Biology of Blood and Marrow Transplantation 13:1-25 (2007)
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1083-8791/07/1301-0001$32.00/0
doi:10.1016/j.bbmt.2006.10.024

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

Denise M. Oliansky,[1] J. Douglas Rizzo,[2] Peter D. Aplan,[3] Robert J. Arceci,[4] Louis Leone,[5] Yaddanapudi Ravindranath,[6] Jean E. Sanders,[7] Franklin O. Smith III,[8] Fiona Wilmot,[9] Philip L. McCarthy Jr,[1] Theresa Hahn[1]

[1]Roswell Park Cancer Institute, Buffalo, New York; [2]Medical College of Wisconsin, Milwaukee, Wisconsin; [3]NIH, NCI, CCR, Genetics Branch, Bethesda, Maryland; [4]Kimmel Comprehensive Cancer Center, Baltimore, Maryland; [5]Children's Oncology Group, Arcadia, California; [6]Childrens's Hospital of Michigan and Wayne State University School of Medicine, Detroit, Michigan; [7]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; [8]Cincinnati Children's Hospital and Medical Center and University of Cincinnati College of Medicine, Cincinnati, Ohio; [9]Blue Shield of California, San Francisco, California

Major funding for this study was provided by the National Marrow Donor Program.

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

Received October 20, 2006; accepted October 23, 2006

ABSTRACT

Clinical research examining the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute myeloid leukemia (AML) 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 the table entitled "Summary of Treatment Recommendations Made by the Expert Panel for Pediatric Acute Myeloid Leukemia" and were reached unanimously by a panel of experts in AML. The identified priority areas of needed future research in pediatric AML include: What is the role of risk group stratification, including the role of cytogenetics, in selection of patients for allogeneic SCT, especially those in first CR? What is the appropriate timing and use of alternative donor SCT, given that matched unrelated donor SCT appears to yield outcomes equivalent to matched related donor SCT? What is the role of reduced intensity SCT (including the use of fludarabine-based preparative regimens) and/or other immunomodulatory approaches to maximize the graft-versus-leukemic effect? and What is the role of biologically targeted agents (ie, tyrosine kinase inhibitors, farnesyl transferase inhibitors, Flt-3 inhibitors, etc) in the treatment of AML, including induction, consolidation, conditioning regimens, and after SCT?
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KEY WORDS

Acute myeloid leukemia • acute myelogenous 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 stem cell transplantation (SCT) in the therapy of selected diseases. The steering committee that was convened to oversee the projects invited an independent panel of disease-specific experts to conduct each review. Four previous reviews have been published in *Biology of Blood and Marrow Transplantation* on diffuse large cell B cell non-Hodgkin lymphoma [1], multiple myeloma [2], pediatric ALL [3], and adult ALL [4].

This is the fifth review to result from this initiative. Its goals are to assemble and critically evaluate all

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

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

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of the evidence regarding the role of SCT in the therapy of pediatric (<21 yr) patients with acute myeloid leukemia (AML) make treatment recommendations based on the available evidence, and identify needed areas of research.

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 August 9, 2005 using the search terms "acute myeloid leukemia" or "acute myelogenous leukemia" and "transplant" limited to human trials, English language, and publication date of 1990 or later. An updated search was conducted on February 9, 2006, limited to the period from July 1, 2005 to March 1, 2006. Articles were excluded if published before 1990, included <25 patients, were not peer reviewed, were editorials, letters to the editor, phase I (dose escalation or dose finding) studies, reviews, consensus conference papers, practice guidelines, laboratory studies with no clinical correlates, did not focus on an aspect of therapy with SCT for the treatment of pediatric AML, or if >50% of the study population was >21 years of age. In addition, for an article to be included, ≥70% of study subjects had to have AML or study results had to be stratified by disease. Abstracts and presentations at national or international meetings were not included as evidence in this review for reasons previously described [3].

This search strategy did not yield any articles specific to acute promyelocytic leukemia (APL) in children. A search on the specific terms "APL" and "transplant" yielded 99 articles limited to English-language and human trials [5-8], but none of these met the inclusion criteria described above. Because transplantation is not the standard for the initial treatment for APL, most studies included in this review excluded patients with APL or retained only a minority proportion (usually <5%) of patients with APL in their study population.

QUALITATIVE AND QUANTITATIVE GRADING OF THE EVIDENCE

The hierarchy of evidence, including a grading scheme for the quality and strength of the evidence and strength of each treatment recommendation, has been established and published as an editorial policy statement in *Biology of Blood and Marrow Transplantation* (2005). Tables 1 and 2 are reprinted from the policy statement and define criteria used to grade the studies included in this review and grade the treatment recommendations. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan also were considered in evaluating

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

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

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the studies. Several multicenter clinical trials were designed to biologically assign patients to a treatment arm based on the availability of a donor ("biologic allocation"). Analysis of related allogeneic (allo) SCT versus chemotherapy is therefore graded as level "2" evidence, not level "1", because it is not based on a statistically randomized, controlled trial design. Autologous (auto) SCT versus chemotherapy was graded as level "1" evidence if the study design included a statistically randomized, controlled trial. Clinical studies are summarized with enough detail to provide a concise summary of study design, sample size, eligibility criteria, and treatment schedule.

All data in the text and tables were abstracted from the original articles first by the first author (DO) and then double checked for accuracy and clarity by 2 other authors (TH and PLM) and 1 additional reviewer (see Acknowledgments). In some articles there were discrepancies within the data reported and, in these cases the data most consistent with the text of the article were presented in this review. The last author (TH) takes responsibility if errors remain. Appendix A lists the common abbreviations used in this review.

TREATMENT RECOMMENDATIONS

The strength of this review is the detail conveyed in the text about the study designs and the presentation of the outcomes in the summary tables at the end of each major section. Table 3 contains the summary of treatment recommendations made by the pediatric AML expert panel. The expert panel deliberated on several treatment recommendations, particularly the use of bone marrow (BM) versus peripheral blood (PB) as the stem cell source. Most pediatric patients with AML have pediatric (minor) donors, which can create an ethical and regulatory dilemma regarding the risks and benefits of subjecting healthy minors to stem cell donation [9,10]. Although the short-term risk of death or life-threatening complications with pediatric BM donation is established and rare (<0.4%), there is little to no evidence of the long-term effects of growth factor administration, central line placement, or use of blood transfusions associated with pediatric PB stem cell donation. Use of BM from a healthy sibling donor, when available, is considered standard of care and the ethics of minor sibling donation of unstimulated BM are generally accepted. The question of whether PB stem cell donation poses an increased unacceptable risk compared with BM donation remains unanswered. Thus, the expert panel consensus was to recommend BM as the preferred stem cell source in the matched related donor allo-SCT setting. This issue is not applicable in the auto-SCT setting, because the donor is the patient and obviates the ethical issues. It is also not applicable with unrelated donor allo-SCT, because all unrelated BM and PB donors are >18 years of age.

BMT VERSUS CHEMOTHERAPY IN PEDIATRIC AML

Evidence is taken from self-described studies of pediatric populations, all of which included patients <21 years of age. The highest quality studies are presented first; studies of equal quality are presented in descending order by sample size. The following text describes the study design of each of the 16 articles included in this section. Table 4 presents a summary of the outcomes for each study. Of the 6 studies investigating auto-BMT versus chemotherapy only, 1 study found a significant difference in DFS between the 2 treatment groups. Of the 16 studies that examined allo-BMT versus chemotherapy only with/without auto-BMT, 6 stated a statistically significant difference in DFS between treatment groups and 3 found a significant difference in overall survival (OS).

Autologous BMT versus Chemotherapy in First CR

Alonzo et al. [11] reported the cumulative outcomes of 1464 pediatric (<21 yr) patients with AML who achieved first CR (CR1) in the 5 Children's Cancer Group (CCG) trials (CCG 251, 213, 2861, 2891, 2941) presented in detail below or in other sections of this review. Children diagnosed with APL, myelodysplastic syndrome (MDS), or Down syndrome (DS) were excluded from these trials. Of the 1464 patients, 186 had unknown data or withdrew from study before assignment. The remaining patients were assigned to allo-BMT (n = 373) if a human leukocyte antigen (HLA)-matched related donor was available, auto-BMT (n = 217), or chemotherapy (n = 688). Approximately 15% of children did not receive the treatment to which they were assigned. Figure 1 compares the disease-free survival (DFS) between the donor and no-donor groups.

Woods et al. [12] presented the results of the CCG 2891 multicenter, randomized, prospective trial, which enrolled 1114 pediatric (<21 yr) patients with AML, that compared chemotherapy, auto-BMT, and allo-BMT. Patients diagnosed with Fanconi anemia and philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML) were excluded from the trial, and those with DS, secondary AML, granulocytic sarcoma, or MDS were excluded from the analysis, leaving 887 analyzable patients. A total of 652 (74%) patients achieved CR1. Patients with 5- or 6-antigen HLA-matched family donors (n = 181) were biologically assigned to receive allo-BMT. Of the remaining 471 patients, 115 refused randomization, leaving 356 patients to be randomized between auto-BMT (n = 177) or 4 cycles of 3 different con-

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

Indication for HSCT	Treatment Recommendation Grade*	Highest Level of Evidence†	Reference No.‡	Treatment Recommendation Comments
TRANSPLANTATION VERSUS CHEMOTHERAPY				
Auto-SCT vs chemotherapy in CR1	A	1++	9	Auto-SCT and chemotherapy have equivalent survival outcomes. Lacking data on QOL, secondary malignancies and other late effects of treatment prevents a recommendation of one therapy over the other.
Allo-SCT vs chemotherapy in CR1	B	2++	9	Allo-SCT has superior OS and LFS compared with chemotherapy and is recommended. Additional prospective data regarding risk subgroups may alter this recommendation.
Allo-SCT vs chemotherapy in CR2	D	2−	24	There is a lack of evidence comparing MRD allo-SCT compared to chemotherapy in CR2; however, the consensus recommendation of the expert panel is MRD allo-SCT if available. A MUD or other alternative donor SCT is recommended in the context of a clinical trial.
TRANSPLANTATION TECHNIQUES				
Auto-SCT vs allo-SCT in CR1	A	1++	9	MRD allo-SCT has superior survival outcomes compared to auto-SCT in CR1. Additional prospective data regarding risk subgroups may alter this recommendation. The consensus recommendation of the expert panel is to use bone marrow as the stem cell source in the MRD allo-SCT setting based on scientific, ethical, regulatory, and practical issues.
Auto-SCT vs allo-SCT in CR2	C	2+	25,34	The consensus recommendation of the expert panel is to use any suitably matched related or unrelated allo- over auto-SCT; however, there is a lack of evidence that one has better outcomes than the other.
Auto-SCT	No recommendation	2+	28,35–40	Current practice is to use PBSCT; however, there are very few patients in the 2 studies that fulfill review criteria. A randomized trial of Auto-BMT vs PBSCT is not feasible due to the infrequent use of auto-SCT for pediatric patients with AML. With current technology, there is a preference for using MUD or alternative donors over auto-SCT if a MRD is not available. There are no effective purging agents currently available, but if one were developed, it would increase interest for a trial of purged vs unpurged auto-SCT.
Related vs unrelated allo-SCT	D	2+	41	There are no data indicating that using one type of suitably matched allo-SCT is better than another. There are differences between institutions with regard to transplantation technique; however, there are no apparent differences in outcomes across institutions.
Related allo-SCT	B	2+	42–46	MRD allo-SCT is preferred in CR1 or CR2; in CR2, alternative donors could be considered if MRD is not available.
Unrelated allo-SCT	No recommendation	2+	47–49	No evidence for one preferred technique for unrelated allo-SCT (ie, T cell depletion, cord blood vs PBSCT vs BMT, etc).
Comparison of allo-SCT myeloablative conditioning regimens	C	2+	50,51	There is no difference or preference of one conditioning regimen over another with respect to survival, LFS, or late effects.
Comparison of auto-SCT myeloablative conditioning regimens	No recommendation	NA	None	No evidence comparing conditioning regimens in the auto-SCT setting.
APL in CR1	Not recommended	4	None	No evidence of a need for SCT.
APL in CR2	D	3	5–8	Standard practice is to use allo-SCT (preferred) or auto-SCT if there is no suitable MRD, MUD, or alternative donor, or a trial comparing haploidentical allo-vs auto-SCT.

