = 9), CR2 (n = 34), or CR ≥3 (n = 9) with an HLA-matched related allogeneic BMT at a single US center between 1989 and 2002. The conditioning regimen consisted of Bu + Cy; GVHD prophylaxis consisted of MTX ± CSA. CR1 duration was ≤18 months in 26 patients and >18 months in 26 patients. At a median follow-up of 8 years, the 3-year EFS was 30%, 36%, and 22% for CR1, CR2, and CR ≥3 patients, respectively (*P* value not stated). Neurocognitive function was assessed in 7 BMT patients before BMT and at 1 year after BMT and did not significantly differ between the 2 time points. Seven normal siblings were also tested for neurocognitive function, and their scores were compared with their affected sibling's pre-BMT scores. Normal siblings scored significantly higher than their affected siblings in overall cognitive function (*P* = .02), verbal skills (*P* = .03), performance skills (*P* = .04), and receptive vocabulary (*P* = .01).

Moussalem et al. [53] retrospectively analyzed the outcomes of 42 pediatric (<15 years at BMT) patients with ALL who underwent allogeneic BMT in CR2 at a single French center between 1983 and 1993. Patients received marrow from HLA-identical siblings (n = 38), unrelated phenotypically identical donors (n = 2), an HLA-mismatched parent (n = 1), or a syngeneic donor (n = 1). Immunophenotype was B lineage (n = 21), T lineage (n = 6), or non B, non T (n = 4); patient karyotype was normal (n = 10) or abnormal (n = 16). Relapse sites were BM (n = 23), combined BM (n = 9), or IE (n = 10); patients were stratified into early (<18 months from CR1; n = 12) or late (n = 30) relapse. The mean interval from diagnosis to BMT was 35 months. The conditioning regimens consisted of Ara-C + melphalan + TBI (n = 20), Cy + TBI (n = 10), Cy + Ara-C + VP + TBI (n = 11), or Cy + Ara-C + Bu + melphalan (n = 1). TBI doses varied from 1000 cGy as a single fraction to 1200 cGy in 6 fractions. GVHD prophylaxis was CSA + MTX (n = 24), CSA alone (n = 15), MTX alone (n = 1), T-cell depletion (n = 1), or none (syngeneic BMT; n = 1). Overall, TRM for the group was 31%. At a median follow up of 36 months, the 4-year EFS was 53%; the only factor that was significantly related to EFS was karyotype (normal versus abnormal, 40% versus 81%; *P* < .05).

Bordigoni et al. [54] conducted a retrospective multicenter study (the number of centers was not stated) of 32 pediatric (<17 years at BMT) patients

**Table 7.** Comparison of Patient Characteristics and Outcomes from Articles Included in the Unrelated Donor Allogeneic SCT Section

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median) Age at Time of Transplantation (y)	Treatment-Related Mortality	Median Follow-Up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS†	OS	Significance: OS†
58	2++	Single UK center	Total 137 Matched 85 Mismatched 52	17 (8)	17%	38	3-y LFS 44.9% 39.9%	Not significant	3-y 48.7% 41.7%	Not significant
60	2+	NMDP registry CR2 ALL patients	363	19 (9)	42%	29	5-y LFS 36%	Not compared	5-y 38%	Not compared
61	2+	Single US center	Total 88 ALL 43	17 (9)	28%	Not stated	3-y DFS 38% CR1 or 2 47% CR3 or Rlps 10%	Not stated	Not stated	Not compared
62	2+	Single US center	35	17.5 (8.8)‡	36%	25.2	2-y DFS 30%	Not compared	Not stated	Not compared
63	2+	Single German center	16	24 (10)§	35%§	34	Not stated	Not compared	2-y 56%	Not compared
64	2-	Single UK center Ph+ patients	15	20 (8.3)	Overall 20% Day 100 7%	Not stated (minimum 7)	2-y DFS 37%	Not compared	2-y 44%	Not compared

LFS indicates leukemia-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; NMDP, National Marrow Donor Program; CR2, second complete remission; ALL, acute lymphoblastic leukemia; CR1, first complete remission; CR3, third complete remission; Rlps, relapse.

\*Quality and strength of evidence definitions are stated in Table 1.

†Not significant:  $P > .05$ .

‡Includes 35 patients with ALL and 15 patients with AML.

§Includes 16 patients with ALL, 7 with AML, 6 with chronic myeloid leukemia, and 2 with juvenile myelomonocytic leukemia.

with ALL in CR1 who received a BMT from an HLA-matched sibling donor between 1980 and 1987. Remission induction, consolidation, and maintenance chemotherapy regimens varied; the median time from CR to BMT was 3 months. Criteria for BMT were a high WBC count ( $>100\,000/\mu\text{L}$ ;  $n = 20$ ), cytogenetic abnormalities [ $t(8;14)$ ,  $t(9;22)$ ,  $t(4;11)$ ,  $t(7;12)$ , and  $Xp+$ ],  $>6$  weeks to achieve CR, lymphoma-leukemia syndrome, and/or adolescence. The conditioning regimen consisted of Cy + TBI (1000-1600 cGy;  $n = 28$ ) or other chemotherapy-based regimens ( $n = 4$ ). There were 4 (12.5%) deaths due to TRM. At a median follow-up of 30 months, the 5-year LFS was 84.4%. The 5-year post-BMT relapse rate was 3.5%.

Coccia et al. [55] performed a prospective feasibility trial of 20 pediatric ( $<16$  years at BMT) patients with ALL treated in CR2 ( $n = 18$ ) or CR3 ( $n = 2$ ) with an HLA-matched sibling allogeneic BMT at a single US center between 1981 and 1986. The conditioning regimen was Ara-C + TBI (1200 cGy in 6 fractions). GVHD prophylaxis consisted of MTX + prednisolone ( $n = 7$ ), MTX ( $n = 2$ ), prednisolone ( $n = 2$ ), or nothing ( $n = 9$ ). At a median follow-up of 58 months, the OS and EFS were 58% and 58%.

The following studies consisted of  $<70\%$  pediatric patients: Wingard et al. [56] presented the results of 74 consecutive patients with ALL ( $>50\%$  were  $<15$  years at the time of BMT) treated in CR1 ( $n = 18$ ), CR2 ( $n = 36$ ), CR3 ( $n = 16$ ), or CR4 ( $n = 4$ ) with an HLA-matched sibling BMT at a single US center from 1978 to 1988. The 18 CR1 patients were high risk, defined as having one of the following: age  $>18$  years,  $\text{WBC} \geq 20\,000/\mu\text{L}$  at diagnosis,  $\text{Ph}^+$ , failure to achieve CR1 in 6 weeks, or extramedullary disease. Twenty percent of all patients had extramedullary disease at the time of BMT; sites of prior relapse were not stated. The median duration of CR1 in the  $\text{CR} \geq 2$  patients was 13 months. All patients received Cy + TBI (1200 cGy in 4 fractions) as a conditioning regimen and low-dose Cy ( $n = 29$ ), low-dose Cy + methylprednisolone ( $n = 8$ ), CSA + methylprednisolone ( $n = 12$ ), or CSA alone ( $n = 25$ ) for GVHD prophylaxis. At a median follow-up of 59 months, the 5-year EFS was 42% in the CR1, 43% in the CR2, 25% in the CR3, and 0% in the CR4 groups ( $P$  value not stated).

