

AUTOLOGOUS BONE MARROW TRANSPLANTATION VERSUS INTENSIVE CONSOLIDATION CHEMOTHERAPY FOR ACUTE MYELOID LEUKEMIA IN CHILDHOOD

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Abstract Background. The value of autologous bone marrow transplantation in the treatment of children with acute myeloid leukemia (AML) is unknown. We compared autologous bone marrow transplantation with intensive consolidation chemotherapy as treatments for children with AML in first remission.

Methods. We induced remission with one course of daunorubicin, cytarabine, and thioguanine, followed by one course of high-dose cytarabine (3 g per square meter of body-surface area for six doses). Patients in remission after the second course of induction therapy were eligible for randomization. Between June 1988 and March 1993, 552 of 649 enrolled patients who could be evaluated (85 percent) entered remission. A total of 209 patients were not eligible for randomization; of the remaining 343 patients, 232 were randomly assigned to receive six courses of intensive chemotherapy (117 patients) or autologous transplantation (115 patients). Of the original 649 patients, 189, including 21 with Down's syndrome, were nonrandomly assigned to receive intensive chemotherapy.

Results. The mean (\pm SE) rates of event-free survival and overall survival for the entire group at three years were 34 ± 2.5 percent and 42 ± 2.6 percent, respectively. For patients who were randomly assigned to one of the

two treatment groups, the rates of event-free survival three years after randomization were not significantly different in the two groups when examined by intention-to-treat analysis: 36 ± 5.8 percent for the intensive-chemotherapy group as compared with 38 ± 6.4 percent for the autologous-transplantation group; and the relative risk of treatment failure for the chemotherapy group as compared with the autologous-transplantation group was 0.81 ($P=0.20$ by the log-rank test; 95 percent confidence interval, 0.58 to 1.12). Overall survival at three years followed a similar pattern. There was a lower relapse rate (31 percent vs. 58 percent, $P<0.001$) but a higher rate of treatment-related mortality (15 percent vs. 2.7 percent, $P=0.005$) in the group treated with autologous transplantation than in the intensive-chemotherapy group. The event-free survival at three years for the nonrandomized intensive-chemotherapy group was 39 ± 5.1 percent, and for a contemporaneous group of patients each of whom received a histocompatible bone marrow transplant from a sibling, it was 52 ± 8.0 percent.

Conclusions. Treatment of children with AML in first remission with either autologous bone marrow transplantation or intensive chemotherapy prolongs event-free survival equally. (N Engl J Med 1996;334:1428-34.)

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CHEMOTHERAPY can induce a remission in up to 85 percent of children with acute myeloid leukemia (AML).¹⁻⁷ However, most patients relapse, and the long-term event-free survival ranges from 29 to 45 percent.¹⁻⁷

The high rates of relapse in these children prompted the use of intensified chemotherapy and bone marrow transplantation after the initial remission. Among children with AML who receive allogeneic bone marrow transplants from histocompatible siblings, approximate-

ly 55 percent can be cured.^{8,9} However, less than 20 percent of children in the United States have suitable family donors for allogeneic transplantation.¹⁰ Another strategy, autologous bone marrow transplantation,^{11,12} has been evaluated in nonrandomized trials conducted in patients with AML in first remission. The results have been encouraging but ambiguous, because of biases in patient selection.¹³⁻¹⁵ We therefore undertook a multicenter, randomized trial to assess autologous transplantation in children with AML in first remission. Our results do not show a significant advantage of autologous bone marrow transplantation over intensive consolidation chemotherapy.

METHODS

Eligibility

Patients under 21 years of age with previously untreated AML or isolated granulocytic sarcoma (chloroma) were eligible for the study. Patients with secondary AML were permitted to register for evaluation of the initial response but not for randomization at the time of remission. Morphologic classification followed the French-American-British system and was centrally reviewed.

Randomization

After giving informed consent, all patients were registered in the study prospectively. Patients who did not enter remission after the second course of induction chemotherapy were withdrawn from the study. Patients with histocompatible sibling donors were offered allogeneic bone marrow transplantation. The remaining patients were el-

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eligible for random assignment to either autologous transplantation or intensive consolidation chemotherapy, provided that they reaffirmed their intention to accept the randomized treatment, that financial support for autologous transplantation was available, and that there was a bed available at 1 of the 16 transplantation centers of the Pediatric Oncology Group. The randomization procedure was aimed at balancing the marginal totals of each morphologic subtype of AML.