QOL indicates quality of life; MRD, matched related donor; MUD, matched unrelated donor; LFS, leukemia-free survival; NA, not available; RCT, randomized controlled trial.

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

†Definitions: Levels of Evidence (Table 1): 1++, high-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias; 1+, well-conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; 1−, meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; 2++, high-quality systematic reviews of case-control or cohort studies, or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and high probability that the relation 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 relation is causal; 2−, case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relation is not causal; 3, nonanalytic studies, eg, case reports, case series; 4, expert opinion.

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

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

Reference #	Quality & Strength of Evidence*	Patient Population	Patient Characteristic†	Risk Groups	Number of Patients by Study Group	Upper Limit (median) Age at Diagnosis	% Treatment Related Mortality	Median Follow-Up (Months)	% DFS/ % EFS/ % RFS (Signif)	Outcome Defined	% OS (Signif)	OS Defined
Autologous BMT versus Chemotherapy in First Complete Remission (CR1)†												
[11]	1++	Combined 5 CCG Trials (251, 213, 2861, 2891, 2941) 1979–1996 Meta-analysis	Age, WBC, Blast %, Gender, FAB, Cytogen.	Not Stated	Total 905 (ITT) Auto 217 Chemo 688	<21 yrs (6.2) (7.0)	8-yr 7 6	Not Stated	8-yr DFS 42 ± 7 34 ± 4 (*P*=.83)	Time from CR1 to relapse or death from any cause	8-yr 49 ± 7 42 ± 4 (*P*=.37)	Time from CR1 to death from any cause
[12]	1+	CCG Trial 2891 Oct 1989 to Apr 1995 Multi-center (236) Randomized trial US, Canada, Australia	Age, WBC, FAB, Cytogen.	Not Stated	Total 356 (ITT) Randomized Auto 177 Randomized Chemo 179	<21 yrs (Not Stated)	Not stated 5 4	Not Stated (min 4 yrs)	8-yr DFS 42 ± 8 47 ± 8 (*P*=.31)	Time from CR1 (event not defined)	8-yr 48 ± 8 53 ± 8 (*P*=.21)	Time from CR1 (event not defined)
[13]	1+	POG Trial 8821 Jun 1988 to Mar 1993 Multi-center (16) Randomized trial US	Race, Age, WBC, FAB, EMD, Induction response, DS, Cytogen.	Not Stated	Total 232 (ITT) Randomized Auto 115 Randomized Chemo 117	<21 yrs (Not Stated)	Not stated 15 2.7	Not Stated	3-yr EFS 38 ± 6.4 36 ± 5.8 (*P*=.20)	Time from randomization until 1st event	3-yr 40 ± 6.1 44 ± 6.0 (*P*=.10)	Time from randomization until death
[14]	1+	UK-MRC 10th AML May 1988 to Mar 1995 Multi-center (41) Randomized trial UK, Rep. of Ireland, New Zealand	Sex, Age, FAB, AML type, CNS, WBC Cytogen.	Good‡ (28%) Standard (52%) Poor (20%)	Total 100 (ITT) Randomized Auto 50 Random. no Therapy 50	<15 yrs (Not Stated)	Not Stated	Not Stated	7-yr DFS 68 46 (*P*=.02)	Time from CR1 to any event	7-yr 70 59 (*P*=.20)	Time from entry to death
[15]	1+	AIEOP LAM 87 Mar 1987 to Mar 1990 Randomized trial Multi-center (29) Italy	Age, Sex, WBC, FAB, EMD, Platelets, Time to CR1, Hepato., Splenom.	Not Stated	Total 72 (ITT) Randomized Auto 35 Randomized Chemo 37	<15 yrs (7 yrs)	Not Stated 3 8	28 mos	5-yr DFS 21 ± 8 27 ± 8 (Not Signif.)	Time from CR1 to 1st event	Not Stated	
[16]	2+	Combined AIEOP LAM 87–92 Trials Mar 1982 to Sep 2001 Retrospective	Age, Sex, WBC, CNS, FAB, Cytogen.	SR, HR (LAM 92 only)	Total 199 Auto 110 Chemo 89	<15 yrs (Not Stated)	Not Stated	Not Stated	5-yr DFS 55 ± 5 28 ± 5 (Not Stated)	Time from CR1 to last follow-up or first event	Not Stated	
Allogenic BMT vs Chemotherapy ± Autologous BMT in CR1												
[11]	2++	Combined 5 CCG Trials (251, 213, 2861, 2891, 2941) 1979-1996 Meta-analysis	Age, WBC, Blast %, Gender, FAB, Cytogen.	Not Stated	Total 1278 (ITT) Allo 373 Auto 217 Chemo 688	<21 yrs (8.9) (6.2) (7.0)	8-yr 17 7 6	Not Stated	8-yr DFS 47 ± 5 42 ± 7 34 ± 4 (Allo vs Chemo *P*=.004)	Time from CR1 to relapse or death from any cause	8-yr 54 ± 5 49 ± 7 42 ± 4 (Allo vs Chemo *P*=.06)	Time from CR1 to death from any cause

Table 4. *Continued*

Reference #	Quality & Strength of Evidence*	Patient Population	Patient Characteristic†	Risk Groups	Number of Patients by Study Group	Upper Limit (median) Age at Diagnosis	% Treatment Related Mortality	Median Follow-Up (Months)	% DFS/ % EFS/ % RFS (Signif)	Outcome Defined	% OS (Signif)	OS Defined
[12]	2+	CCG Trial 2891 Phase III Oct 1989 to Apr 1995 Multi-center (236) US, Canada, Australia	Age, WBC, FAB, Cytogen.	Not Stated	Total 537 (ITT) Allo 181 Randomized Auto 177 Randomized Chemo 179	<21 yrs (Not Stated)	Not stated 14 5 4	Not Stated (min 4 yr)	8-yr DFS 55 ± 9 42 ± 8 47 ± 8 (Allo vs Chemo *P*=.01)	Time from CR1 (event not defined)	8-yr 60 ± 9 48 ± 8 53 ± 8 (Allo vs Chemo *P*=.05)	Time from CR1 (event not defined)
[13]	2+	POG Trial 8821 Jun 1988 to Mar 1993 Multi-center (16) US	Race, Age, WBC, FAB, EMD, Induction response, DS, Cytogen.	Not Stated	Total 321 (ITT) Allo 89 Randomized Auto 115 Randomized Chemo 117	<21 yrs (Not Stated)	Not stated Not stated 15 2.7	Not Stated	3-yr EFS 52 ± 8 38 ± 6.4 36 ± 5.8 (Allo vs Chemo *P*=.06)	Time from randomization until 1st event	3-yr Not Stated 40 ± 6.1 44 ± 6.0 (Allo vs Chemo *P*=.15)	Time from date of randomization until death
[14]	2+	UK-MRC 10th AML May 1988 to Mar 1995 Multi-center (41) UK, Rep. of Ireland, New Zealand	Sex, Age, FAB, AML type, CNS, WBC, Cytogen.	Good* (28%) Standard (52%) Poor (20%)	Total 315 (ITT) Donor 85 No Donor 230	<15 yrs (Not Stated)	Not Stated 9 1	Not Stated	Not Stated	Time from CR1 to any event	7 yr 70 60 (*P*=.10)	Time from entry to death
[15]	2+	AIEOP LAM 87 Mar 1987 to Mar 1990 Multi-center (29) Italy	Age, Sex, WBC, FAB, EMD, Platelets, Time to CR1, Hepato, Splenom.	Not Stated	Total 96 (ITT) Allo 24 Randomized Auto 35 Randomized Chemo 37	<15 yrs (7 yrs)	Not Stated 0 3 8	28 mos	5-yr DFS 34 ± 10 21 ± 8 27 ± 8 (Allo vs Other *P*=.03)	Time from CR1 to 1st event	Not Stated	
[16]	2+	Combined AIEOP LAM 87–92 Trials Mar 1982 to Sep 2001 Retrospective	Age, Sex, WBC, CNS, FAB, Cytogen.	SR, HR (LAM 92 only); Favorable cytogen.§ vs Other	Total 277 Allo 78 Auto 110 Chemo 89	<15 yrs	Not Stated	Not Stated	5-yr DFS 64 ± 6 55 ± 5 28 ± 5 (Allo vs Other *P*-value Not Stated)	Time from CR1 to last follow-up or first event	Not Stated	
[17]	2+	CCG 213 Trial Jan 1986 to Feb 1989 Multi-center (35) US and Canada	Age, Sex, Race, WBC, FAB	Not Stated	Total 411 (ITT) Donor 113 No Donor 298	<22 yrs (Not Stated)	Not Stated	5.3 yrs (63.6 mos)	5-yr DFS 46 (CI 36–56) 38 (CI 32–44) (*P*=.06)	Time from end of induction to relapse or death	5-yr 52 (CI 42–62) 46 (CI 36–56) (*P*=.13)	Time from end of induction to death
[18]	2+	CCG 251 Trial Sept 1979 to Oct 1983 Multi-center (34) US and Canada	Age, Sex, WBC, FAB	Not Stated	Total 381 (ITT) Donor 89 No Donor 252	≤21 yrs 48% <8 y 60% <8 y	Not Stated	5 yrs (60 mos)	5-yr DFS 45 33 (*P*<.05)	Time from SCT to relapse or death from any cause	5-yr 50 36 (*P*<.05)	Time from SCT to death from any cause