Fleming et al. [57] reported the results of 16 HLA-matched and 32 HLA-mismatched consecutive related donor BMTs in patients with ALL conducted at a single US center between 1987 and 1992. Fifty-six percent of the matched and 66% of the mismatched BMT patients were  $<15$  years at the time of BMT. Remission states at the time of BMT were CR2 ( $n = 9$ ), CR3 ( $n = 16$ ), relapse 1 ( $n = 7$ ), relapse 2 ( $n = 9$ ), relapse 3 ( $n = 4$ ), and relapse 4 ( $n = 3$ ). Sites of prior relapse and duration of CR1 were not stated in the article. All mismatched and 2 matched BMT patients

received *ex vivo* T-cell depletion with mAb and rabbit complement. Conditioning regimens varied; additional *in vivo* GVHD prophylaxis was given to all patients as one of 5 regimens. At a median follow-up of 46 months, LFS was not significantly different between the HLA-matched versus -mismatched BMT patients (median LFS, 49 versus 41 months;  $P = .48$ ). The LFS in the 6/6, 5/6, 4/6, and 3/6 HLA-matched BMT patients was 38%, 50%, 36%, and 30%, respectively ( $P = .89$ ).

## UNRELATED DONOR ALLOGENEIC STEM CELL TRANSPLANTATION

Table 7 summarizes the grading criteria, study populations, patient characteristics, and outcomes from pediatric studies included in the URD allogeneic SCT section. Evidence in this section is taken from self-described studies of pediatric populations, all of which included patients  $<21$  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.

Green et al. [58-59] retrospectively compared the results of HLA matching in 137 pediatric ( $<18$  years at BMT) patients with ALL who underwent URD BMT at a single UK center from 1988 to 1999. Patients underwent transplantation in CR1 ( $n = 24$ ), CR2 ( $n = 88$ ), CR3 ( $n = 18$ ), CR4 ( $n = 2$ ), or relapse ( $n = 5$ ); relapse sites included isolated or combined BM ( $n = 94$ ) or IE ( $n = 19$ ). For patients in CR1, the median time from diagnosis to transplantation was 314 days. Eighty-five patients underwent transplantation with HLA-matched (at -A, -B, -DR, and -DQ) BM, and 52 transplants were mismatched. *Ex vivo* T-cell depletion (using Campath [Genzyme, Cambridge, MA]) and CSA were used as GVHD prophylaxis in 134 (98%) patients; in addition, 43 patients also received MTX because of HLA disparity. Conditioning regimens were either Campath + Cy + TBI ( $n = 134$ ) or Campath + Cy + Bu ( $n = 3$ ). Overall, 23 (17%) patients died of TRM. At a median follow-up of 38 months, the 3-year LFS rates for the matched versus mismatched groups were 44.9% versus 39.9%, and the 3-year OS rates were 48.7% versus 41.7% ( $P$  value was not stated for each comparison). In a multivariate analysis of the 88 CR2 patients, the only significant factor predicting prolonged LFS was a CR1 duration  $>730$  days ( $P = .007$ ), although the median CR1 duration was not stated.

Bunin et al. [60] retrospectively examined the outcome of 363 pediatric ( $\leq 19$  years at BMT) patients with ALL in CR2 who received an URD BMT at multiple centers (the number of centers was not stated) facilitated by the National Marrow Donor Program between 1988 and 2000. The median CR1

duration was 24 months; extramedullary disease was present in 52 patients (14.3%). Donors were mismatched at HLA-A, -B, or -DR in 24% of transplant patients. Most patients (91%) received TBI-based conditioning regimens; 40% received *in vitro* T-lymphocyte depletion by mAb + complement (58.3%), elutriation (16.7%), lectin/sheep cell rosetting (12.5%), or other methods (12.5%). The 5-year TRM was 42%; significant factors for increased TRM by multivariate analysis were HLA mismatch ( $P \leq .0001$ ), patient age  $>15$  years ( $P = .0009$ ), Karnofsky performance score  $<90$  ( $P = .02$ ), CR1 duration  $<12$  months ( $P = .02$ ), and the time-dependent covariate of grades III and IV acute GVHD ( $P < .0001$ ). At a median follow-up of 29 months, the 5-year LFS and OS were 36% and 38%, respectively. Significant multivariate predictors of longer LFS were HLA match ( $P \leq .0001$ ), Karnofsky performance score  $\geq 90$  ( $P = .03$ ), lower diagnostic WBC count ( $P = .002$ ), age  $<15$  years ( $P = .006$ ), and CR1 duration  $\geq 6$  months ( $P = .002$ ). T-cell depletion did not affect TRM or LFS. Acute GVHD grade III or IV occurred in 29% of patients. Chronic GVHD occurred in 39% of patients and was significantly more frequent for female patients who received marrow from female donors ( $P = .0009$ ).

Balduzzi et al. [61] performed a prospective phase II study of URD BMT in 88 children ( $\leq 17$  years at BMT) diagnosed with chronic myeloid leukemia ( $n = 16$ ), ALL in CR1 or CR2 ( $n = 15$ ), more advanced stage ALL ( $n = 28$ ), AML ( $n = 13$ ), or another hematologic disease ( $n = 16$ ) at a single US center between 1985 and 1993. All patients received an identical conditioning regimen of Cy + TBI and a GVHD prophylaxis regimen of CSA + MTX. URDs for ALL patients were HLA identical ( $n = 23$ ) or minor mismatched ( $n = 20$ ). TRM occurred in 28% of patients overall and was significantly associated with HLA matching and chronic GVHD ( $P = .04$  and  $P = .02$ , respectively). The 3-year DFS in ALL patients was 47% for patients in CR1 or CR2 and 10% in relapse or CR3 patients. Disease-specific multivariate analyses were not presented.

Davies et al. [62] reported the results of 50 consecutive pediatric ( $<18$  years at BMT) patients with high-risk acute leukemia (AML,  $n = 15$ ; ALL,  $n = 35$ ) who received an URD BMT between 1985 and 1994 at a single US center. Twenty-eight (80%) of the ALL patients underwent transplantation in CR  $\geq 2$ . Sites of prior relapse and duration of CR1 were not stated. Overall, 60% of patients had HLA-identical donors, but this information was not stratified by diagnosis. Duration of CR1 and site(s) of relapse were not stated. All ALL patients received TBI-based conditioning regimens. GVHD prophylaxis consisted of CSA + MTX in 78% of patients; T-cell depletion and other prophylaxis combinations were used in the remaining

22%. The day +100 TRM was 36%. At a median follow-up of 25 months, the 1- and 2-year DFS for ALL patients was 37% and 30%, respectively, and was not significantly different between HLA-matched versus mismatched donors.

Lang et al. [63] performed a prospective feasibility trial of CD34<sup>+</sup>-selected PBSCT from URDs in 31 pediatric (1 patient was  $>18$  years) patients with ALL ( $n = 16$ ), AML ( $n = 7$ ), chronic myeloid leukemia ( $n = 6$ ), or juvenile myelomonocytic leukemia ( $n = 2$ ) at a single German center from 1997 to 2000. Of the 31 patients, 15 were HLA matched, 13 were 1-antigen mismatched, and 3 were 2-antigen mismatched. The ALL patients were in CR  $\geq 2$  ( $n = 14$ ) or relapse  $\geq 1$  ( $n = 2$ ) at the time of PBSCT. The duration of CR1 and sites of prior relapse were not stated. Conditioning regimens for patients with ALL were Cy or thiotepa with ATG + TBI (1200 cGy in 6 fractions;  $n = 14$ ) and Bu + Cy + VP + ATG ( $n = 2$ ). No patients received posttransplantation immunosuppression. At a median follow-up of 2.8 years, the 2-year OS was 56% for all patients with ALL and 63% for patients with ALL in remission.