Treatment

Induction therapy was given in two courses. The first course consisted of 45 mg of daunorubicin per square meter of body-surface area per day on days 1, 2, and 3; 100 mg of cytarabine per square meter per day by continuous infusion on days 1 through 7; and 100 mg of thioguanine per square meter per day, orally, on days 1 through 7; this was followed by high-dose cytarabine (3 g per square meter as a 3-hour infusion, every 12 hours for six doses).⁷ The second course of this treatment started on day 15 if the bone marrow showed residual leukemia; otherwise, it was begun when the absolute neutrophil count was 1000 per cubic millimeter or higher and the platelet count was 100,000 per cubic millimeter or higher. Intrathecal cytarabine (40 mg per square meter) was given on days 1 and 8 of the first course of induction therapy. Additional intrathecal cytarabine was given on days 12 and 19 to patients who had central nervous system leukemia at the time of diagnosis. Patients who entered remission (defined as having M1 marrow [≤ 5 percent blasts] or M2a marrow [5 to 15 percent blasts]) were eligible for randomization. After randomization, all the patients received one course of etoposide (250 mg per square meter per day) on days 1, 2, and 3; azacytidine (300 mg per square meter per day) on days 4 and 5; and intrathecal cytarabine (40 mg per square meter) on days 1 and 7. The combination of etoposide and azacytidine was chosen as a consolidation therapy because of its low hematopoietic toxicity¹⁶ and hence the lower risk of serious infections in patients waiting for marrow transplantation. At this point the patients received either intensive chemotherapy, autologous transplantation, or allogeneic transplantation, depending on their treatment group.

Intensive Consolidation Chemotherapy

Patients assigned to receive intensive chemotherapy received six additional courses of therapy, each administered successively at three-week intervals or when the absolute neutrophil count was at least 1000 per cubic millimeter and the platelet count was at least 100,000 per cubic millimeter. The first drug course consisted of 45 mg of daunorubicin per square meter on day 1 and cytarabine as in the second induction course; the second course consisted of daunorubicin for two days and cytarabine and thioguanine for five days, with drug doses as in the first induction course; the third course consisted of etoposide and azacytidine, with drug doses as described above; the fourth course consisted of high-dose cytarabine, as in the second induction course; the fifth course was the same as the second course; and the sixth course was the same as the third. The cumulative dose of daunorubicin was 350 mg per square meter. Local radiotherapy was permitted for patients with central nervous system or extracranial mass lesions.

Autologous Bone Marrow Transplantation

Patients who were to undergo autologous transplantation had to be in complete remission after the consolidation course of etoposide and azacytidine and free of disseminated fungal disease. The protocol required harvesting the patient's bone marrow 6 to 12 weeks after the start of etoposide and azacytidine. To eliminate myeloblasts, the harvested marrow was treated under sterile conditions for 30 minutes with perfosfamide (4-hydroperoxycyclophosphamide) at a concentration of 100 μg per milliliter and an incubation hematocrit of 5 to 10 percent.

Patients were prepared for autologous marrow transplantation with 4 mg of busulfan per square meter per day, administered orally every six hours, on days 9, 8, 7, and 6 before transplantation and 50 mg of cyclophosphamide per kilogram, given intravenously, on days 5, 4, 3, and 2 before transplantation. After a day of rest, the cryopreserved marrow was thawed and infused (day 0). All patients received

phenytoin (on days 11 through 4 before transplantation) as prophylaxis against seizures.

Allogeneic Bone Marrow Transplantation

Allogeneic transplantation was not a primary focus of this study because many Pediatric Oncology Group centers offer this treatment to any patient with a histocompatible family donor. The preparative regimen consisting of busulfan and cyclophosphamide was strongly recommended, but a variety of conditioning regimens were used.

Statistical Analysis

It was necessary to have at least 150 randomized patients in order to achieve a power of 80 percent at the 0.05 significance level to detect a difference of 20 percentage points (40 percent vs. 60 percent) in event-free survival two years after randomization between patients who underwent autologous transplantation and those who received intensive consolidation chemotherapy.