Table 4. *Continued*

Reference #	Quality & Strength of Evidence*	Patient Population	Patient Characteristic†	Risk Groups	Number of Patients by Study Group	Upper Limit (median) Age at Diagnosis	% Treatment Related Mortality	Median Follow-Up (Months)	% DFS/ % EFS/ % RFS (Signif)	Outcome Defined	% OS (Signif)	OS Defined
[19]	2+	LAME 89, LAME 91 and LAME SP Trials 1989-1998 Multi-center (18)	Age, Sex, WBC, FAB, Cytogen.	Favorable vs Others (LAME 89/91 only)	Total 277 Allo 74 Chemo 203	< 20 yrs (6.9 yrs)	Not Stated	Not Stated	5-yr DFS 57 ± 7 52 ± 4 (*P*=.18)	Time from CR1 to 1st event	5-yr 70.5 ± 7 55.4 ± 4 (*P*=.006)	Time from DX 1st event or last follow-up
[21]	2+	NOPHO-AML93 Jan 1993 to Dec 2000 Multi-center (21) Denmark, Finland, Iceland, Norway, Sweden	Age, Sex, WBC, CNS, FAB, Induction response, Cytogen.	Not Stated	Total 200 (ITT) Allo 53 Chemo 147	<18 yr (6 yrs)	Not Stated	Not Stated	7-yr DFS 64 51 (*P*=.04)	Time from CR1 to relapse or death	7-yr 69 71 (Not Signif.)	Time from CR1 to death
[22]	2+	EORTC 58921 Oct 1992 to Dec 2000 Multi-center (21) Europe	Sex, Age, WBC, CNS, FAB, Cytogen.	Favorable‖ (15%) Intermed. (25%) Unfavorable (60%)	Total 145 (ITT) Donor 39 No Donor 106	<18 yrs (6 yrs)	5 yr 8 3	5.5 yr (66 mos)	5-yr DFS 63 ± 13 57 ± 5 (Not Stated)	Time from CR1 to date of first event or last follow-up	5-yr 78 ± 7 65 ± 5 (Not Stated)	Time from CR1 to death or last follow-up
[23]	2+	TPOG-AML-97A Jan 1997 to Dec 2002 Multicenter Taiwan	Age, Sex, WBC, FAB, Cycles to CR1, CNS, Cytogen.	Not Stated	Total 105 (ITT) SCT 29¶ Chemo 76	<18 yrs (Not Stated)	Not Stated	Not Stated	5-yr DFS 60 ± 9.5 68 ± 5.4 (*P*=.63)	Time from SCT to failure	Not Stated	
[24]	2+	AML-80 Trial Apr 1980 to Oct 1983 Multi-center (7) US	Age, Sex, Race, WBC, FAB, CNS, Platelets, Auer rods, Coag. Abnorm.	Not Stated	Total 61 (ITT) Allo 19 Chemo 42	<20 yrs (11.3)	Not Stated 26 5	6 yrs (72 mos)	6-yr DFS 43 ± 13 31 ± 7 (*P*=.30)	Time from CR1 to relapse or death due to any cause	Not Stated	
[25]	2+	CCG 2941 Jan 1995 to Feb 1996 Multi-center (10) US	Age, Sex, Race, WBC, EMD, FAB	Not Stated	Total 57 (ITT) Allo 14 Chemo 43	≤20 (Not Stated)	Not Stated 22 (Overall)	Not Stated	3-yr DFS 46 ± 14 53 ± 8 (*P*=.70)	Time from CR1 to relapse or death from disease progress.	3-yr 63 ± 13 69 ± 7 (*P*=.14)	Not Stated
[26]	2+	CCG Trial 2951 Aug 1997 to Jan 2000 Multi-center (11) US	Age, Sex, Race, WBC, FAB, Splen., Hepato., Platelets, CR1 Duration, Cytogen.	Not Stated	Total 48 Allo 35 Chemo 13	<22 yrs (10.2 yrs)	Not Stated 37 15	17.6 mos 15.5 mos	2-yr DFS 43 51 (Not Signif.)	Time from CR to relapse or death	2-yr 40 50 (Not Signif.)	Time from start of therapy to death

ITT indicates intent to treat; DX, diagnosis; Chemo, chemotherapy; CCG, Children's Cancer Group; POG, Pediatric Oncology Group; MRC, Medical Research Council; AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; LAM, Leucemia Acuta Mieloide; NOPHO, Nordic Society for Paediatric Haematology and Oncology; LAME, Leucémie Aiguë Myéloblastique Enfant; EORTC, European Organization of Research and Treatment of Cancer; TPOG, Taiwan Pediatric Oncology Group; RFS, relapse-free survival; WBC count, WBC count at diagnosis; EMD, extramedullary disease; SR, standard risk; HR, high risk.

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

†Auto versus allo outcomes are presented in Table 5.

‡Stevens et al. [14]: good indicates (8;21), t(15;17), M3, inv(16); poor, >1 induction, monosomy 5 or 7, del(5q), abnormal 3q, >4 abnormalities; standard indicates all other patients.

§Pession et al. [16]: favorable cytogenetics indicates t(8;21), inv(16), t(15;17).

‖Entz-Werle et al. [22] according to Keating risk classification (Keating et al., *Leukemia.* 1988;2:403–412): favorable indicates t(8;21), inv(16), t(15;17); intermediate, all others; unfavorable, t(9;11), −5, 5q−, −7, 7q−, complex abnormalities.

¶79% = allo-SCT (23 of 29).

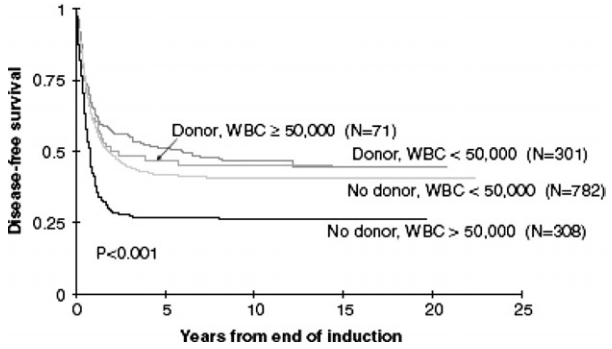


Figure 1. DFS from end of induction by diagnostic WBC count and matched family donor status for patients with AML in CR1. Reprinted with permission [11].

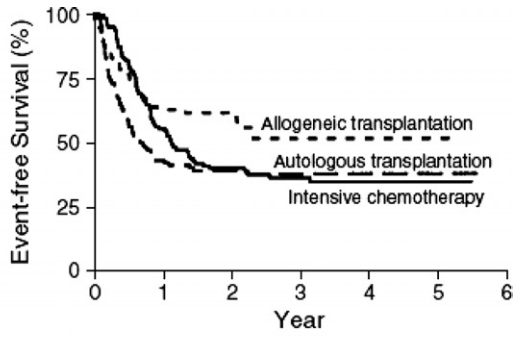
solidation chemotherapy regimens (n = 179), each lasting 4-6 weeks. There were no statistically significant differences in cytogenetic abnormalities or WBC count at diagnosis among the 3 treatment groups.

Ravindranath et al. [13] presented the results of a prospective, multicenter, randomized study of 649 pediatric (<21 yr) patients with AML enrolled in the Pediatric Oncology Group (POG) 8821 trial, comparing auto-BMT, allo-BMT, and chemotherapy. Of 649 patients, 552 (85%) achieved CR1. Eighty-nine (16%) patients had histocompatible donors and were offered allo-BMT, and all 89 chose that option. Of the remaining 463 patients, 120 (26%) were not eligible for randomization to chemotherapy only or auto-BMT due to insufficient funds (n = 64), nonprotocol auto-BMT (n = 18), lack of beds at a POG BMT facility (n = 14), relapse or death before randomization (n = 11), or other reasons (n = 8). In addition, 111 patients declined randomization, leaving 232 (68% of 343 eligible patients) randomly assigned to auto-BMT (n = 115) or chemotherapy (n = 117). Median time from randomization to marrow harvest for auto-BMT patients was 49 days (range, 21-106 d). Patients in the chemotherapy group received 6 courses, each administered successively at 3-week intervals. The 2 randomized groups had similar distributions of clinical, morphologic, and cytogenetic features. Figure 2 compares the EFS for the allo-BMT, auto-BMT, and intensive chemotherapy groups.

Stevens et al. [14] reported the results of 364 pediatric (<15 yr) patients with AML enrolled in the Medical Research Council (MRC) AML10 multicenter trial. Children with secondary AML (after prior treatment or antecedent MDS), DS, or aggressive MDS (RAEB-t) were included. The CR1 rate was 92%. Allo-BMT was recommended for patients with an HLA-matched sibling donor, and the remaining patients were randomized between auto-BMT and no further treatment. Of those eligible for randomization (n = 200), 50% refused randomization, leaving 50 children randomized to auto-BMT and 50 to no further treatment. Of the 50 children allocated to auto-BMT, 44 received a transplant. None of the children in the no further treatment arm received a BMT in CR1. Median time from CR1 to transplantation was 155 days.

Amadori et al. [15] presented the results of 173 pediatric (<15 yr) patients with newly diagnosed AML enrolled in a prospective, randomized, multicenter (Associazione Italiana Ematologia ed Oncologia Pediatrica [AIEOP]/Leucemia Acuta Mieloide [LAM] 87) trial comparing chemotherapy, auto-BMT, and allo-BMT. Of 161 evaluable patients, 127 (79%) achieved CR1. Patients with an HLA-matched sibling donor (n = 24, 19%) were assigned to allo-BMT, of which 22 received a transplant. Of the remaining 103 patients, 72 (70%) were randomized between auto-BMT (n = 35) and a consolidation chemotherapy regimen (n = 37). Of these, 23 went on to undergo auto-BMT and 32 received chemotherapy. Median time from CR1 to allo-BMT was 3.2 months and from CR1 to auto-BMT was 3.4 months. There were no significant differences among the 3 treatment groups in age, French-American-British morphology (FAB) classification, WBC count at diagnosis, organomegaly, presence of extramedullary disease, or time to CR1. Cytogenetic data were not reported.

Pession et al. [16] retrospectively examined outcomes in 559 pediatric (≤15 yr) patients with AML enrolled in 4 AIEOP/LAM (87-92) trials, including those in the LAM 87 study discussed above [15]. Patients with granulocytic sarcoma, secondary AML, MDS, and DS were excluded from the analysis. Patients with APL were excluded from the LAM 92 study, but included in LAM 87 and LAM 87M. Combined across trials, 78 patients underwent allo-SCT, 110 underwent auto-SCT, and 89 were treated with chemotherapy alone. Figure 3 compares the DFS for the allo-SCT, auto-SCT, and chemotherapy groups.



No. at Risk						
Intensive chemotherapy	117	64	39	25	13	7
Autologous transplantation	115	47	32	22	13	6
Allogeneic transplantation	89	53	37	20	14	4

Figure 2. EFS from the time of randomization or assignment to allo-BMT. Reprinted with permission [13].

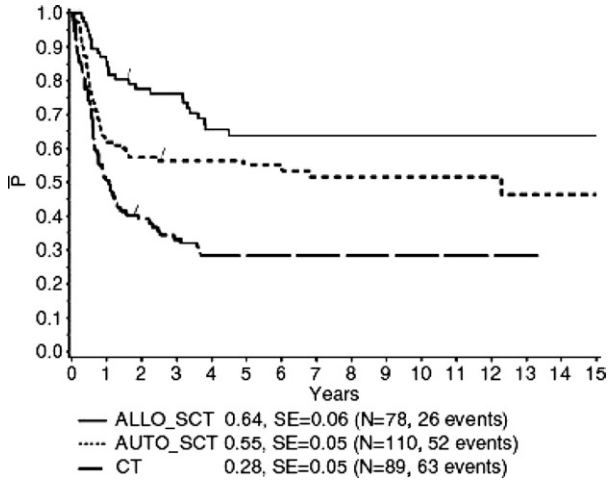


Figure 3. Estimated probability of 5-yr DFS in patients of AIEOP AML 87-92 studies by postremission treatment: allo-SCT, auto-SCT, or chemotherapy (CT). Slash indicates the patient without an event and with the shortest follow-up. Reprinted with permission [16].

Allogeneic BMT versus Chemotherapy with/without Autologous BMT in CR1

The first 6 studies [11-16] listed in this section of Table 4 provide the outcomes related to the allo-BMT versus chemotherapy with/without auto-BMT comparisons from those studies described in Auto-BMT versus Chemotherapy in First CR.

Wells et al. [17] presented the long-term follow-up of 621 pediatric (<21 yr) patients with *de novo* AML enrolled in the prospective, multicenter CCG 213 trial comparing allo-BMT with chemotherapy. Excluded from the trial were infants <2 years old with acute monoblastic leukemia (n = 7), patients without AML (n = 12), and others for unspecified reasons (n = 11). Outcome data from diagnosis were based on the remaining 591 patients, of whom 439 achieved CR1 (74%). There were 113 patients who had an HLA-identical sibling donor or a related donor with a single-antigen mismatch at the HLA-A or HLA-B loci and, of these, 92 were assigned to allo-BMT and 83 went on to receive a transplant. Four patients whose HLA status was unknown (n = 3) or who did not have an HLA-identical sibling donor (n = 1) were also treated with allo-BMT. Median time from end of induction to transplantation was 27 days (range, 0-159 d). Patients not assigned to transplantation were given 3 cycles of consolidation chemotherapy consisting of different regimens (n = 343). There were no significant differences in baseline patient clinical characteristics between the allo-BMT and chemotherapy groups. Cytogenetic data were not reported.