Marks et al. [64] retrospectively examined 15 pediatric ( $<19$  years at diagnosis) patients with Ph<sup>+</sup> ALL who received T cell-depleted URD BMT at a single UK center between 1990 and 1996. Patients were in CR1 ( $n = 9$ ), CR2 ( $n = 3$ ), CR3 ( $n = 1$ ), CR4 ( $n = 1$ ), or relapse ( $n = 1$ ). Sites of relapse and duration of CR1 were not stated in the article. All patients received Campath + Cy + TBI as conditioning; T-cell depletion was performed by using either Campath ( $n = 12$ ) or CD34<sup>+</sup> selection ( $n = 3$ ). In addition, CSA  $\pm$  MTX was given for GVHD prophylaxis. Eleven donor/recipient pairs were identical at HLA-A, -B, -DRB1, and -DQB1, and 4 were mismatched at 1 or 2 loci. Overall, 3 (20%) patients died of TRM; 100-day TRM was 7%. Two-year DFS and OS are 37% and 44%, respectively. None of the mismatched donor patients survived versus 64% of patients with matched donors ( $P < .05$ ).

## RELATED VERSUS UNRELATED DONOR ALLOGENEIC STEM CELL TRANSPLANTATION

Table 8 summarizes the grading criteria, study populations, patient characteristics, and outcomes from pediatric studies included in the related versus URD allogeneic SCT section. Evidence in this section is taken from self-described studies of pediatric populations, all of which included patients  $<21$  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.

Dini et al. [65] analyzed the outcomes of 167 pediatric ( $<17$  years at BMT) patients with ALL who

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

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median) Age at Time of Transplantation (y)	Treatment-Related Mortality	Median Follow-Up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS	OS	Significance: OS
65	2+	AIEOP centers	Total 167 URD 60 Alt Donor 40† Chemo 67	16 (7.6)	Overall 47% 30% 7%	65	3-y DFS 31.6% 25.4% Not stated	Not compared	3-y 31.6% 30.8% Not stated	Not compared
66	2+	Single Danish center	Total 67‡ 1985–1989 Related 32 1990–1996 Related 19 1990–1996 URD 16	19 (8) 19 (8) 19 (12)	3-y 6% 21% 25%	41	3-y LFS 72% 28% 67%	$P < .01$ §	Not stated	Not compared
67	2+	Population-based Nordic registry	Total 43 Related 14 URD 29	15 (not stated)	Overall 14% 17%	Not stated	Overall EFS 45% 65%	Not significant	Not stated	Not compared
68	2–	Nordic ALL protocols	Total 65‡ Related 37 URD 28	20 (not stated)	Overall 19% 11%	54	5-y EFS 39% 54%	Not significant	Not stated	Not compared

LFS indicates leukemia-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; AIEOP, Associazione Italian di Ematologica ed Oncologica Pediatrica; URD, unrelated donor; Alt Donor, alternative donor; Chemo, chemotherapy; ALL, acute lymphoblastic leukemia.

\*Quality and strength of evidence definitions are listed in Table 1.

†Includes 17 autologous, 16 haploidentical relative, 5 unrelated cord blood, and 2 related cord blood.

‡Fourteen patients in reference 66 are also included in reference 68.

§The  $P$  value comparing the related BMT 1985–1989 versus 1990–1996 groups;  $P < .002$  comparing related BMT 1990–1996 versus URD 1990–1996.

|| $P > 0.05$ .

had a URD search performed through the Italian Bone Marrow Donor Registry from 1989 to 1998. All patients had experienced a BM relapse before search initiation and had achieved at least a CR2 before SCT. The duration of CR1 was <30 months in 71% of patients. A matched URD was found for 70 (42%) patients at a median of 5.4 months after search initiation, of whom 46 underwent a URD SCT in CR2, 14 had a URD SCT in CR >2, 1 had a haploidentical related SCT, and 9 were treated with chemotherapy at multiple centers (the number of centers was not stated). A URD was not found for 97 (58%) patients, of whom 17 underwent alternative donor SCT in CR2 (9 autologous, 4 unrelated cord blood transplant, 2 related cord blood transplant, and 2 haploidentical parent), 22 underwent alternative donor SCT in CR3 (8 autologous, 13 haploidentical relative, and 1 unrelated cord blood transplant), and 58 were treated with chemotherapy. At a median follow-up of 5.4 years, the 3-year DFS in all patients was 15.1%. The 3-year DFS was significantly better in the patients whose CR1 duration was >30 months compared with a duration of <30 months, regardless of the treatment received (34.7% versus 6.4%;  $P < .001$ ). The 3-year DFS for the URD SCT group was 31.6% versus 25.4% for the alternative donor SCT group ( $P$  value not stated).

Lausen et al. [66] present the results of a population-based single-institution study of all Danish pediatric (<20 years at BMT) patients with ALL ( $n = 67$ ) who underwent allogeneic BMT between 1985 and 1996. Patients were stratified into 3 groups: patients with HLA-matched sibling donors who underwent transplantation between 1985 and 1989 (group 1;  $n = 32$ ), family donors between 1990 and 1996 (group 2;  $n = 19$ , including 11 HLA-matched siblings, 5 HLA-matched other family members, and 3 HLA-mismatched siblings), and URDs between 1990 and 1996 (group 3;  $n = 16$ , including 12 HLA-matched and 4 HLA-mismatched donors). Sixty-seven percent of patients underwent transplantation in CR2, 16% in CR1, and 16% in CR >2, with no significant differences between the donor groups. Neither sites of relapse nor IE disease was specified. Median CR1 duration was 28 months for each donor group. The median time from diagnosis to BMT ranged from 30 to 34 months and was not significantly different between the donor groups. Conditioning regimens consisted of Cy + TBI (1200 cGy; 87%) or Bu + Cy (13%); ATG was given to patients receiving marrow from donors other than HLA-identical siblings. GVHD prophylaxis consisted of CSA  $\pm$  MTX. The 3-year TRM for the 3 groups was 6%, 21%, and 25%, respectively. At a median follow-up of 41 months, the 3-year LFS of all family donors (groups 1 and 2) and URD donors (group 3) was 56% and 67%, respectively; LFS for HLA-identical sibling donors versus

other family members was 55% and 58%, respectively. Comparing family versus URD donors who underwent transplantation during the same time period (groups 2 versus 3), LFS was significantly higher for URD transplants (67% versus 28%;  $P = .002$ ). LFS was significantly worse for patients receiving both CSA and MTX versus patients receiving either as a single agent for GVHD prophylaxis ( $P = .0005$ ).

Saarinen-Pihkala et al. [67] analyzed a population-based cohort of all consecutive pediatric (<16 years at diagnosis) patients diagnosed with ALL in 5 Nordic countries from 1992 to 2000. A total of 1456 patients were registered in the database, 426 (29%) of whom were defined as high or very high risk. Of these, 43 patients were treated with a related ( $n = 14$ ) or unrelated ( $n = 29$ ) BMT in CR1 if they had one of the following high-risk features: t(9;22),  $n = 19$ ; t(4;11),  $n = 1$ ; WBC >200 000/ $\mu$ L + other factors,  $n = 11$ ; WBC >100 000/ $\mu$ L + other factors,  $n = 5$ ; or poor response,  $n = 7$ . Median follow-up, conditioning regimens, and GVHD prophylaxis regimens were not stated. There was no difference in TRM between the related and unrelated BMT groups (14% versus 17%;  $P$  not stated). There was no significant difference in the overall EFS between the 2 groups (45% versus 65%;  $P = .20$ ).