Event-free survival was defined as the length of time until the first event — that is, treatment failure (relapse or failure to enter remission) or death. Overall survival was defined as the length of time until death. Calculations of event-free and overall survival for the entire group started from the date of registration; for the randomized groups they started from the date of randomization. Actuarial curves showing event-free and overall survival were constructed according to the Kaplan-Meier method.¹⁷ The relative risks were estimated with the Cox proportional-hazards model.¹⁸ Findings with respect to event-free and overall survival were tested for statistical significance by the log-rank test,¹⁹ according to the intention-to-treat principle. All P values reported in this article are two-sided.

RESULTS

Between June 1988 and March 1993, 666 patients, 1 day to 20.9 years of age, were registered. Seventeen could not be evaluated, because of wrong diagnoses (10), major protocol violations (3), or withdrawal before induction therapy was completed because of toxicity or a parent's refusal of further therapy (4). Of the 649 patients who could be evaluated, 552 (85 percent) entered remission (507 had M1 marrow and 45 had M2a marrow). Death accounted for 26 of the 97 induction failures (27 percent); the other 71 patients who failed to enter remission had resistant disease. Figure 1 shows the numbers of patients at each stage of treatment; 209 were not eligible for randomization because a suitable donor was available for allogeneic transplantation (89) or because of nonprotocol autologous transplantation (18), secondary AML (5), insufficient funds (64), lack of beds at a Pediatric Oncology Group transplantation institution (14), death before randomization (6), withdrawal due to drug toxicity (5), relapse before randomization (5), or other reasons (3). Thus, 343 of the 552 patients (62 percent) who entered remission were eligible for randomization. Of these, 232 (68 percent) were randomly assigned to a treatment group — 117 to the intensive-chemotherapy group and 115 to the autologous-transplantation group. The remaining 111 patients (32 percent), including 21 children with Down's syndrome, or their parents declined randomization.

Clinical and Disease Characteristics

The two randomized groups had similar distributions of clinical, morphologic, and cytogenetic features

(Table 1), except for a slight excess of extramedullary disease in the autologous-transplantation group. A stratified log-rank test adjusting for extramedullary disease failed to show a significant difference in event-free survival between the randomized groups ($P=0.21$).

Patterns of Treatment Failure in Randomized Patients

Table 2 summarizes the reasons some patients did not complete the randomized treatment and shows the patterns of failure. More than a third of the patients (44 of 115, or 38 percent) assigned to autologous transplantation did not receive the intended treatment. Twenty-one patients relapsed before their marrow could be harvested. The parents of 14 patients chose intensive chemotherapy after randomization, 3 patients had disseminated fungal sepsis, the families of 5 opted for allogeneic transplantation, and 1 was lost to follow-up. The outcomes of these patients were included with those of the autologous-transplantation group in the intention-to-treat analysis. In contrast, only four patients (3.4 percent) assigned to intensive chemotherapy changed treatment options. The number of treatment-related deaths was significantly higher after autologous transplantation (11 of 71, or 15 percent) than after chemotherapy (3 of 113, or 2.7 percent; $P=0.005$).

Event-free and Overall Survival

For all eligible patients, the mean (\pm SE) rates of event-free and overall survival at three years were

34 ± 2.5 percent and 42 ± 2.6 percent, respectively. The estimated event-free survival three years after randomization, according to the intention-to-treat analysis, was 36 ± 5.8 percent in the intensive-chemotherapy group and 38 ± 6.4 percent in the autologous-transplantation group ($P=0.20$) (Fig. 2). The relative risk of treatment failure was 0.81 (95 percent confidence interval, 0.58 to 1.12) for the chemotherapy group as compared with the autologous-transplantation group. The rates of event-free and overall survival at three years for the nonrandomized chemotherapy group were 39 ± 5.1 percent and 49 ± 5.2 percent, respectively.

The estimated rates of overall survival three years after randomization (Fig. 3) for the chemotherapy and autologous-transplantation groups were 44 ± 6.0 percent and 40 ± 6.1 percent, respectively ($P=0.10$ by the log-rank test), with a relative risk of death of 0.75 (95 percent confidence interval, 0.53 to 1.06) for the chemotherapy group as compared with the autologous-transplantation group.