Nesbit et al. [18] evaluated allo-BMT versus chemotherapy in the multicenter, prospective CCG 251 trial. Of the 508 pediatric (≤ 21 yr) patients with AML enrolled in the study, 490 were treated and CR1 was achieved in 381 (78%) patients. Of these, 89 (23%) had an HLA-compatible sibling donor and were eligible for allo-BMT, 252 had no matched sibling donor and were eligible for randomization to 2 chemotherapeutic maintenance programs, and for 40 patients the match status was not determined or data were not known. No significant differences were found in the clinical characteristics of the donor versus no-donor groups. Cytogenetic data were not reported.

Perel et al. [19] and Michel et al. [20] presented the results of the French, multicenter Leucémie Aiguë Myéloblastique Enfant (LAME) 89/91 trials. Patients with secondary AML, FAB M0, MDS, or DS were excluded. Of 309 pediatric (≤20 yr) patients with AML, 277 achieved CR1 (90%). All 74 patients with an HLA-identical sibling donor were offered and underwent allo-BMT. Median duration from CR1 to allo-BMT was 82 days. The remaining patients received consolidation chemotherapy (n = 180) or other postremission therapy (n = 23).

Lie et al. [21] reported the outcomes for 219 pediatric (<18 yr) patients with AML (without DS) who were enrolled in the international (Denmark, Finland, Iceland, Norway, and Sweden), multicenter, Nordic Society for Paediatric Haematology and Oncology (NOPHO)-AML93 trial comparing allo-BMT with chemotherapy. Of the 219 patients, 200 (91%) achieved CR1. Fifty-three (27%) patients underwent allo-SCT (46 from a matched family donor, 7 from a matched unrelated donor). An additional 16 patients underwent auto-BMT; they were analyzed with the chemotherapy group (n = 147). Figure 4 compares the DFS for the allo-SCT and chemotherapy groups.

Entz-Werle et al. [22] compared outcomes of allo-BMT versus chemotherapy in 188 pediatric (<18 yr)

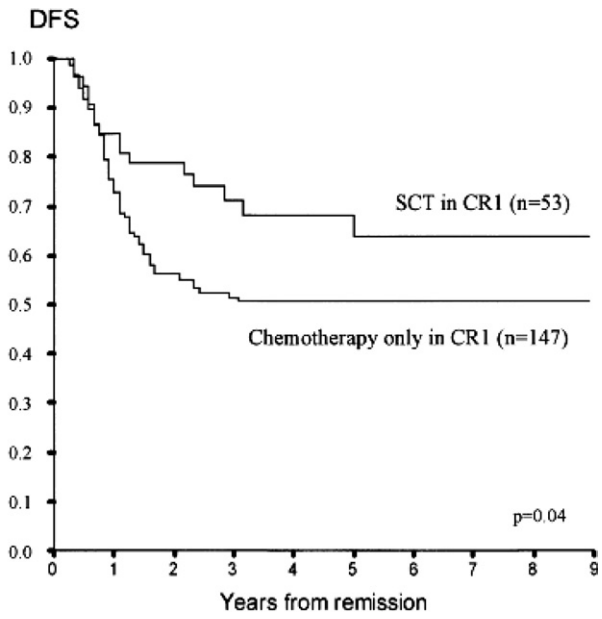


Figure 4. Probability of 7-yr DFS in NOPHO-AML93 according to postremission therapy in CR1. Reprinted with permission [21].

Table 5. *Comparison of Patient Characteristics and Outcomes from Studies Included in the Allo-SCT versus Auto-SCT Section*

Reference #	Quality & Strength of Evidence*	Patient Population	Patient Characteristics	Risk Groups	Number of Patients by Study Group	Upper Limit (median) Age at Diagnosis	% Treatment Related Mortality	Median Follow-Up (Months)	%DFS/ %EFS/ %RFS (Signif)	Outcome Defined	% OS (Signif)	OS Defined
Allogenic vs Autologous SCT in CR1												
[11]	1++	Combined 5 CCG 1979-1996 Meta-analysis	Age, WBC, Blast %, Sex, FAB, Cytogen.	Not Stated	Total 1278 (ITT) Allo 373 Auto 217	<21 yrs (8.9) (6.2)	8-yr 17 7	Not Stated	8-yr DFS 47 ± 5 42 ± 7 (*P*=.075)	Time from CR1 to relapse or death from any cause	8-yr 54 ± 5 49 ± 7 (*P*=.03)	Time from CR1 to death from any cause
[12]	2+	CCG Trail 2891 Phase III Oct 1989 to Apr 1995 Multi-center (236) US, Canada, Australia	Age, WBC, FAB, Cytogen.	Not Stated	Total 537 (ITT) Allo 181 Auto 177	<21 yrs	Not Stated 14 5	Not Stated (min 4 yr)	8-yr DFS 55 ± 9 42 ± 8 (*P*=.001)	Time from CR1	8-yr 60 ± 9 48 ± 8 (*P*=.002)	Time from CR1
[13]	2+	POG Trial 8821 Jun 1988 to Mar 1993 Multi-center (16) US	Race, Age, WBC, FAB, EMD, Induction Response, DS, Cytogen.	Not Stated	Total 321 (ITT) Allo 89 Auto 115	<21 yrs (Not Stated)	Not Stated Not Stated 15	Not Stated	3-yr EFS 52 ± 8 38 ± 6.4 (*P*=.01)	Time from randomization until 1st event	3-yr Not Stated 40 ± 6.1 (*P*=.007)	Time from randomization until death
[27]	2+	EBMT Registry Jan 1987 to Dec 1992 Europe Retrospective	Age, Sex, FAB, Cond. Reg, Time to BMT	Not Stated	Total 242 Allo 129 Auto 113	≤15 yrs (10 yrs) (11 yrs)	4-yr 9 ± 3 8 ± 4	27 mos 20 mos	4-yr LFS 68 47 (*P*=.001)	Time in continuous CR	Not Stated	
[28]	2+	ANZCCSG AML 1&2 Trials Dec 1986 to May 1999 Multi-center (8) Australia, New Zealand	Age, WBC, FAB, CNS	Good (22.5%) Standard (55%) Poor (10%) Not known (12.5%)	Total 191 Allo 35 Auto 156	<18 yrs (AML 1 6.3 yr) (AML 2 7 yr)	3 mos 9 0	AML 1 103 mos AML 2 42 mo	5-yr DFS 69 52 (Not Signif.)	Time from CR1 to relapse or death in CR	5-yr 79 63 (Not Signif.)	Time from study entry to death or last follow-up
[29]	2+	CCG 2861 Apr 1988 to Oct 1989 Multi-center (27) US	Age, WBC, FAB, EMD, DS	Not Stated	Total 74 Allo 16 Auto 58	<21 yrs (Not Stated)	<70 days 6 5	31 mos 34 mos	3-yr DFS 55 51 ± 12 (*P*=.92)	Time from the end of induction therapy to last day of contact	3-yr 54 57 ± 14 (*P*=.56)	Time from the end of induction therapy to last day of contact
[30]	2+	Kyushu-Yamaguchi CCSG ANLL93 Jul 1993 to Dec 1997 Japan ANLL93 Trial Multi-center (23)	WBC, FAB, Cytog.	Normal vs. t(8;21), t(11;19), t(9;11), inv(16)	Total 59 Allo 22 Auto 37	<18 yrs (8.8 yrs)	Not Stated	45 mos	5-yr EFS 70.8 ± 9.3 43 ± 8.1 (*P*=.08)	Time from DX to an event (failure to reach CR1, death during induction, death during CR, or relapse)	Not Stated	
[31]	2+	Kousei-Shou ANLL91 Feb 1986 to May 1998 Single Center Japan Retrospective	WBC, FAB	Not Stated	Total 52 Allo 31 Auto 21	≤16 yrs (7 yrs)	Not Stated 10 0	70 mos	5-yr DFS 84 81 (Not Signif.)	Time from BMT to relapse or death	Not Stated	

Table 5. *Continued*

Reference #	Quality & Strength of Evidence*	Patient Population	Patient Characteristics	Risk Groups	Number of Patients by Study Group	Upper Limit (median) Age at Diagnosis	% Treatment Related Mortality	Median Follow-Up (Months)	%DFS/ %EFS/ %RFS (Signif)	Outcome Defined	% OS (Signif)	OS Defined
[32]	2+	AML-88 Trial Apr 1988 to May 2001 Single Center Spain High Risk Pts.	Age, Sex, WBC, FAB, Cytogen, >1 Induction Cycle	Unfavor. vs Others	Total 48 Allo 17 Auto 31	<15 yrs (5 yrs)	Not Stated 5.9 3.2		8-yr EFS 74.5 74.2 (Not Signif.)	Time from DX to relapse, death from any cause, or last follow-up	Not Stated	
[34]	2−	AIEOP Jan 1985 to Dec 1998 Multi-center (19) Italy Retrospective	Not Stated	Not Stated	Total 278 Allo 115: *Sibling donor 103* *Other donor 12* Auto 163	<18 yrs (Not Stated)	Not Stated	Not Stated	5-yr EFS 63.1 ± 5.3 48.6 ± 14.8 46.6 ± 4.4 (Not Stated)	Time to relapse or death from any cause, whichever occurs first	Not Stated	
[35]	2−	MRC10 protocol 1992 to 2002 Single Center Turkey Retrospective	Age, Sex, FAB	Not Stated	Total 67 Allo 31 Auto SCT: *Auto-BMT 20* *Auto PBSCT 16*	≤17 yrs (8 yrs)	Not Stated 19 5	62 mos 70 mos 36 mos	5-yr DFS 61 50 75 (Allo vs Auto BMT *P*=.48; Allo vs PBSCT *P*=.067)	Time from DX (event not defined)	Not Stated	
Allogeneic vs Autologous SCT in CR2												
[36]	2+	LAME 89/91 Dec 1988 to Dec 1998 Multicenter (19) France	Age, Sex, WBC, FAB, CR1 Duration, Cytogen.	Favorable† vs. Other	Total 53 Matched Allo 12 Unrelated Allo 16 Auto 25	<20 yrs (Not Stated)	Not Stated 16 31 4	65 mo	5-yr DFS 60 44 47 (Not Signif.)	Time from CR2 to attainment of event (not defined)	Not Stated	
[27]	2+	EBMT Registry Jan 1987 to Dec 1992 Europe Retrospective	Age, Gender, FAB, Time to BMT, CR1 Duration	Not Stated	Total 52 Allo 17 Auto 35	≤15 yrs (9 yrs) (10 yrs)	4-yr 18 12	38 mos 33 mos	4-yr LFS 39 40 (Not Signif.)	Time in continuous CR	Not Stated	
[34]	2−	AIEOP Jan 1985 to Dec 1998 Multi-center (19) Italy Retrospective	Not Stated	Not Stated	Total 69 Allo 16: *Sibling donor 11* *Other donor 5* Auto 53	<18 yrs (Not Stated)	Not Stated	Not Stated	5-yr EFS 63.1 ± 5.3 48.6 ± 14.8 46.6 ± 4.4 (Not Stated)	Time to relapse or death from any cause, whichever occurs first	Not Stated	

ANLL indicates acute nonlymphocytic leukemia; ANZCCSG, Australian and New Zealand Children's Cancer Study Group; EBMT, European Group for Blood and Marrow Transplantation; LFS, leukemia-free survival; ITT, intent to treat; DX, diagnosis; Chemo, chemotherapy; CCG, Children's Cancer Group; POG, Pediatric Oncology Group; MRC, Medical Research Council; AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; LAM, Leucemia Acuta Mieloide; NOPHO, Nordic Society for Paediatric Haematology and Oncology; LAME, Leucémie Aiguë Myéloblastique Enfant; EORTC, European Organization of Research and Treatment of Cancer; TPOG, Taiwan Pediatric Oncology Group; RFS, relapse-free survival; WBC count, WBC count at diagnosis; EMD, extramedullary disease; SR, standard risk; HR, high risk.