Saarinen-Pihkala et al. [68] performed a population-based study of all 65 pediatric (<16 years at diagnosis) patients with ALL who underwent BMT in CR2 from either matched sibling donors ( $n = 37$ ) or URDs ( $n = 28$ ) between 1990 and 1997 at 7 Nordic centers. All patients were treated with common Nordic ALL protocols. Relapse for sibling and URD groups occurred as isolated BM ( $n = 26$  and 16), combined BM ( $n = 6$  and 7), or IE ( $n = 5$  and 5). The median CR1 duration was not stated; however, 41% of patients with matched sibling donors versus 18% of patients with URD relapsed >6 months after completing therapy ( $P < .05$ ). Conditioning regimens were TBI based ( $n = 43$ ), Bu  $\pm$  Cy  $\pm$  ATG ( $n = 17$ ), or other ( $n = 4$ ) [editorial note: numbers for conditioning regimens do not add up but are given as stated in the article]. GVHD prophylaxis in the matched sibling group consisted of CSA in all patients; MTX was also given in 67% of patients. GVHD prophylaxis in the URD group consisted of CSA + MTX; 64% also received ATG, and 11% received T-cell depletion. TRM was 11% and 19% for the URD and sibling groups, respectively. The incidence of grade II to IV acute GVHD was significantly higher in the URD group (64% versus 38%;  $P < .05$ ); chronic GVHD was also significantly more common in the URD group (58% versus 26%;  $P < .05$ ). At a median follow-up of 4.5 years, the EFS and OS for the URD versus sibling group were not significantly different: 54% versus 39% and 54% versus 42%, respectively.

**Table 9.** Comparison of Patient Characteristics and Outcomes from Articles Included in the Comparison of Conditioning Regimens in Allogeneic Transplantation Section

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median) Age at Transplantation (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS‡	OS	Significance: OS‡
<b>69</b>	<b>1+</b>	<b>Multicenter US RCT</b>	<b>Total 43</b> <b>Bu/VP/Cy 21</b> <b>TBI/VP/Cy 22</b>	<b>20 (8)</b>	<b>Overall</b> <b>24%</b> <b>9%</b>	<b>43.3</b>	<b>3-y EFS</b> <b>29%</b> <b>58%</b>	<b>P = .03</b>	<b>3-y</b> <b>47%</b> <b>67%</b>	<b>P = .09</b>
<b>70</b>	<b>2++</b>	<b>IBMTR database, 144 institutions</b>	<b>Total 627</b> <b>Cy + TBI 451</b> <b>Bu + Cy 176</b>	<b>20 (12.9)</b> <b>20 (11.3)</b>	<b>3-y</b> <b>15%</b> <b>23%</b>	<b>37</b>	<b>3-y LFS</b> <b>50%</b> <b>35%</b>	<b>P = .005</b>	<b>3-y</b> <b>55%</b> <b>40%</b>	<b>P = .003</b>
<b>71</b>	<b>2++</b>	<b>Single US center</b>	<b>Total 123</b> <b>Cy + TBI 80</b> <b>Ara-C + TBI 15</b> <b>Cy + hfTBI 28</b>	<b>61 (14)</b>	<b>Day 100</b> <b>17%†</b> <b>63%</b> <b>17%†</b>	<b>94</b>	<b>5-y DFS</b> <b>29%</b> <b>27%</b> <b>32%</b>	<b>Not significant</b>	<b>Overall</b> <b>34%</b>	<b>Not compared</b>
<b>72</b>	<b>2-</b>	<b>Single Australian center</b>	<b>Total 51</b> <b>Bu/Cy/Mel 26</b> <b>TBI + other 25</b>	<b>Not stated</b> <b>(not stated)</b>	<b>Day 100</b> <b>31%</b> <b>8%</b>	<b>58</b> <b>117</b>	<b>EFS</b> <b>27%</b> <b>36%</b>	<b>Not significant</b>	<b>OS</b> <b>34%</b> <b>40%</b>	<b>Not significant</b>
<b>&lt;70% Pediatric patients</b>										
<b>73§</b>	<b>2++</b>	<b>2 Spanish centers</b>	<b>Total 156</b> <b>Bu + other 42</b> <b>TBI + other 114</b>	<b>49 (15)</b> <b>59 (18)</b>	<b>18-mo</b> <b>22%</b> <b>17%</b>	<b>48+</b> <b>72+</b>	<b>6-y EFS</b> <b>22%</b> <b>43%</b>	<b>P = .01</b>	<b>Not stated</b>	<b>Not compared</b>

LFS indicates leukemia-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; RCT, randomized controlled trial; Bu, busulfan; VP, etoposide; Cy, cyclophosphamide;

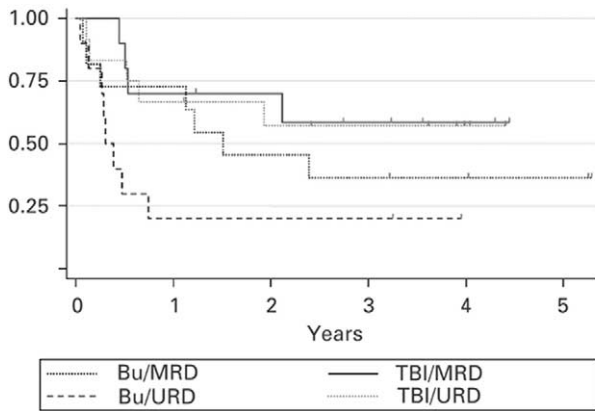
TBI, total body irradiation; IBMTR, International Bone Marrow Transplant Registry; Ara-C, cytosine arabinoside; hf, hyperfractionated; Mel, melphalan.

\*Quality and strength of evidence definitions are listed in Table 1.

‡Not significant:  $P > .10$ .

†Both the Cy + TBI and CY + hfTBI groups combined had a day 100 TRM of 17%, which was significantly lower than the Ara-C + TBI group ( $P < .0001$ ).

§<70% of patients met inclusion criteria.



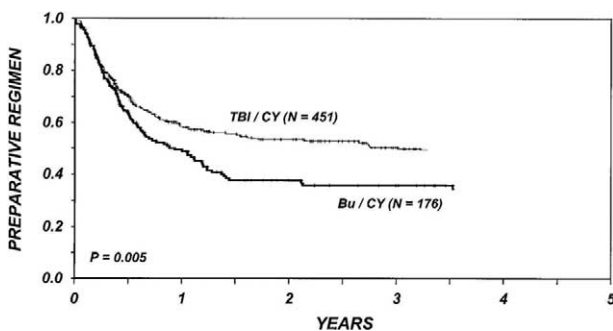
**Figure 8.** Kaplan-Meier survival estimates by conditioning and donor. MRD indicates matched related donor. Reprinted with permission.<sup>69</sup>

There was no correction for time-to-transplantation bias.

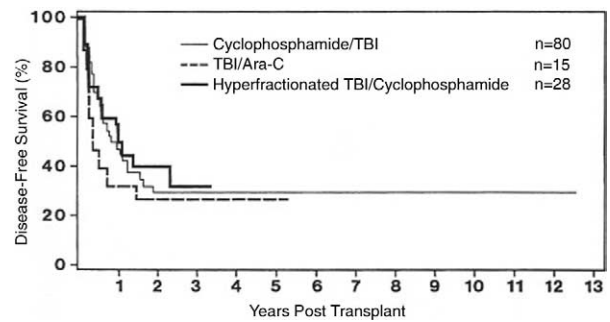
#### COMPARISON OF CONDITIONING REGIMENS IN ALLOGENEIC STEM CELL TRANSPLANTATION PATIENTS

Table 9 summarizes the grading criteria, study populations, patient characteristics, and outcomes from pediatric studies included in the comparison of conditioning regimens in allogeneic SCT section. Evidence in this section is taken from self-described studies of pediatric populations, all of which included patients <21 years of age. Evidence is presented in descending order with the largest sample size first.