Children with Down's Syndrome

As the study evolved, the superior survival of children with Down's syndrome became evident,²⁰ and thereafter the vast majority of these patients were assigned to receive chemotherapy, according to their physicians' preference. Thus, of 27 children with Down's syndrome who entered remission, 26 received intensive chemotherapy and 1 underwent allogeneic transplantation. Patients with Down's syndrome as a group had a three-year event-free survival of 77 ± 2.1 percent. Removal of these patients (and three with isolated cases of granulocytic sarcoma) from the randomized groups did not alter the results (three-year event-free survival was 37 percent and 34 percent, respectively, for the autologous-transplantation and intensive-chemotherapy groups; $P=0.28$).

Allogeneic Transplantation

Sixteen percent of the patients entering remission (89 of 552) had histocompatible donors and their families opted for allogeneic transplantation. The event-free survival three years after randomization was marginally better for the children who underwent allogeneic transplantation (52 ± 8 percent) than for those given intensive consolidation chemotherapy ($P=0.06$) and significantly better than that for children who underwent autologous transplantation ($P=0.01$ by the log-rank test) (Fig. 2). Overall survival after allogeneic transplantation was similar to that

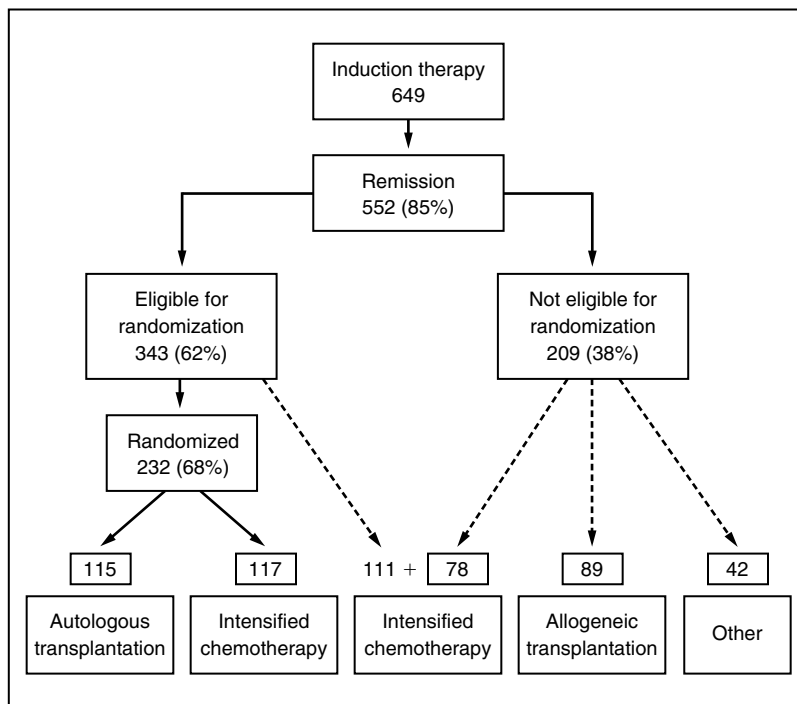


Figure 1. Treatment Plan and Patient Assignments in the Study.

The numbers are the numbers of patients who could be evaluated at each treatment step. Descriptions of the treatments and the reasons for ineligibility are given in the Methods section.

Table 1. Characteristics of the Patients in Remission after Induction Therapy.

CHARACTERISTIC	RANDOMIZED GROUPS		NONRANDOMIZED GROUPS		TOTAL (N=510)	P VALUE*
	INTENSIVE CHEMOTHERAPY (N = 117)	AUTOLOGOUS TRANSPLANTATION (N = 115)	ALLOGENEIC TRANSPLANTATION (N = 89)	INTENSIVE CHEMOTHERAPY (N = 189)		
Race or ethnic group						
White	81	77	70	117	345	0.031
Black	22	22	9	27	80	
Hispanic	8	11	7	28	54	
Other	6	5	3	17	31	
Age						
<2 yr	26	26	13	50	115	0.34
≥2 yr	91	89	76	139	395	
White-cell count						
<15,000/mm ³	59	55	40	94	248	0.94
15,000–25,000/mm ³	19	10	7	20	56	
25,001–50,000/mm ³	17	17	15	29	78	
>50,000/mm ³	22	33	27	46	128	
FAB classification†						
M1 or M2	38	42	34	73	187	0.76
M3	5	8	2	15	30	
M4	20	17	21	22	80	
M5	15	17	9	23	64	
M6	1	1	2	2	6	
M7	7	6	3	16	32	
Granulocytic sarcoma	2	2	0	2	6	
Not reviewed or other	29	22	18	36	105	
Extramedullary disease						
None	98	84	67	157	406	0.27
Central nervous system only	7	12	15	9	43	
Extramedullary disease without central nervous system	8	11	1	10	30	
Extramedullary disease and central nervous system	4	8	6	13	31	
Cytogenetic features						
Not reviewed	24	23	19	43	109	0.76
t(8,21) or inv16	20	16	12	23	71	
t(15,17) or normal	31	28	22	48	129	
Other	42	48	36	75	201	
Down's syndrome						
Present	4	2	0	21	27	<0.001
Absent	113	113	89	168	483	
Response						
M1 marrow	109	104	80	175	468	0.77
M2a marrow	8	11	9	14	42	
Response to induction therapy						
Course 1	64	59	56	119	298	0.04
Course 2	53	56	33	70	212	
3-Yr event-free survival (%)‡	36±5.8	38±6.4	52±8.0	39±5.1	40±3.1	