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

†Favorable = t(8;21), t(15;17), inv(16).

patients with AML enrolled in the prospective, multicenter European Organization of Research and Treatment of Cancer (EORTC) 58921 trial. Patients with DS or APL were excluded. Of 145 patients (82%) who achieved CR1, 39 had an HLA-identical sibling donor (donor group), 33 (85%) of whom underwent allo-BMT. One hundred six patients were assigned to the no-donor (chemotherapy) group, of whom 3 underwent allo-BMT in CR1, 17 underwent allo-BMT in second CR (CR2), and 4 underwent auto-BMT in CR2.

Liang et al. [23] reported the outcomes of 117 pediatric (<18 yr) patients with AML enrolled in the prospective, multicenter, Taiwan Pediatric Oncology Group (TPOG)-AML-97A trial comparing SCT with chemotherapy. Ninety percent (n = 105) of patients attained CR1. SCT was performed "as feasible," with 29 patients undergoing some form of SCT (allo-BMT, n = 17; allo-PBSCT, n = 6; auto-BMT, n = 2; auto-PBSCT, n = 4) and 76 patients receiving chemotherapy only. Median time from CR1 to transplantation was not stated.

Dahl et al. [24] presented the results of a prospective, multicenter trial (AML-80) of 87 pediatric (<20 yr) patients with AML comparing allo-BMT with chemotherapy. Sixty-five patients (75%) achieved CR1. Patients without donors (n = 42) were assigned to receive intensive consolidation chemotherapy and 19 patients with HLA-compatible donors were recommended to undergo allo-BMT, 15 of whom received a transplant. Median time from CR1 to allo-BMT was 65 day.

Lange et al. [25] reported the outcomes of 93 pediatric (<20 yr) patients with AML enrolled in a prospective, multicenter, CCG 2941 trial comparing allo-BMT with chemotherapy. Patients with DS or APL were excluded. Fifty-seven (61%) patients achieved CR1 after induction therapy. Fourteen patients then underwent matched related allo-BMT and 43 received chemotherapy.

Allogeneic BMT versus Chemotherapy in CR2

Wells et al. [26] presented the outcomes of allo-BMT versus chemotherapy only for 101 pediatric (≤21 yr) patients with refractory (16%) or first relapse (84%) AML enrolled in the CCG 2951 trial. Of the patients with relapsed AML (n = 85), 73% had a CR1 duration ≤12 month and 27% had a CR1 >12 months. After salvage induction and/or intensification, 13 patients received further consolidation chemotherapy and 35 patients underwent allo-BMT from a variety of donor sources (30 from unrelated, 4 from related, 1 from unknown donors). Twelve of the patients who underwent allo-BMT received a transplant after reinduction and 23 underwent allo-BMT after intensification.

AUTOLOGOUS SCT VERSUS ALLOGENEIC SCT

The following text describes the study design of each of the 12 articles included in this section. Table 5 presents a summary of the outcomes for each study. The highest quality studies are presented first in the text and table; studies of equal quality are presented in descending order by sample size. Of the 12 studies investigating allo-SCT versus auto-SCT, 3 indicated a significant difference in DFS (or EFS) between the 2 treatment groups, and 3 stated a significant difference in OS.

First CR

The first 3 studies listed in Table 5 [11-13] were described under Auto-BMT versus Chemotherapy in CR1. The outcomes related to the allo- versus auto-BMT comparisons from those studies are presented in this section of Table 5.

Gorin et al. [27] presented a retrospective study on the outcomes of auto-BMT versus allo-BMT in 242 pediatric (≤15 yr) patients with AML reported to the acute leukemia European Group for Blood and Marrow Transplantation (EBMT) registry after transplantation in CR1 by the EBMT. Of the 242 patients, 129 underwent allo-BMT and 113 underwent auto-BMT. The clinical characteristics of the treatment groups were similar, with 2 exceptions: more patients after allo-BMT received TBI-containing conditioning regimens (59% versus 43%, $P = .01$) and more underwent transplantation earlier (77 versus 131 week, $P < .0001$) compared with patients who underwent auto-BMT. Cytogenetic data were not reported.

O'Brien et al. [28] reported the results for 280 pediatric (<18 yr) patients with AML enrolled in 2 consecutive Australian and New Zealand Children's Cancer Study Group (ANZCCSG) AML clinical trials (AML1 and AML2) comparing the outcomes of auto-BMT versus allo-BMT. Patients with APL (n = 12, 12%, in the AML1 trial; n = 19, 12%, in the AML2 trial) were included, whereas patients with MDS, secondary AML, and DS-related leukemic disorders were excluded from the analysis. Eight patients died before treatment and 10 did not receive protocol treatment. Of the 262 evaluable patients, 242 (92%) achieved CR1. Fifty-two (22%) patients did not proceed to BMT (relapse or death, n = 36; removal from study, n = 5; preference or refusal, n = 5; other, n = 6). Thirty-five patients underwent allo-BMT (33 matched sibling, 1 matched related cord blood, 1 matched unrelated) and patients without an HLA-identical sibling underwent auto-BMT (n = 156). Median times from diagnosis to BMT were 6 and 5 months for the AML1 and AML2 trials, respectively. Patients were classified as having good (n = 59, t(8;21), t(15;17), inv(16), or FAB type M3), poor (n = 26, monosomy 5 or 7, deletions or abnormalities of chro-

mosomes 5 or 3, or complex karyotypes), or standard (n = 144, all remaining patients) cytogenetic risk. There were no major differences between patients in the AML1 and AML2 trials in terms of age, WBC count at diagnosis, CNS disease, FAB classification, or cytogenetic risk groups.

Woods et al. [29] compared the effect of auto-BMT versus allo-BMT in 142 pediatric (<21 yr) patients with AML enrolled in the CCG 2861 trial. Patients with Ph^+ chromosome CML, chronic myelomonocytic leukemia, juvenile CML, or Fanconi anemia were excluded from the trial. Children with DS were included but assigned only to auto-BMT. Overall, 108 (76%) patients achieved CR1 and were eligible for BMT; of these, 28 withdrew from study, 2 relapsed before BMT, and 3 patients had unknown BMT status. Of the remaining 75 patients, 58 underwent 4-hydroperoxycyclophosphamide purged auto-BMT, 16 underwent an HLA-identical sibling donor allo-BMT, and 1, who died from complications and was not included in further analyses, underwent unrelated donor allo-BMT. Median time from CR1 to BMT was 43 days. Cytogenetic data were not reported.

Matsuzaki et al. [30] compared the outcomes of auto-BMT versus allo-BMT in 64 pediatric (<18 yr) patients with AML enrolled in the Kyushu-Yamaguchi Children's Cancer Study Group ANLL93 trial. Patients with DS or APL were excluded from the trial. Overall, 59 (92%) patients achieved CR1, and of these, 22 (37%) with an HLA-identical sibling were assigned to allo-BMT and 18 actually received a transplant. Of the 37 patients who did not undergo allo-BMT, 11 underwent auto-PBSCT, 6 auto-BMT, 6 chemotherapy alone, 3 unrelated allo-BMT, 1 CBT from a sibling, and 10 patients relapsed or died before transplantation. Median times from diagnosis to transplantation were 7.4 months for auto-PBSCT and 8.6 month for auto-BMT (allo-BMT not stated). There were no differences in clinical or cytogenetic characteristics at time of diagnosis among patients who underwent allo-BMT, auto-BMT, and auto-PBSCT.

Matsuyama et al. [31] provided a retrospective analysis of 52 pediatric (≤16 yr) patients with AML treated with allo-BMT or auto-BMT according to the Kousei-Shou ANLL91 protocol at a single institution in Japan. All patients (100%) achieved CR1, after which 31 (60%) underwent allo-BMT (24 sibling, 4 family, 1 HLA single-antigen mismatched family, 2 unrelated donor) and 21 (40%) underwent auto-BMT. Median times between diagnosis and transplantation were 6 months for allo-BMT and 7 months for auto-BMT. Cytogenetic data were not reported.

Ortega et al. [32] compared the outcomes of auto-BMT versus allo-BMT in 50 pediatric (<15 yr) patients with AML enrolled in the prospective, single-institution AML 88 trial and identified as high risk according to the Berlin-Frankfurt-Münster (BFM) criteria [33] based on morphology, cytogenetics, and response to induction treatment. CR1 was achieved in 46 patients (92%) and partial remission was attained in 2 patients. Of the 48 responding patients, 17 had an HLA-identical sibling donor and all underwent allo-BMT. The remaining 31 had no donor and underwent auto-BMT (purged, n = 24; purged and unpurged or unpurged alone, n = 7). Clinical characteristics of the 2 groups were similar. Median time from CR1 to BMT was 3 months.

Pession et al. [34] retrospectively examined the outcomes of allo-BMT and auto-SCT in 278 pediatric (<18 yr) patients with AML in CR1 treated at 19 AIEOP centers. Stem cell sources for patients undergoing auto-SCT (n = 163) included BM, PB, or a combination of PB and BM. Of the 115 who underwent allo-BMT, 103 had sibling donors and 12 had matched or partially matched unrelated donors. Cytogenetic data were not reported.

Anak et al. [35] provided the results of 92 pediatric (≤17 yr) patients with AML treated according to the MRC 10 protocol at a single center in Turkey. Five patients with APL were excluded. Of the 78 (90%) patients who achieved CR1, 31 were assigned to allo-BMT if an HLA matched sibling was available, 36 were randomized to auto-SCT (20 BMT, 16 PBSCT), and 11 dropped out or received chemotherapy. Median times to transplantation after diagnosis were 6, 10, and 6 months in the allo-BMT, auto-BMT, and auto-PBSCT groups, respectively. Cytogenetic data were not reported.

Second CR

Aladjidi et al. [36] presented the outcomes of 106 pediatric (<20 yr) patients with relapsed AML in the French prospective LAME 89/91 protocol. Median duration of CR1 was 10 months. Ten patients (9%) received only palliative treatment. Reinduction was attempted in 96 patients, and CR2 was attained in 68 (71%). Of these, 53 (78%) patients underwent auto-BMT (n = 25), matched sibling donor allo-BMT (n = 12), or alternative allo-SCT (n = 16; 11 unrelated donors, 3 HLA-mismatched familial donors, and 2 unrelated cord blood cells). For 9 children this was a second transplantation.

The retrospective EBMT study by Gorin et al. [27] presented under Allo-SCT versus Auto-SCT in CR1 also examined the outcomes of 52 pediatric (≤15 yr) patients with AML who underwent transplantation in CR2 and received an auto-BM transplant (n = 35) or an allo-BM transplant (n = 17). Cytogenetic data were not reported.