Bunin et al. [69] performed a prospective randomized trial of 43 pediatric (<21 years at BMT) patients with ALL treated with an allogeneic BMT at 11 centers of the Pediatric Blood and Marrow Transplant Consortium from 1997 to 2000. Patients were randomized to receive Bu + VP + Cy (n = 21) or TBI (1200 cGy in 6 fractions) + VP + Cy (n = 22) as a conditioning regimen. Randomization was stratified



**Figure 9.** Actuarial probability of leukemia-free survival after HLA-identical sibling bone marrow transplantation for childhood ALL, by pretransplantation conditioning regimen. Reprinted with permission.<sup>70</sup>



**Figure 10.** Comparison of 3 conditioning regimens used for allogeneic BMT for ALL: disease-free survival. Follow-up after BMT differs because the cyclophosphamide/TBI (single-dose and fractionated) regimens were used from 1979 to 1983 (thin line), TBI/AraC was used from 1984 to 1987 (dashed line), and hyperfractionated TBI/cyclophosphamide was used from 1987 to 1991 (bold line). Reprinted with permission.<sup>71</sup>

by CR1 duration, remission status at BMT, and prior cranial irradiation. Patients in the Bu + VP + Cy group had a matched related donor (n = 11) or matched URD (n = 10). Patients in the TBI + VP + Cy group had a matched related donor (n = 10) or matched URD (n = 12). TRM was higher in the Bu-treated group (24% versus 9%), but the *P* value was not stated for the comparison. At a median follow-up of 43.3 months, the 3-year EFS was significantly better in the TBI + VP + Cy group (58% versus 29%; *P* = .03; Figure 8). There was no significant difference in the 3-year OS for the 2 groups (67% for the TBI group versus 47% for the Bu group; *P* = .09). There was no difference in EFS between the patients who received a BMT from a related versus URD (46% versus 40%; *P* = .30).

Davies et al. [70] compared the outcomes of 2 conditioning regimens in a retrospective cohort study of the International Bone Marrow Transplant Registry. Pediatric (<20 years at BMT) patients from 144 institutions with ALL who underwent transplantation between 1988 and 1995 and who received Cy + TBI (total, n = 451; fractionated  $\leq$ 1200 cGy, n = 253; fractionated >1200 cGy, n = 117; unfractionated  $\leq$ 1000 cGy, n = 72; unfractionated >1000 cGy, n = 9) or Bu + Cy (n = 176) as a conditioning regimen for an HLA-identical sibling BMT were included. For the Cy + TBI group, disease status at BMT was CR1 (n = 134), CR2 (n = 194), CR  $\geq$ 3 (n = 51), or not in CR (n = 72), with a median CR1 duration (for patients who underwent transplantation beyond CR1) of 18.98 months and a median interval between CR1 and BMT of 3.95 months (for patients who underwent transplantation in CR1). For the Bu + Cy group, disease status at BMT was CR1 (n = 51), CR2 (n = 73), CR  $\geq$ 3 (n = 27), or not in CR (n = 25), with a median CR1 duration of 23.16 months (for patients who underwent transplantation beyond CR1), and the me-

dian interval between CR1 and BMT was 4.96 months (for patients who underwent transplantation in CR1). Sites of relapse (BM versus extramedullary) were not significantly different between the 2 groups ( $P = .30$ ); however, the rates of relapse sites were not specifically stated. The 3-year cumulative incidence of TRM was 15% versus 23% for the Cy + TBI and Bu + Cy cohorts, respectively ( $P = .02$ ). At a median follow-up of 37 months, the 3-year LFS rates were 50% and 35% ( $P = .005$ ; Figure 9), and the 3-year OS rates were 55% versus 40% for the Cy + TBI versus Bu + Cy groups, respectively ( $P = .003$ ). In the univariate and multivariate analyses, the OS and LFS of the Cy + TBI group were significantly greater, the risk of TRM was lower, and the risk of relapse was not significantly different from those of the Bu + Cy group. Other factors (in addition to conditioning regimen) that were associated with lower survival rates by multivariate analysis were BMT while not in CR, short duration of CR1, presence of t(4;11) translocation, and use of T-cell depletion or combined MTX + CSA versus CSA or MTX alone for GVHD prophylaxis.

Weisdorf et al. [71] retrospectively compared the long-term outcomes of 4 conditioning regimens used for HLA-matched sibling allogeneic BMTs for 123 patients with ALL (75% were <20 years at BMT) treated at a single US center from 1979 to 1991. Eighty-five percent of patients underwent transplantation in CR  $\geq 2$ . The duration of CR1 was <18 months in 35% of all patients. Thirty-seven (30%) patients had extramedullary disease at any site. Conditioning regimens included Cy + TBI  $\pm$  VM-26 + Ara-C (750 cGy in a single dose; 1979-1981;  $n = 35$ ), Cy + fractionated TBI (1320 cGy in 8 fractions; 1982-1984;  $n = 45$ ), Ara-C + TBI (850 cGy in a single dose; 1984-1987;  $n = 15$ ), and Cy + hyperfractionated TBI (1320 cGy in 11 fractions; 1987-1991;  $n = 28$ ). The first 2 groups were combined for the analysis. At a median follow-up of 7.8 years, there was no significant difference in the 5-year DFS for these groups (Cy + TBI, 29%; Ara-C + TBI, 27%; Cy + hyperfractionated TBI, 32%;  $P = .60$ ; Figure 10). Day 100 TRM was significantly higher for the Ara-C + TBI group versus the Cy + TBI groups (63% versus 17%;  $P < .0001$ ).

Carpenter et al. [72] performed a study comparing chemotherapy versus TBI-based conditioning regimens in pediatric (upper age limit not defined) patients with ALL treated with an allogeneic BMT (donor relation not defined) at a single Australian center. Patients in the chemotherapy conditioning regimen group ( $n = 26$ ) were prospectively enrolled between 1988 and 1993 and received Bu + Cy + melphalan. Patients in the TBI-based conditioning regimen group were a historical control group ( $n = 25$ ) treated between 1979 and 1988 and received Cy + TBI ( $n =$

22; single-fraction 1000 cGy,  $n = 2$ ; 1200-1320 cGy in 6 fractions,  $n = 20$ ); 3 patients in the Cy + TBI group also received Ara-C or Bu + Cy ( $n = 3$ ). Day 100 TRM for the chemotherapy-based conditioning regimen group was 31%; at a median follow-up of 58 months, EFS and OS were 27% and 34%, respectively. Day 100 TRM for the TBI-based conditioning regimen group was 8%; at a median follow-up of 117 months, EFS and OS were 36% and 40%, respectively. Differences in EFS, OS, and relapse rates were not statistically significant between the groups. The only significant difference between the 2 groups was death due to GVHD, which was higher in the chemotherapy group ( $P < .05$ ).

The following study consists of <70% pediatric patients: Granados et al. [73] retrospectively compared the outcomes of TBI-based ( $n = 114$ ) versus Bu-based ( $n = 42$ ) conditioning regimens in 156 consecutive patients with ALL (>50% were  $\leq 18$  years old at BMT) treated with an autologous ( $n = 66$ ) or matched sibling allogeneic ( $n = 90$ ) BMT at 2 Spanish centers from 1983 to 1997. Most patients received Cy in combination with Bu or TBI (1200 cGy in 4 [ $n = 29$ ] or 6 [ $n = 85$ ] fractions) for conditioning. Forty-six percent underwent transplantation in CR1, 33% in CR2, and 22% in more advanced disease. Sites of prior relapse were not stated. The median duration of CR1 was 7.5 versus 5.3 months for the TBI- versus Bu-based groups ( $P = .15$ ). Five of the autologous BMT patients received grafts purged with mAbs. GVHD prophylaxis consisted of CSA + MTX in most allogeneic BMTs (the exact number was not stated). At a median follow-up of >4 years in the Bu-based group and 6 years in the TBI-based group, the 6-year EFS was significantly different (22% versus 43%;  $P = .01$ ). Significant risk factors for shorter EFS by multivariate analysis were Bu-based regimens ( $P = .01$ ), advanced disease ( $P = .0001$ ), absence of chronic GVHD ( $P = .008$ ), shorter duration of CR1 ( $P = .02$ ), and development of veno-occlusive disease ( $P = .006$ ).