*P values are for comparisons between the randomized patients and the patients in the nonrandomized intensive-chemotherapy group.

†Morphologic classification followed the French–American–British system and was centrally reviewed.

‡Values are means ±SE. Event-free survival was calculated from the time of randomized or nonrandomized treatment assignment.

after intensive consolidation chemotherapy ($P=0.15$) but superior to that after autologous transplantation ($P=0.007$) (Fig. 3).

Autologous Transplantation

The protocol called for bone marrow to be harvested 42 days after the consolidation course of etoposide and azacitidine (with a maximal allowable delay of 84 days). In actuality, the median time from randomization to the harvesting of marrow was 49 days (range, 21 to 106). In three patients, the marrow was harvested more than 84 days after treatment with etoposide and azacy-

tidine. Delays were due for the most part to an unexpected biphasic pattern of recovery of blood counts after consolidation therapy. As a result, the interval between the consolidation therapy and the harvesting of bone marrow exceeded the minimal target of 42 days in 76 percent of the patients (it was more than 84 days in 20 percent of the patients).

The length of time until engraftment (defined as an absolute neutrophil count of more than 500 per cubic millimeter and a platelet count of more than 50,000 per cubic millimeter) ranged from 11 to 445 days or more (median, 43). Eleven patients died before engraftment. One received marrow from a sibling donor because of nonengraftment of autologous marrow, and backup autologous marrow was used in one patient.

DISCUSSION

High-dose chemotherapy or allogeneic bone marrow transplantation after the induction of remission has improved the survival of children with AML. The limited availability of histocompatible family donors and the encouraging results obtained with autologous transplantation in refractory AML prompted several trials of autologous transplantation in adults with AML who were in their first remissions.^{13-15,20-26} Our results, when analyzed on an intention-to-treat basis, did not show that autologous transplantation was superior to intensive consolidation chemotherapy in prolonging event-free survival.

We encountered important problems in our study. A relatively large proportion (32 percent) of eligible patients were not randomized. After randomization to the autologous-transplantation group, 18 percent of the patients dropped out, often because they had relapses before the marrow could be harvested, and among the patients who actually received autologous transplants, the treatment-related mortality was 15 percent.

Other investigators have also encountered these difficulties. In a recent European study of AML,²⁶ 35 percent (139 of 393) of patients who were in remission and who did not have histocompatible donors could not be randomized; an additional 26 percent (33 of 125) assigned to undergo autologous transplantation did

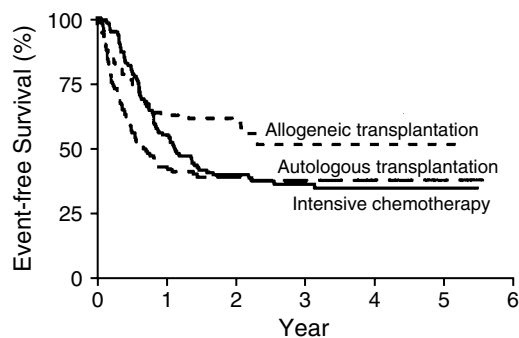
Table 2. Patterns of Treatment Failure.