Pession et al. [34], whose study was also presented under Allo-SCT versus Auto-SCT in CR1, examined the outcomes of 69 pediatric (<18 yr) patients who

Table 6. *Comparison of Patient Characteristics and Outcomes from Studies Included in the Autologous Transplantation Section*

Reference No.	Quality and Strength of Evidence*	Patient Population	Patient Characteristics	Risk Groups	No. of Patients by Study Group	Upper Limit (Median) Age at DX	%TRM	Median Follow-up (mo)	%DFS/ %RFS/ %EFS/ %LFS	Outcome Defined	%OS	OS Defined
Auto-SCT (purged and unpurged auto-SCT)												
37	2+	ABMTR, 1989-1998, US, Canada, Central and South America, retrospective	Age, sex, race, WBC count, FAB, CNS, KPS, disease status, time to CR1, cytogenetics	Good† (13%) Intermediate (52%) Poor (6%) Not known (29%)	Auto-BMT 219	<21 yr (10 yr)	Not stated	80 mo	3-yr LFS 54 (95% CI, 47–60)	Time in continuous CR	3-yr 62 (95% CI, 54–68)	Not stated
38	2+	AML-91 protocol, 2-CDA, induction therapy, June 1991-December 1996, 2 US centers	Age, sex, WBC count, hemoglobin, platelets, FAB, cytogenetics	Not stated	Auto-BMT 40	<19 yr (4.9 yr)	Not stated	Not stated	Overall 5-yr. EFS 40 ± 8	Time from enroll. to relapse, disease progress, death from any cause, or last follow-up	Not stated	
Unpurged auto-SCT												
39	2+	January 1997-May 2002, single center, Korea	Age, sex, FAB, cytogenetics	Poor‡ (11%) Good (36%)	Auto-PBSCT 28 (BCVAC conditioning)	<15 yr (not stated)	Not stated 0	30.5 mo	Overall EFS 71.4 ± 8.5	Time from DX to first event (relapse or therapy-related death)	Not stated	
40	2+	JCSG/PBSCT, CCLSG 9205, and CCLSG 9411, May 1989-October 1996, multicenter, Japan, retrospective	Age, WBC count, FAB, time to CR1	Not stated	Auto-PBSCT 24	≤18 yr (8 yr)	Not stated 4	55 mo	5-yr DFS 49 (95% CI, 39–60)	Time from SCT to relapse or death	5-yr 53 (95% CI, 41–64)	Time from SCT to death
41	2+	Auto-BMT, November 1984-January 1991, single center, Australia	Age, sex, WBC count, EMD, cytogenetics	Not stated	Auto-BMT 24 (high-dose melphalan conditioning)	<16 yr (7 yr)	Not stated 0	57 mo	5-yr EFS 87 (95% CI, 71–100)	Time from BMT to failed CR, relapse, or death from any cause	5-yr 92 (95% CI, 76–100)	Time from BMT to death from any cause
Purged auto-SCT												
42	2+	AIEOP, auto-BMT, January 1988-October 1998, multicenter (6), Italy	Age, sex, FAB, WBC count, cytogenetics	Poor§ (21%) Standard (79%)	Auto-BMT 53 (TBI and melphalan conditioning)	≤18 yr (6 yr)	1 yr 4	40 mo	5-yr DFS 68 (95% CI, 55–81)	Time from BMT to relapse or death in remission from any cause	5-yr 78 (95% CI, 65–90)	Not stated

Table 6. *Continued*

Reference No.	Quality and Strength of Evidence*	Patient Population	Patient Characteristics	Risk Groups	No. of Patients by Study Group	Upper Limit (Median) Age at DX	%TRM	Median Follow-up (mo)	%DFS/ %RFS/ %EFS/ %LFS	Outcome Defined	%OS	OS Defined
Auto-BMT vs auto-PBSCT												
30	2+	Kyushu-Yamaguchi CCSG, ANLL93 trial, multicenter (23), Japan	WBC count, FAB, cytogenetics	Normal t(8;21), t(11;19), t(9;11), inv(16)	Total 17 Auto-BMT 6 Auto-PBSCT 11	< 18 yr (8.8 yr)	Not stated	45 mo	5-yr EFS 83.3 41.6 (Not Signif.)	Time from DX to first event (failed CR, death during induction or CR, or relapse)	Not stated	
35	I–	MRC10 protocol, 1992-2002, single center, Turkey	Age, sex, FAB	Not stated	Total 36 Randomized auto-BMT 20 Randomized auto-PBSCT 16	< 17 yr (8 yr)	Not stated 0 5	70 mo 36 mo	5-yr DFS 50 75 ($P = .046$)	Time from DX (event not defined)	Not stated	

ANLL, acute non-lymphocytic leukemia; ABMTR, Autologous Blood and Marrow Transplant Registry; LFS, leukemia-free survival; KPS, Karnofsky performance status; ITT, intent to treat; DX, diagnosis; Chemo, chemotherapy; CCG, Children's Cancer Group; POG, Pediatric Oncology Group; MRC, Medical Research Council; AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; LAM, Leucemia Acuta Mieloide; NOPHO, Nordic Society for Paediatric Haematology and Oncology; LAME, Leucémie Aiguë Myéloblastique Enfant; EORTC, European Organization of Research and Treatment of Cancer; TPOG, Taiwan Pediatric Oncology Group; RFS, relapse-free survival; WBC count, WBC count at diagnosis; EMD, extramedullary disease; SR, standard risk; HR, high risk.

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

†Good prognosis indicates 16q, t(8;21); intermediate, +8, +21, t(1;7), t(6;9), t(8;16), normal cytogenetics; poor, −5/5q−, −7/7q−, −20/20q−, 3q, 11q, t(5;7), t(9;22), complex karyotypes.

‡Good indicates t(8;21), inv(16); poor, ≥2 courses of induction, WBC count >100 000 at diagnosis.

§Standard indicates normal karyotype, other cytogenetic abnormalities, unknown cytogenetic data; poor, monosomy 5 or 7, 11q, t(6;9), t(8;16), t(1/22).

underwent transplantation in CR2. Of these, 53 received an auto-BM transplant, and of 16 who received allo-BM transplants, 11 had sibling donors and 5 had matched or partially matched unrelated donors. Cytogenetic data were not reported.

AUTOLOGOUS SCT

The data from the 8 auto-SCT studies included in this section are presented in Table 6. The highest quality studies are presented first in each section of the table; studies of equal quality are presented in descending order by sample size.

Of the 8 auto-SCT studies, 6 presented the results of single-arm, noncomparative studies examining purged and unpurged auto-SCT (2 studies), unpurged auto-SCT (3 studies), and purged auto-SCT (1 study). The remaining 2 studies in this section [30,35], previously described under Auto-SCT versus Allo-SCT, compared outcomes from auto-BMT versus auto-PB-SCT.

ALLOGENEIC SCT

The data from the 9 allo-SCT studies included in this section are presented in Table 7. The highest quality studies are presented first in each subsection of the table; studies of equal quality are presented in descending order by sample size.

Of the 9 allo-SCT studies, 1 was a comparative study [43] that presented the outcomes of related (n = 12) versus unrelated (n = 20) donor allo-SCT in a retrospective study of 32 pediatric (<6 yr) patients with AML reported to the Eurocord Registry. The remaining 8 allo-SCT studies presented the results of single-arm, noncomparative studies examining related and unrelated allo-SCT in CR2 (1 study), related allo-SCT (4 studies), unrelated allo-SCT (1 study), and T cell depleted (or partially depleted) allo-SCT (2 studies).

CONDITIONING REGIMENS

Two comparative studies of conditioning regimens are summarized in this section; neither study found statistically significant differences in outcomes between conditioning regimens.

Michel et al. [52] retrospectively analyzed the outcomes of 74 pediatric (≤16 yr) patients with AML treated with HLA-identical related allo-SCT in CR1 and reported to a French BMT registry. Conditioning consisted of busulfan (Bu; oral) plus 120 mg/kg of cyclophosphamide (Cy; Bu + Cy 120 group, n = 23), Bu (oral) plus 200 mg/kg Cy (Bu + Cy 200 group, n = 19), or based on TBI, usually in combination with 120 mg/kg Cy (TBI group, n = 32). Median times

Table 7. *Comparison of Patient Characteristics and Outcomes from Studies Included in the Allogeneic Transplantation Section*

Reference No.	Quality and Strength of Evidence*	Patient Population	Patient Characteristics	Risk Groups	No. of Patients by Study Group	Upper Limit (Median) Age at DX	%TRM	Median Follow-up	%DFS/ %RFS/ %EFS/ %LFS	Outcome Defined	%OS	OS Defined
Related vs unrelated allo-SCT												
43	2+	Eurocord Group, April 1990-December 1997, multicenter (41), retrospective	Age, weight, sex, donor, disease status, cytogenetics	Good (72%) Poor (28%)	Allo UCBT 32 Related 12 Unrelated 20	Overall ≤15 yr (5.5 yr) (AML only not stated)	1 yr 18 42	Overall 34 mo 14 mo (AML only not stated)	2-yr EFS 58 32 (*P*=.19)	Time from CBT to relapse or death in CR	Not Stated	
Allo-SCT (related and unrelated)												
44	2+	CR2, relapsed, or refractory patients, January 1990-December 1999, single US center, retrospective	Age, sex, FAB, EMD, CR1 duration, disease status, disease burden, cytogenetics	Not stated	Allo 58 (related and unrelated)	<18 yr (7.4 yr)	<100 d 16	9 yr	5-yr DFS 24 (95% CI, 14–36)	Time to relapse or death (start point not defined)	Not Stated	
Related allo-SCT												
45	2+	CCG 2891, October 1989-April 1995, multicenter, US	Sex, FAB, cytogenetics, splenomegaly, hepatosplenomegaly, donor, induction	Not stated	Related allo 150	<21 yr (not stated)	Not stated	Not stated	6-yr DFS 57 (95% CI, 48–65)	Time from CR1 to relapse or death from any cause	6-yr 67 (95% CI, 58–74)	Time from CR1 to death
46	2+	June 1979-December 1990, multicenter (13), France, retrospective	Age, WBC, FAB, CMV, conditioning regimen, time from DX to BMT	Not stated	Related Allo 74	≤16 yr (10 yr)	<18 mo 22	46 mo	6-yr EFS 59 ± 12	Time from CR1 to relapse or death from any cause	6-yr 62 ± 11	Not stated
47	2+	AIEOP, August 1980-June 1990, multicenter (11), Italy, retrospective	Sex, age, WBC count, FAB, induction, cytogenetics	Not stated	Related allo 59	<15 yr (9 yr)	Not stated 33 (1980-1987) 4 (1988-1990)	59 mo	5-yr RFS 57.8 (95% CI, 43.7–71.9)	Time from SCT to relapse, progress, or death in CR	5-yr 61.3 (95% CI, 47.3–75.2)	Not stated
48	2+	January 1985-August 2000, single US center, retrospective	Sex, age, WBC count, FAB, induction, cytogenetics	Not stated	Related allo 41	≤18 yr (11 yr)	Not stated for children only	5.5 yr	7-yr EFS 63	Time from SCT to graft rejection, relapse, or death	Not Stated	
Unrelated allo-SCT												
49	2+	Eurocord Group, 1994-March 2002, multicenter (49), retrospective	Age, WBC, FAB, CNS, cytogenetics	Abnormal Normal	Allo UCBT 95	≤15 yr (4.8 yr)	Day 100 20 ± 4	31 mo	2-yr LFS 42 ± 5	Time from CBT to relapse or death in CR	2-yr 49 ± 5	Time from CBT to death from any cause