## AUTOLOGOUS VERSUS ALLOGENEIC STEM CELL TRANSPLANTATION

Table 10 summarizes the grading criteria, study populations, patient characteristics, and outcomes from pediatric studies included in the autologous versus allogeneic SCT section. Evidence in this section is taken from self-described studies of pediatric populations, all of which included patients <21 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.

Weisdorf et al. [74] compared the outcomes of 214 consecutive patients with ALL who received autologous BMT from 1987 to 1993 at 2 US centers with

**Table 10.** Comparison of Patient Characteristics and Outcomes from Articles Included in the Autologous versus Allogeneic SCT Section

Reference	Quality and Strength of Evidence*	Patient Populations	No. of Patients	Upper Limit (Median) Age at Time of Transplantation (y)	Treatment-Related Mortality	Median Follow-up (mo)	LFS/EFS/DFS	Significance: LFS/EFS/DFS
74	2+	2 US centers and NMDP	Total 551 Auto 214 URD 337	Not stated† Not stated†	Overall 15.9% 49.9%	34 25	DFS in CR1/CR2 42%/20% 32%/42%	P = .03/.02
75	2+	Italian AIEOP multicenter study‡	Total 75 Auto 29 Allo 46	18 (8.5)	Day 180 7% 15.8%	34	3-y EFS 39% 64%	Not stated
76	2+	Single US center§	Total 74 Auto 57 Allo 17	At diagnosis 15 (4.2) 18 (4.1)	Day 100 7% 18%	58 55	3-y EFS 47% 53%	Not stated
77	2-	MRC UKALL RI protocol	Total 256 (CR 243) Chemo 123 Auto 15 Related 63 URD 42	At diagnosis 15 (not stated)	Overall 12%	59	5-y EFS 47% 47% 45% 53%	Not stated
78	2-	Italian AIEOP multicenter study; ALL R-87 protocol	Total 48 Auto 30 Allo 18	No. ≤15 y 27 12	10% 11%	12 23	55-mo DFS 12.7% 43.3%	P = .0114
82	2+	EBMT (Auto) IMUST (URD)	Total 354 Auto 236 URD 118	56 (16) 54 (14)	Overall 17% 42%	9 23	2-y LFS 32% 39%	Not stated
83	2-	Single US center	Total 68 Auto 52 Allo 16	45 (not stated) 45 (not stated)	1-y 13% 44%	Not stated	3-y DFS 15% 31%	P = .58
84	2-	Single US center	Total 32 Auto 25 Allo 7	43 (18) 17 (13)	36% 43%	Not stated	Not stated	Not compared

LFS indicates leukemia-free survival; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; NMDP, National Marrow Donor Program; Auto, autologous; URD, unrelated donor; AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; Allo, allogeneic; MRC, Medical Research Council; ALL, acute lymphoblastic leukemia; Chemo, standard chemotherapy comparison group; EBMT, European Group for Blood and Marrow Transplant; IMUST, International Marrow Unrelated Search and Transplant.

\*Quality and strength of evidence definitions are listed in Table 1.

†A total of 75% of the autologous BMT group were ≤18 years; 64% of the unrelated allogeneic BMT group were ≤18 years.

‡This study overlaps with reference 13.

§This study overlaps with reference 28.

||Less than 70% of patients were pediatric.

those of 337 unrelated allogeneic BMT patients treated during the same period and reported to the National Marrow Donor Program. Seventy-five percent of the autologous and 64% of the unrelated BMT group were  $\leq 18$  years at the time of BMT. Remission status for autologous BMT patients were 23.8% CR1, 45.8% CR2, 24.8% CR  $\geq 3$ , and 5.6% relapsed/primary induction failure. Remission status for unrelated allogeneic BMT patients were 15.6% CR1, 31.7% CR2, 27.8% CR  $\geq 3$ , and 24.9% relapsed/primary induction failure. Patient age, remission status at BMT, year of BMT, and conditioning regimen were significantly different between the 2 groups. National Marrow Donor Program patients did not have information regarding 3 prognostic factors: diagnostic WBC, duration of CR1, and site(s) of relapse. At a median follow-up of 34 months in the autologous and 25 months in the unrelated allogeneic BMT groups, the DFS, relapse, and TRM rates significantly differed by remission status, age, and sex. Multivariate analysis demonstrated a significantly better DFS with unrelated allogeneic BMT in female patients  $\leq 18$  years old (34.1% versus 17.5%;  $P = .04$ ). There was no significant difference between unrelated allogeneic and autologous BMT for adults ( $>18$  years) or male children ( $\leq 18$  years).

Uderzo et al. [75] investigated the efficacy of a novel conditioning regimen in 75 consecutive pediatric ( $\leq 18$  years at diagnosis) patients with ALL who received allogeneic or autologous BMT in CR2 at 7 AIEOP centers between 1986 and 1993. There is overlap with Uderzo et al. [13]. All patients received the same first-line therapy; second-line treatment was according to AIEOP protocol or a BFM-like multiple-drug relapse protocol. Patients with HLA-identical (HLA-A, -B, and -DR) sibling donors ( $n = 46$ ) underwent allogeneic BMT, and the remainder underwent autologous BMT ( $n = 29$ ). Relapse sites for the allogeneic BMT group were isolated or combined BM relapse ( $n = 33$ ) or IE ( $n = 13$ ). Relapse sites for the autologous BMT group were isolated or combined BM relapse ( $n = 23$ ) or IE ( $n = 6$ ). The median CR1 duration was 26 and 25 months for allogeneic and autologous BMT patients, respectively. All patients received an identical conditioning regimen of high-dose vincristine + Cy + TBI (1200 cGy in 6 fractions). Twenty-three of 29 autologous BMT patients received *in vitro* purged marrow with vincristine + prednisolone ( $n = 13$ ), mafosfamide ( $n = 8$ ), or mAbs ( $n = 2$ ). GVHD prophylaxis consisted of CSA for allogeneic BMT patients. Day +180 TRM occurred in 15.8% and 7% of patients in the allogeneic and autologous BMT groups, respectively. Grade III or IV acute GVHD occurred in 11.9% of the allogeneic BMT group; chronic GVHD occurred in 20.5%. At a median follow-up of 34 months, the 3-year EFS was 64% for the allogeneic BMT group versus 39% for

the autologous group ( $P = .09$ ). In patients with IE relapse, the 3-year EFS was 76.9% and 83.3% for the allogeneic and autologous groups, respectively.

Parsons et al. [76] performed a retrospective cohort study of 74 relapsed pediatric ( $<18$  years at BMT) patients with B-precursor ALL in CR  $\geq 2$  who received allogeneic ( $n = 17$ ) or autologous ( $n = 57$ ) BMT at a single US center between 1986 and 1992. There is overlap with Billet et al. [28]. All patients in both groups met the same eligibility criteria: age  $<18$  years, in CR  $\geq 2$  after at least one BM relapse, B-lineage ALL, and the absence of high-risk features [ie, induction failure,  $t(9;22)$ , or T-cell disease]. Autologous marrow was purged *in vitro* with antibody and complement. Both groups received TBI-based conditioning regimens (TBI was administered in 175-cGy doses for 8 fractions totaling 1400 cGy). GVHD prophylaxis was MTX alone ( $n = 13$ ) or MTX + CSA ( $n = 4$ ) for the allogeneic group. The median CR1 duration for the autologous and allogeneic groups were 36.0 and 33.4 months, respectively. Disease status for the autologous and allogeneic groups was CR2 ( $n = 34$  and 14, respectively), CR3 ( $n = 20$  and 3, respectively), and CR  $>3$  ( $n = 3$  and 0, respectively). Day 100 TRM was 7% for autologous and 18% for allogeneic transplantations. At median follow-ups of 4.8 and 4.6 years, EFS at 3 years was 47% versus 53% for the autologous versus allogeneic groups, respectively ( $P = .77$ ).