REASON FOR FAILURE	RANDOMLY ASSIGNED TO INTENSIVE CHEMOTHERAPY (N = 117)	RANDOMLY ASSIGNED TO AUTOLOGOUS TRANSPLANTATION (N = 115)	NONRANDOMLY ASSIGNED TO ALLOGENEIC TRANSPLANTATION (N = 89)
Removed from study for other treatment options*	4	23	5
Relapse before transplantation	—	21	5
Treated as assigned	113	71	79
Relapse after assigned treatment	66	22	18
Death during remission†	3	11	5
Alive, in first remission	42	37	51
3-Yr event-free survival (%)‡	36±5.8	38±6.4	52±8

*The 4 patients from the chemotherapy group underwent allogeneic transplantation; of the 23 from the autologous-transplantation group, 5 underwent allogeneic transplantation, 17 underwent intensive chemotherapy, and 1 received other treatment; and the 5 patients from the allogeneic-transplantation group underwent intensive chemotherapy.

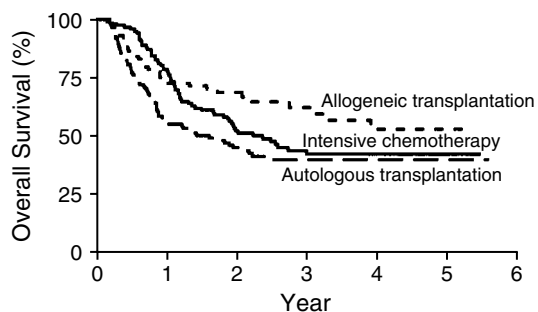
†Deaths from toxicity in the intensive-chemotherapy group were due to sepsis (1), hemorrhage (1), and cardiotoxicity (1); those in the autologous-transplantation group were due to infection (8), hemorrhage (2), and veno-occlusive disease (1).

‡Values are means ±SE. Event-free survival was calculated from the time of randomized or nonrandomized treatment assignment.



No. AT RISK	0	1	2	3	4	5	6
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. Event-free Survival from the Time of Randomization or Assignment to Allogeneic Bone Marrow Transplantation.



No. AT RISK	0	1	2	3	4	5	6
Intensive chemotherapy	117	92	52	30	18	7	
Autologous transplantation	115	62	40	26	17	8	
Allogeneic transplantation	89	61	41	24	14	4	

Figure 3. Overall Survival from the Time of Randomization or Assignment to Allogeneic Bone Marrow Transplantation.

not complete the planned therapy. Stevens et al. reported that 30 percent of patients in remission in a British study of childhood AML could not be randomized.²⁷ The unusually high rate of relapse before marrow harvest in our study may have been related to the slow recovery of the peripheral blood count after the course of consolidation therapy with etoposide and azacytidine. The death rate of 15 percent from toxic effects in patients who received autologous marrow grafts was related to the slow engraftment of perfosamide-purged bone marrow.

Zittoun et al. have recently reported that treatment of adults with AML in first remission with autologous transplantation (with unpurged marrow) resulted in better outcomes than intensive consolidation chemotherapy.²⁶ In their study, patients were randomized after the first consolidation course, whereas we randomized our patients after they completed induction chemotherapy. Moreover, there were a total of four courses of chemotherapy in the study by Zittoun et al. and nine in our study. These differences in the study design and the characteristics of patients (children vs. adults) preclude any comparisons between the two studies.

Three trials of autologous transplantation in children with AML have been reported.²⁷⁻²⁹ Amadori et al. found no significant difference in event-free survival five years after randomization between 37 patients who underwent chemotherapy (27 percent) and 35 who underwent autologous transplantation with unpurged marrow (21 percent).²⁸ In Children's Cancer Group Study 2861, allogeneic transplantation was compared with autologous transplantation with the use of perfosamide-purged marrow.²⁹ The rate of event-free survival three years after transplantation was 51 percent among 58 patients who underwent autologous transplantation, and 55 percent among 17 who underwent allogeneic transplantation. The authors of the Medical Research Council's AML 10 trial,²⁷ conducted in 347 children, concluded that allogeneic transplantation or autologous transplantation after four courses of intensive chemotherapy offered no survival advantage.