Table 7. *Continued*

Reference No.	Quality and Strength of Evidence*	Patient Population	Patient Characteristics	Risk Groups	No. of Patients by Study Group	Upper Limit (Median) Age at DX	%TRM	Median Follow-up	%DFS/%RFS/ %EFS/%LFS	Outcome Defined	%OS	OS Defined
T cell depleted allo-SCT												
50	2+	MRC or BFM protocols, June 1991-October 1999, single center, England	Age, sex, CMV, disease status, FAB, donor, CRI duration	Not stated	Allo 39† (T cell depleted, unrelated donor)	≤19 yr (n = 33); 19–40 yr (n = 6) (10 yr)	Not stated	44 mo	44 mo- DFS 57 ± 8	Not stated	44 mo 61 ± 8	Not stated
51	2+	1990-2001, single US center	Age, donor, conditioning regimen	Not stated	Allo 35‡ (partial T cell depleted, matched or mismatched unrelated or partially matched related donor)	Overall ≤21 yr 10.3 yr (AML only not stated)	Not stated for AML only	63 mo	3-yr EFS 34.3	Time to relapse or nonrelapse mortality (start point not defined)	3-yr 34.3	Not stated

UCBT indicates unrelated CBT; LFS, leukemia-free survival; ITT, intent to treat; DX, diagnosis; Chemo, chemotherapy; CCG, Children's Cancer Group; POG, Pediatric Oncology Group; MRC, Medical Research Council; AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; LAM, Leucemia Acuta Mieloide; NOPHO, Nordic Society for Paediatric Haematology and Oncology; LAME, Leucémie Aiguë Myéloblastique Enfant; EORTC, European Organization of Research and Treatment of Cancer; TPOG, Taiwan Pediatric Oncology Group; RFS, relapse-free survival; WBC count, WBC count at diagnosis; EMD, extramedullary disease; SR, standard risk; HR, high risk.

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

†Eight-five percent of sample was ≤19 yr old.

‡AML, n = 30 (86%)

from CR1 to SCT for the 3 conditioning groups were 81 ± 14, 75 ± 16, and 96 ± 19 days, respectively (not significantly different). The mean age of patients was significantly older in the TBI group than in the Bu + Cy 120 ($P < .01$) and Bu + Cy 200 ($P < .01$) groups. Cytogenetic data were not reported. There was lower EFS in the Bu + Cy 120 group (46 ± 24%, $P = .07$) than in the Bu + Cy 200 (82 ± 18%) and TBI (80 ± 14%) groups at median follow-ups of 28, 31, and 48 months, respectively; however, this was not statistically different. Probabilities of TRM occurring while patients were in CR were 0 ± 11%, 5 ± 11%, and 10 ± 11%, respectively, for the 3 groups.

Ayas et al. [53] retrospectively compared the outcomes of 66 pediatric (<15 yr) patients with AML in CR1 at a single institution who underwent HLA-matched related allo-BMT after conditioning with Bu (oral) + Cy (n = 18) or Bu (oral) + Cy + etoposide (n = 48). Median time from CR1 to BMT and cytogenetic data were not reported. Patient clinical characteristics were similar in both groups. There was no significant difference in 5-year OS (50% versus 53.3%, $P = .09$) or EFS (35.9% versus 53.9%, $P = .38$) between the Bu + Cy and Bu + Cy + etoposide groups.

SECOND BMT AFTER FAILED FIRST BMT

Two single-arm, noncomparative studies of second BMT after a failed first BMT are summarized in the following text.

Meshinchi et al. [54] reported outcomes for 25 pediatric (<18 yr) patients with AML who underwent allo-SCT (12 HLA-matched related, 9 HLA-mismatched related, 4 HLA minor-mismatched unrelated) for recurrent disease after a prior auto-SCT (n = 11) or allo-SCT (n = 14). Median time from first SCT to relapse was 6.2 months. Median time between first and second SCT was 9.6 months. Cytogenetic data were not reported. OS at 10 year after the second transplantation was 48%, DFS was 44%, and TRM at day 100 was 12%. DFS for patients who underwent second transplantation in remission was higher than that for those who underwent transplantation while in relapse (70% versus 27%, $P = .05$).

The following study consists of <25 patients but is included due to the paucity of data in this section. Hale et al. [55] retrospectively examined the outcomes of 23 pediatric (<17 yr) patients (87% *de novo* AML) at a single institution who underwent allo-BMT (9 HLA-matched related, 14 HLA-matched unrelated) for recurrent disease after a prior auto-BMT. Median time to disease recurrence after auto-BMT was 161 days. Median time between auto-BMT and allo-BMT was 291 days. Cytogenetic data were not reported. DFS at 4 years was 39% and the cumulative incidence of TRM at 2 years was 34.8%.

Table 8. *Prognostic Factors Related to Outcome (DFS, EFS, and/or OS), Regardless of Treatment*

Reference No./Trial	Univariate Analysis	Multivariate Analysis
62/CCG 213	Poor 7-yr OS: Platelets <20 000/μL at diagnosis (*P* = .047) Hepatomegaly present (*P* = .004) Day 14 BM >15% blasts (*P* = .018) Better 7-yr OS: Cytogenetics: abnormal chromosome 16 (*P* = .001) Not significant for OS: Gender, age, race, WBC count diagnosis, hemoglobin, FAB, MDS, splenomegaly, chloroma, CNS at diagnosis, Auer rods	Better 7-yr OS: Cytogenetics: abnormal chromosome 16 (*P* = .001) Poor 7-yr OS: Hepatomegaly present (*P* = .005) Day 14 BM >15% blasts (*P* = .024)
11/5 CCG trials combined	Not reported	Not significant for 8-yr OS: WBC count (*P* = .065) FAB (*P* = .059) Better 8-yr DFS: WBC count <50 000/μL (*P* < .001)
63/NOPHO-AML93, multivariate; 21/ NOPHO-AML93, univariate	Better 7-yr EFS: Induction response good* (*P* < .01) WBC count ≤50 000/μL at diagnosis (*P* < .01) Age <10 yr (*P* = .04) FAB ≠ M1 (*P* = .03) Cytogenetics t(9;11) (*P* < .01) Having t(9;11), t(8;21), or abnormal chromosome 16 vs not having (*P* = .02)	Better 5-yr EFS: Induction response good* (*P* < .01) WBC count <50 000/μL at diagnosis (*P* = .02) Age <10 yr (*P* = .05)
22 /EORTC-58921	Not reported	Better 5-yr OS: Cytogenetics favorable [inv(16) or t(8;21)] (*P* = .008) Not significant for 5-yr OS and EFS: Age (*P* value not stated) WBC count (*P* value not stated)
64/MRC AML 10 and 12	Not reported	Poor 5-yr OS: Older age (continuous variable) (*P* = .02) WBC count higher at diagnosis (continuous variable; *P* < .001) FAB ≠ M5 (*P* = .02) Cytogenetics poor risk (*P* < .001) Better 5-yr DFS: WBC lower at diagnosis (continuous variable; *P* < .001) FAB M5 (*P* = .03) Day 14 BM <15% blasts (*P* < .001) MRC risk group: good† (*P* < .001) Not significant for 5-yr DFS: Age (continuous variable; *P* = .06) Better 5-yr EFS: Younger age (continuous variable; *P* = .02) WBC count lower at diagnosis (continuous variable; *P* < .001) FAB M5 (*P* = .01) Cytogenetics: favorable risk (*P* < .001)
14/MRC AML 10	Poor 7-yr OS: MRC risk group poor† (*P* < .0001) Poor 7-yr DFS: MRC risk group poor† (*P* < .0001)	Not reported
65/MRC AML 10 and 12	Poor 5-yr OS: Status after 1 course resistant disease (blasts >15%; *P* = .0001) MRC risk group: poor† (*P* < .0001) Cytogenetics: adverse risk (*P* = .0007) Poor 5-yr DFS: MRC risk group: poor† (*P* < .0001)	Not reported
66/POG 8821, univariate; 67/POG 8821, multivariate	Poor 4-yr EFS: Cytogenetics 11q23 (*P* = .0013) Better 4-yr EFS: Cytogenetics inv(16) (*P* = .007) t(8;21) (*P* = .014) Normal karyotype (*P* = .012) Single karyotypic abnormality (*P* = .0003)	Poor 4-yr EFS: FAB M5 (*P* = .0003) Cytogenetics other than t(8;21), inv(16) (*P* = .0001) Better 4-yr EFS: Age >2 (*P* = .003) WBC count <50 000/μL at diagnosis (*P* = .049) Cytogenetics t(8;21), inv(16) (*P* = .0003) normal chromosomes (*P* = .031)

Table 8. *Continued*

Reference No./Trial	Univariate Analysis	Multivariate Analysis
23/Taiwan POG	Poor 5-yr OS: WBC count ≥100 000/μL at diagnosis (*P* = .003) Induction response poor‡ (*P* = .002) Poor 5-yr EFS: WBC count ≥100 000/μL at diagnosis (*P* = .011) Induction response poor‡ (*P* = .001)	Not reported
19/LAME 89/91	Better 5-yr OS: WBC count <100 000/μl at diagnosis (*P* = .01) Day 20 BM <20% blasts (*P* = .03) Allo-BMT in CR1 (*P* = .006) Cytogenetics favorable = t(8;21), t(9;11), inv (16) vs others (*P* = .005) Not significant for OS: Gender, Age, CNS, FAB Better 5-yr EFS: WBC count <100 000/μL at diagnosis (*P* = .02) Not significant for EFS: Age, FAB, percent blasts at day 20, cytogenetics	Not reported
16/AIEOP LAM92	Poor 5-yr EFS: Risk high§ (*P* = .04) WBC count >100 000/μL at diagnosis (*P* value not stated)	Not reported

*Induction response: good indicates no evidence of leukemia after 2–3 wk.

†Medical Research Council (MRC) risk groups derived from cytogenetics and response to induction: good risk indicates t(15;17), t(8;21), inv(16), FAB M3; poor risk indicates monosomy 5 or 7, del 5, abnormal chromosome 3, complex cytogenetics (≥5 abnormalities), or resistant disease (>15% BM blasts after first induction course); standard risk indicates all others.

‡Poor induction indicates ≥2 courses of therapy to attain remission.

§Risk: standard indicates patients with FAB M2/M2 or M4eo subtypes, with Auer rods, or who did not have these characteristics but did have t(8;21), inv(16), or t(15;17); high risk, all other children.

THERAPY-RELATED AML

One single-arm, noncomparative study on the use of BMT in therapy-related AML is summarized as follows. Woodard et al. [56] reported outcomes of 38 pediatric (<22 yr) patients treated with allo-BMT (matched sibling, n = 16; mismatched family member, n = 3; or matched unrelated donor, n = 19) for therapy-related AML (n = 27, 71%) or therapy-related MDS (n = 11) that developed after treatment for a prior hematologic malignancy or solid tumor. Median time from achievement of CR1 to allo-BMT was not reported. The 3-year OS and EFS for the 27 patients with therapy-related AML were 18.5 ± 7.5% and 18.7 ± 7.5%, respectively. The 3-year cumulative risk of TRM was 59.6 ± 8.4%.