Lawson et al. [77] presented the results of 256 pediatric ( $<15$  years at diagnosis) patients with relapsed ALL enrolled in the multicenter MRC UKALL R1 protocol between 1991 and 1995 (the number of centers was not stated). All patients received standardized reinduction and consolidation regimens. Of the 243 patients who achieved CR2, 120 proceeded to autologous ( $n = 15$ ), related ( $n = 63$ ), or unrelated ( $n = 42$ ) BMT. For the transplantation group, CR1 duration was  $<2$  years ( $n = 25$ ), 2 to 2.5 years ( $n = 42$ ), or  $>2.5$  years ( $n = 53$ ); sites of relapse were BM ( $n = 96$ ), isolated CNS ( $n = 14$ ), or other ( $n = 10$ ). GVHD prophylaxis and conditioning regimens were not specified. Fourteen (12%) transplant patients (7 related and 7 unrelated) died of TRM. The 5-year EFS rates for autologous, related, and URD BMT were 47%, 45%, and 52%, respectively.

Giona et al. [78-81] reported the prospectively designed Italian multicenter ALL R-87 study of 147 consecutive pediatric (81% of BMT patients were  $<15$  years at diagnosis) patients with relapsed or refractory ALL at 13 AIEOP centers between 1987 and 1992. Patients were treated with a reinduction and consolidation phase and, if a CR was achieved ( $n = 97$ ), were eligible to receive an autologous ( $n = 30$ ) or allogeneic ( $n = 18$ ) BMT. Thirty patients had an early relapse, and 19 withdrew from the study. The median duration of CR1 and sites of relapse were stated for

the 147 enrolled patients, but not for the 48 BMT patients. Thirty-five patients (24 autologous and 11 allogeneic) received Bu + Cy, 9 (3 autologous and 6 allogeneic) received Cy + TBI, and 4 patients received other regimens as conditioning. Marrow was purged with mafosfamide in 20 of 30 autologous transplants. At a median follow-up of 12 months in the autologous group and 23 months in the allogeneic group, the DFS was significantly improved in the allogeneic group (43.3% versus 12.7%;  $P = .0114$ ).

The following studies consist of <70% pediatric patients: Ringden et al. [82] conducted a matched-pair analysis that compared 118 matched unrelated allogeneic BMT patients treated for ALL and registered in the International Marrow Unrelated Search and Transplant study from 1987 to 1994 with 236 autologous BMT ALL patients reported to the European Group of Blood and Marrow Transplant registry from the same time period. Half of the autologous and unrelated BMT groups were  $\leq 16$  and  $\leq 14$  years at the time of BMT, respectively. Cases were matched 2:1 with controls on disease status at the time of transplantation (CR1, CR2, or CR3), age (<20, 20-40, or >40 years), and year of BMT. Sites of relapse and duration of CR1 were not stated. Unrelated BMT patients were excluded from the analysis if they did not have a matched autologous control ( $n = 88$ ), were a second BMT ( $n = 31$ ), had missing values ( $n = 23$ ), or had secondary ( $n = 11$ ) or undifferentiated ( $n = 7$ ) leukemia. TRM was significantly higher in the unrelated allogeneic BMT group (42% versus 17%;  $P < .0001$ ), whereas the relapse rate was significantly higher in the autologous BMT group (61% versus 32%;  $P < .0001$ ). At a median follow-up of 9 and 23 months in the autologous and unrelated BMT groups, respectively, the 2-year LFS (32% versus 39%;  $P = .45$ ) and OS (43% versus 39%;  $P = .15$ ) were not significantly different.

Woods et al. [83] performed a prospective trial of a single conditioning regimen for both autologous and allogeneic BMT in patients with ALL (65% were <16 years at BMT) at a single US center from 1985 to 1987. The conditioning regimen consisted of Ara-C + TBI (850 cGy in a single fraction). Allogeneic BMT patients received MTX + ATG + prednisone as GVHD prophylaxis. Autologous BMT patients received marrow purged with mAbs  $\pm$  4-hydroperoxycyclophosphamide; BM was harvested in the same remission as the transplantation. Median follow-up was not stated. The 3-year DFS was similar between the autologous versus allogeneic groups (15% versus 31%;  $P = .58$ ). There was also no significant difference in the 3-year OS (16% versus 38%;  $P = .74$ ).

Bostrom et al. [84] reported the results of 25 patients with ALL (50% were  $\leq 18$  years at BMT) with advanced disease who received a purged autologous BMT and 7 pediatric ALL patients (100% were

<18 years at BMT) who received a related allogeneic BMT from 1987 to 1988 at a single US center. The remission status of the purged autologous BMT patients were CR2 ( $n = 6$ ), CR  $\geq 3$  ( $n = 6$ ), relapse 1 ( $n = 3$ ), relapse  $\geq 2$  ( $n = 9$ ), or primary induction failure ( $n = 1$ ). The remission status of the related allogeneic BMT patients were relapse 1 ( $n = 3$ ) and relapse  $\geq 2$  ( $n = 4$ ). Purging methods included 4-hydroperoxycyclophosphamide and either anti-B (anti-CD9, -CD10, and -CD24) or anti-T (anti-CD5 and -CD7) mAbs. All patients received VP + Cy + TBI (850 cGy in a single dose) as a conditioning regimen; GVHD prophylaxis consisted of MTX + ATG + prednisone. Nine (36%) autologous and 3 (43%) allogeneic BMT patients died of TRM within 7 months after BMT. All remaining patients who received a purged autologous BMT relapsed by a median of 4.2 months after BMT. One (14%) patient who received an allogeneic BMT survived disease free for 15 months after BMT.

## FUTURE DIRECTIONS

### Additional Ongoing Studies

Several studies addressing critical issues that will affect the treatment recommendations in Table 3 have been published in abstract form, were recently completed, or are currently accruing patients. Rheingold et al. [85] described a feasibility trial of an intensive multiagent chemotherapy reinduction/reintensification regimen for pediatric patients with ALL who relapse on therapy. Fifty-three patients were treated from 1992 to 2002; 14 patients proceeded to allogeneic BMT in CR2. Jacobsohn et al. [86] reported the results of 15 infants (<15 months) with high-risk ALL treated with a cord blood or related donor allogeneic SCT in CR1 since 1992. Locatelli et al. [87] reviewed the outcomes of 175 pediatric patients with ALL treated with a related or URD SCT in CR2 at any of 11 AIEOP centers from 1998 to 2002. Gharib et al. [88] conducted a trial of alemtuzumab + Cy + TBI as the conditioning regimen for matched or mismatched URD SCT with T cell-replete grafts in 35 pediatric patients with relapsed ALL. Watanabe et al. [89] reported the results of the Children's Cancer and Leukemia Study Group of Japan ALL 941 protocol, in which 463 pediatric patients with ALL were treated from 1994 to 1999 with one of 4 treatment protocols, including 44 children who received an autologous PBSCT in CR1. Eapen et al. [90] compared the results of URD BMT/cord blood transplantation with those of related donor BMT in 135 infants (<18 months) with ALL or AML reported to the International Bone Marrow Transplant Registry from 1990 to 2001. Lang et al. [91] compared the results of CD34<sup>+</sup>-selected and/or CD133<sup>+</sup>-selected haploidentical related allogeneic SCT ( $n = 30$ ) with those of

unmanipulated matched related allogeneic SCT (n = 18) in pediatric patients with ALL treated between 1995 and 2003.