LATE EFFECTS

Parsons et al. [57] performed a retrospective Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment (Q-TWiST) analysis of the POG 8821 [13] trial data to assess patients' quality of life based on treatment modality (chemotherapy, auto-BMT, or allo-BMT). Three clinical health states were defined: TOX, the period of treatment-related symptomatic toxicities with grade ≥3; TWiST, the period representing the best possible quality of life during which patients experience no toxicities of treatment or symptoms of disease; and REL, all time after disease relapse. Intent-to-treat analysis assessed the average number of months patients spent in each state during the first 60 months of follow-up. There was no significant difference between the chemotherapy (n = 117) and auto BMT (n = 115) groups in time spent in TOX (2.2 versus 2.4 mo, $P = .16$) or TWiST (27.3 versus 25.4 mo, $P = .55$). In contrast, patients in the allo-BMT group (n = 89) spent significantly more time than those in the chemotherapy and auto-BMT groups in TOX (3.4 mo, $P < .001$). Time spent in TWiST for the allo-BMT group was 33.9 months, which was significantly longer than that in the auto-BMT group ($P = .02$) and the chemotherapy group ($P = .06$). Time after REL was not significantly different among the chemotherapy (6.2 mo), auto-BMT (3.5 mo), and allo-BMT (4.5 mo) groups.

Leung et al. [58] reported the incidence of late effects by treatment in 77 patients at a single institution who survived >10 years after the diagnosis of pediatric AML. Treatment types included chemotherapy (group A, n = 44), chemotherapy and cranial irradiation (group B, n = 18), or chemotherapy, cranial irradiation, and allo-BMT (group C, n = 15). At

a median follow-up of 16.7 year, the development of academic difficulties and greater decrease in height Z score* were significantly associated with younger age at diagnosis (P = .011 and .0084, respectively), younger age at initiation of radiation therapy (P = .011 and = .026, respectively), higher dose of cranial radiation (P = .010 and .0001, respectively), and treatment groups B (P = .028 and .0001, respectively) and C (P = .009 and .0008, respectively). Patients in treatment group C compared with group A had a significantly higher risk for a greater decrease in weight Z score (P = .0005) and the development of growth hormone deficiency (P = .003), hypothyroidism (P = 047), hypogonadism (P < .0001), infertility (P < .0001), and cataracts (P < .0001).

Leahey et al. [59] conducted a retrospective study of long-term survivors of pediatric AML at a single institution. Late effects in weight and height and in endocrine, ophthalmologic, renal, and cardiac functions were compared in patients (<25 years old at follow-up) treated with chemotherapy with/without radiation therapy (n = 26) or BMT with/without TBI (n = 26) at mean follow-ups of 7.4 and 5.6 years, respectively. The only statistically significant difference between the 2 groups was in the higher use of estrogen supplementation in females who underwent BMT (n = 9) versus chemotherapy (n = 11; 67% versus 0%, P = .002).

Locatelli et al. [60] reported that, at a median follow-up of 5 years, 49 (33%) of 147 pediatric patients with AML surviving >18 months after auto-BMT had at least 1 late complication. The late effects examined were impairment in growth velocity (n = 21), abnormal thyroid (n = 20) or cardiac (n = 3) function, hypogonadism (n = 13), and acquired secondary myelodysplasia (n = 1). The use of TBI during conditioning was the only factor significantly associated with the development of late complications (data not provided).

Michel et al. [61] investigated late effects among 45 pediatric patients with AML treated with allo-BMT from an HLA-matched related donor after conditioning with Bu (oral) + Cy (n = 26) or with TBI (n = 19). Patients who received TBI versus Bu + Cy were significantly more likely to have impaired growth at a median follow-up of 5 year (P < .01) and an increased probability of hypothyroidism at 6 years (P < .02). The 6-year probabilities of cataracts were 70 ± 13% in the TBI group and 0% in the Bu + Cy group (P value not stated).

*Z score statistic measures the distance in standard deviations of a sample from the mean.

PROGNOSTIC FACTORS

A comprehensive review of prognostic factors that affect the outcome of SCT in pediatric patients with AML is beyond the scope of this evidence-based review. However, Tables 8 and 9 provide summaries of those prognostic factors that were identified through univariate and/or multivariate analyses as positively or negatively affecting patient outcomes in the major cooperative group, phase III studies presented earlier in this review. Table 8 presents prognostic factors related to outcomes regardless of treatment, and Table 9 presents prognostic factors related to outcome by treatment type.

AREAS OF NEEDED RESEARCH

Clinical and translocational research in allo-SCT should focus on improving antileukemic treatment efficacy and decreasing toxicity of such treatment. After reviewing the evidence, the panel recommends the following as the most important areas of needed research.

1. What is the role of risk group stratification, including the role of cytogenetics, in selection of patients for allo-SCT, especially those in CR1?
2. What is the appropriate timing and use of alternative donor SCT, given that matched unrelated donor SCT appears to yield outcomes equivalent to those of matched related donor SCT?
3. What is the role of reduced intensity SCT (including the use of fludarabine-based preparative regimens) and/or other immunomodulatory approaches to maximize the graft-versus-leukemic effect? Can reduced intensity SCT be used as a platform for vaccination strategies? Can reduced intensity SCT decrease the incidence and severity of late effects? Can the use of donor (and host) genotyping aid in identifying better donor grafts (ie, killer cell Ig-like receptor mismatching, pharmacogenomic testing, etc)?
4. What is the role of biologically targeted agents (ie, tyrosine kinase inhibitors, farnesyl transferase inhibitors, Flt-3 inhibitors, etc) in the treatment of AML, including induction, consolidation, conditioning regimens, and after SCT?

DISCUSSION

The authors recommend methodology standardization, including study design, endpoint definitions, and reporting of study results. Studies must stratify results by age and disease and give as much information as possible on cytogenetics and other risk factors. This information will facilitate disease- and age-specific applications of therapy. In addition, publication of preliminary analyses should be reserved for studies

Table 9. *Prognostic Factors Related to Outcome (DFS, EFS, and/or OS), by Treatment Type*

Reference No./Trial	Univariate Analysis	Multivariate Analysis
11/CCG combined trials	Not reported	Better 8-yr OS: Donor better than no donor for WBC count <50 000/μL and ≥50 000/μL at diagnosis (P = .028) FAB M1/M2 (P = .004; True for all FAB types, but survival rates and P values not stated) Cytogenetics t(8;21) (P = .028) Better 8-yr DFS: Donor better than no donor for WBC count <50 000/μL and ≥50 000/μL at diagnosis (P = .008) Cytogenetics t(8;21) (P = .04) Normal karyotype (P = .013)
12/CCG 2891	Better 8-yr OS: Allo-BMT better than auto-BMT for Age ≤1 yr (P = .03) FAB M4 (P = .003) Cytogenetics inv(16) (P = .04) Better 8-yr OS: Chemotherapy better than auto-BMT (P = .009) for Age <1 yr (P = .009) Cytogenetics inv(16) (P = .05)	Not reported
20/LAME 89/91	Poor 4-yr DFS: Chemotherapy group Age <1 yr (P < .01) WBC count > 50 000/μL at diagnosis (P = .03) FAB M5 vs others (P < .01)	Poor 4-yr DFS: Chemo group Age <1 yr (P = .01) FAB M5 vs others (P = .01) Better 4-yr DFS: BMT better than chemotherapy for Age >1 yr (P = .01) Better 4-yr DFS: BMT group BMT in CR1, yes vs no (P = .05) Not significant for DFS: BMT group Age, WBC count at diagnosis, FAB, hepatosplenomegaly, meningeal involvement

in which the trial was terminated early due to excessive toxicity or to 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 manuscript 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 treatment outside the scope of the trial.

Many current 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 [68]. Due to the rarity of AML in children, all pediatric patients with AML should be studied in large cooperative group settings to enroll enough patients to answer clinical trial questions.

LIMITATIONS OF THIS EVIDENCE-BASED 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 1990. Unpublished data, which were not included in this review, often represent "negative" findings and do not undergo peer review. Also excluded were data published in abstract form because the data are usually not peer reviewed, are presented in an abbreviated format, and most often represent preliminary rather than final data analyses.

Limitations specific to this review include the variability in reporting patient characteristics before SCT and changing treatment modalities over time. Chemotherapy regimens, particularly pre-SCT conditioning regimens, and post-SCT supportive care have changed considerably over the >15 years of trials included in this review. Studies varied substantially in study onset and endpoint definitions, conditioning regimen drugs, and reporting of cytogenetic and other risk data, making it difficult to compare SCT outcomes across studies. Randomized controlled trial data were lacking in many areas of this review, leading to several treatment recommendations based on small prospective studies and/or large retrospective registry reports. Any randomized controlled trials comparing

allogeneic transplantation are limited by the inability to provide level "1" evidence (ie, randomized controlled trials) due to the low rate of patients randomized to the allo-SCT arm who would actually receive the assigned treatment (~35% of patients have a matched related donor [69]). Therefore, for a trial applying biologic allocation of related allo-SCT, "2" is the highest level of evidence that can be practically used.

ACKNOWLEDGMENTS

The American Society for Blood and Marrow Transplantation and Drs. Hahn and McCarthy are indebted to the members of the AML review expert panel and the American Society for Blood and Marrow Transplantation evidence-based review steering committee who voluntarily and enthusiastically participated in this endeavor. The authors of this review and the American Society for Blood and Marrow Transplantation thank the National Marrow Donor Program, especially Jeffrey Chell, MD and Michael Boo, for their support of this project. The authors acknowledge Dr. C. Fred LeMaistre for pioneering and supporting this effort, Alan Leahigh and Dianne O'Rourke for their invaluable administrative assistance, and Amy Gillen for serving as the literature abstractor and additional reviewer of this report. The authors are grateful to all patients who participated in the clinical trials that led to the evidence on which this review is based.

APPENDIX A. GLOSSARY OF TERMS

AIEOP	**Associazione Italiana Ematologia ed Oncologia Pediatrica**
Allo	**Allogeneic**
AML	**Acute myeloid leukemia**
ANLL	**Acute non-lymphocytic leukemia**
ANZCCSG	**Australian and New Zealand Children's Cancer Study Group**
APL	**Acute promyelocytic leukemia**
Auto	**Autologous**
BFM	**Berlin-Frankfurt-Munster**
BM	**Bone marrow**
BMT	**Bone marrow transplantation**
Bu	**Busulfan**
CBT	**Cord blood transplantation**
CCG	**Children's Cancer Group**
CML	**Chronic Myeloid Leukemia**
CNS	**Central nervous system**
CR1	**First complete remission**
CR2	**Second complete remission**
Cy	**Cyclophosphamide**
DFS	**Disease-free survival**
DS	**Down syndrome**
EBMT	**European Group of Blood and Marrow Transplantation**
EFS	**Event-free survival**
EORTC	**European Organization of Research and Treatment of Cancer**
FAB	**French-American-British morphology classification**
HLA	**Human leukocyte antigen**
LAM	**Leucemia Acuta Mieloide**
LAME	**Leucemie Aigue Myeloblastique Enfant**
LFS	**Leukemia-free survival**
MDS	**Myelodysplastic syndrome**
MRC	**Medical Research Council**
MRD	**Matched related donor**
MUD	**Matched unrelated donor**
NOPHO	**Nordic Society for Paediatric Haematology and Oncology**
OS	**Overall survival**
PB	**Peripheral blood**
PBSCT	**Peripheral blood stem cell transplantation**
Ph+	**Philadelphia chromosome positive**
POG	**Pediatric Oncology Group**
QOL	**Quality of life**
Q-TWiST	**Quality-adjusted time without symptoms or treatment toxicity**
RCTs	**Randomized controlled trials**
RFS	**Relapse-free survival**
SCT	**Stem cell transplantation**
t-AML	**Therapy-related (or treatment-related) acute myeloid leukemia**
t-MDS	**Therapy-related (or treatment-related) myelodysplastic syndrome**
TPOG	**Taiwan Pediatric Oncology Group**
TBI	**Total body irradiation**
TRM	**Treatment-related mortality**
URD	**Unrelated donor**
WBC	**White blood cell**

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