Other studies that are still accruing patients include the following: (1) a Children's Oncology Group phase II multicenter trial of the effectiveness of combination chemotherapy with or without related donor allogeneic PBSCT in pediatric ( $\leq 21$  years) patients with very-high-risk ALL that includes a dose-escalation study of imatinib mesylate in patients with Ph<sup>+</sup> ALL; (2) a Fred Hutchinson Cancer Research Center/National Cancer Institute phase II multicenter trial of nonmyeloablative related or unrelated allogeneic PBSCT in pediatric and adult ( $\leq 70$  years) patients with Ph<sup>+</sup> ALL or chronic myeloid leukemia that has previously responded to imatinib mesylate; (3) a Fred Hutchinson Cancer Research Center/National Cancer Institute phase I/II trial of biologic therapy with CD8<sup>+</sup> Wilms tumor (WT1) gene-specific cytotoxic T-lymphocyte clones and interleukin 2 in pediatric and adult ( $\leq 75$  years) patients with HLA-A2–positive or HLA-A24–positive AML or ALL at high risk of relapse after allogeneic SCT; and (4) an International Coordination Unit phase III multicenter trial of induction therapy followed by consolidation and reinduction with or without late intensification followed by a maintenance regimen of allogeneic BMT in infants ( $\leq 1$  year) with ALL.

### 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: (1) high-quality randomized controlled trials and other level 1 evidence to answer the questions addressed in this review; (2) studies to identify patients who are at very high risk for relapse (in addition to Ph<sup>+</sup> patients) and for whom more effective treatment approaches are needed; (3) unrelated marrow or blood donor versus unrelated cord blood donor allogeneic SCT; (4) alternative nonfamily allogeneic donor versus autologous SCT; and (5) studies that address the issue of adolescent and young adult patients to determine the appropriate age cutoff for pediatric versus adult ALL.

### DISCUSSION

The authors recommend methodology standardization, including study design, end-point definitions, and reporting of study results. Multicenter 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, a minimum of 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 or for making a true assessment of the widespread applicability or effect of the treatment outside the scope of the trial.

Many of today's therapies for cancer result from the randomized clinical trial process. It is currently estimated that 60% of pediatric cancer patients participate in cancer clinical trials [92]. 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 (due to geographic, transportation, cultural, and other barriers), 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.

### 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 most often represent preliminary (not final) data analyses.

Limitations specific to this review topic include the variability in reporting patient characteristics before SCT, the 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 first CR; many published studies did not report this information, thus 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 over the >20 years of trials included in this review. The effectiveness of salvage regimens affects attainment of second or greater CR,

which in turn influences the effectiveness of SCT. Finally, randomized controlled trial data were lacking in many areas of this review, which led to several treatment recommendations based on small prospective studies or large retrospective registry reports.

## FUTURE INITIATIVES

This comprehensive systematic review of the available evidence for the role of cytotoxic therapy with hematopoietic SCT in the therapy of pediatric ALL is the third in a series of sequential articles sponsored by the American Society for Blood and Marrow Transplantation. Each review will summarize the evidence regarding the role of cytotoxic therapy with SCT in the treatment of a specific disease by using defined methodology and grading criteria. The

next review in the series will address the role of SCT in the therapy of adult ALL and will be published in *Biology of Blood and Marrow Transplantation*.

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## Appendix A. Glossary of Terms

<b>AIEOP</b>	<b>Associazione Italiana di Ematologia ed Oncologia Pediatrica</b>
<b>ALL</b>	<b>Acute lymphoblastic leukemia</b>
<b>ALL-REZ (Rezidiven)</b>	<b>Relapsed ALL</b>
<b>AML</b>	<b>Acute myeloid leukemia</b>
<b>Ara-c</b>	<b>Cytarabine; cytosine arabinoside</b>
<b>ATG</b>	<b>Anti-thymocyte globulin</b>
<b>BFM</b>	<b>Berlin-Frankfurt-Munster</b>
<b>BM</b>	<b>Bone marrow</b>
<b>BMT</b>	<b>Bone marrow transplantation</b>
<b>Bu</b>	<b>Busulfan</b>
<b>c-ALL</b>	<b>Common acute lymphoblastic leukemia</b>
<b>CCG</b>	<b>Children's Cancer Group</b>
<b>CCR</b>	<b>Continuous complete remission</b>
<b>CI</b>	<b>Confidence interval</b>
<b>CNS</b>	<b>Central nervous system</b>
<b>CR</b>	<b>Complete remission</b>
<b>CR1</b>	<b>First complete remission</b>
<b>CR ≥ 1</b>	<b>First or greater complete remission</b>
<b>CR2</b>	<b>Second complete remission</b>
<b>CR ≥ 2</b>	<b>Second or greater complete remission</b>
<b>CR3</b>	<b>Third complete remission</b>
<b>CR ≥ 3</b>	<b>Third or greater complete remission</b>
<b>CR4</b>	<b>Fourth complete remission</b>
<b>CSA</b>	<b>Cyclosporine</b>
<b>Cy</b>	<b>Cyclophosphamide</b>
<b>DFS</b>	<b>Disease-free survival</b>
<b>EBMT</b>	<b>European Group of Blood and Marrow Transplant</b>
<b>EFS</b>	<b>Event-free survival</b>
<b>GITMO</b>	<b>Gruppo Italiano Trapianto di Midollo Osseo</b>
<b>GVHD</b>	<b>Graft versus host disease</b>
<b>HLA</b>	<b>Human leukocyte antigen</b>
<b>IBMTR</b>	<b>The International Bone Marrow Transplant Registry</b>
<b>IE</b>	<b>Isolated extramedullary</b>
<b>IMUST</b>	<b>International Marrow Unrelated Search and Transplant</b>
<b>KPS</b>	<b>Karnofsky Performance Scale</b>
<b>LFS</b>	<b>Leukemia-free survival</b>
<b>mAb(s)</b>	<b>Monoclonal antibody(ies)</b>
<b>MRC</b>	<b>Medical Research Council</b>
<b>MTX</b>	<b>Methotrexate</b>
<b>OKT3</b>	<b>Orthoclone® anti-CD3 antibody</b>
<b>OS</b>	<b>Overall survival</b>
<b>PBSCT</b>	<b>Peripheral blood stem cell transplantation</b>
<b>Ph+</b>	<b>Philadelphia chromosome positive</b>
<b>POG</b>	<b>Pediatric Oncology Group</b>
<b>RCTs</b>	<b>Randomized controlled trials</b>

RR  
SCT  
SFGM  
TBI  
TRM  
UKALL  
URD  
VM-26  
VP  
WBC

Relative risk  
Stem cell transplantation  
Société Française de Greffe de Moelle  
Total body irradiation  
Treatment-related mortality  
United Kingdom Acute Lymphoblastic Leukemia  
Unrelated donor  
Teniposide  
Etoposide  
White blood cell count

## Appendix B. Outline of Article

**Abstract**  
**Introduction**  
**Literature Search Methodology**  
**Qualitative and Quantitative Grading of the Evidence**  
**Treatment Recommendations**  
**Transplantation vs. Chemotherapy in Pediatric Acute Lymphoblastic Leukemia (ALL)**  
**First Complete Remission (CR1)**  
**Second or greater CR (CR  $\geq$  2)**  
**Autologous SCT**  
**Unpurged Autologous SCT**  
**Purged Autologous SCT**  
**Purged and Unpurged Autologous SCT**  
**Related Donor Allogeneic SCT**  
**Unrelated Donor Allogeneic SCT**  
**Related vs. Unrelated Donor Allogeneic SCT**  
**Comparison of Conditioning Regimens in Allogeneic SCT patients**  
**Autologous vs. Allogeneic SCT**  
**Future Directions**  
**Additional Ongoing Studies**  
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**Future Initiatives**  
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