Finally, a comment is in order with respect to overall survival in this study as compared with that in other recent AML trials in children. Both the Medical Research Council trial²⁷ and the Berlin-Frankfurt-Münster 87 study of 307 children³⁰ reported overall survival of approximately 50 percent, as compared with 42±2.6 percent in our study. These differences may reflect different characteristics of the patients and the use of a more intensive induction regimen in the Medical Research Council and Berlin-Frankfurt-Münster trials. Intensification of induction chemotherapy can influence survival, regardless of post-remission therapy.³¹

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APPENDIX

The following institutions and principal investigators also participated in the Pediatric Oncology Group: Alberta Pediatric Oncology Consortium, Edmonton, Alta., Canada — M. Coppes; All Children's Hospital, St. Petersburg, Fla. — J. Barbosa; Boston Floating Hospital, Boston — C. Kretschmar; Bowman Gray School of Medicine, Winston-Salem, N.C. — A. Chauvenet; Brooke Army Medical Center, Fort Sam Houston, Tex. — T. Pick; Cancer Center of Hawaii, Honolulu — R. Wilkinson; Carolinas Medical Center, Charlotte, N.C. — B. Golemb; Children's Hospital and Health Center, San Diego, Calif. — R. Kadota; Children's Hospital, Greenville Health System, Greenville, S.C. — C. Stroud; Children's Hospital of New Orleans, New Orleans — R.P. Warrior; Children's Memorial Hospital, Chicago — M. Kletzel; Christ Hospital and Medical Center, Oak Lawn, Ill. — S. Salvi; City of Hope National Medical Center, Duarte, Calif. — R. Chilcote; Cook-Fort Worth Children's Medical Center, Fort Worth, Tex. — P. Bowman; Dana-Farber Cancer Institute, Boston — H. Grier; Dartmouth-Hitchcock Medical Center, Lebanon, N.H. — E. Larsen; Duke University, Durham, N.C. — J. Kurtzberg; East Carolina University School of Medicine, Greenville, N.C. — T. Holbrook; Fairfax Hospital, Falls Church, Va. — J. Greenberg; Hackensack Medical Center, Hackensack, N.J. — M. Harris; Joe DiMaggio Children's Hospital at Memorial, Hollywood, Fla. — P. Sprinz; Johns Hopkins University, Baltimore — C. Schwartz; Kaiser Permanente Medical Center, Santa Clara, Calif. — L. Young; Keesler Air Force Medical Center, Santa Clara, Calif. — T. Abshire; MDA Cancer Center, Orlando, Fla. — V. Giusti; Maine Children's Cancer Program, Portland — C. Hurwitz; Massachusetts General Hospital, Boston — W. Ferguson; McGill University, Montreal — M. Whitehead; Medical College of Virginia, Richmond — E.C. Russell; Medical University of South Carolina, Charleston — J. Laver; Miami Children's Hospital, Miami — E. Escalon; Mount Sinai School of Medicine, New York — J. Lipton; Naval Regional Medical Center, San Diego, Calif. — D. Reardon; Nemours Children's Clinic, Jacksonville, Fla. — P. Pitel; Oklahoma University Health Sciences Center, Oklahoma City — R. Nitschke; Rhode Island Hospital, Providence — E. Forman; Roswell Park Memorial Institute, Buffalo, N.Y. — M. Brecher; Rush-Presbyterian-St. Luke's Medical Center, Chicago — A. Green; Sacred Heart Children's Hospital, Pensacola, Fla. — T. Jenkins; St. Christopher's Hospital, Philadelphia — E. Douglass; St. Francis Regional Medical Center, Wichita, Kans. — D. Rosen; St. John Hospital, Detroit — H. Sawaf; St. Joseph's Cancer Institute, Tampa, Fla. — C. Tebbi; St. Vincent Hospital, Green Bay, Wis. — D. Ganick; Stanford University, Palo Alto, Calif. — M. Link; State University of New York at Syracuse, Syracuse — R. Dubowy; Swiss Pediatric Oncology Group, Bern, Switzerland — H. Wagner; Tripler Army Medical Center, Tripler, Hawaii — S. Reddoch; University of Alabama, Birmingham — R. Castleberry; University of Arizona Health Sciences Center, Tucson — J. Hutter; University of Arkansas, Little Rock — D. Becton; University of California at Davis, Sacramento — J. Ducore; University of California at San Diego, San Diego — F. Kung; University of Florida, Gainesville — P. Mehta; University of Kansas, Kansas City — T. Vats; University of Massachusetts Medical School, Worcester — M. Schwenn; University of Miami School of Medicine, Miami — S. Toledano; University of Mississippi Medical Center, Jackson — J. Pullen; University of Missouri, Columbia — N. Hakami; University of Puerto Rico, San Juan — N. Barrios; University of Rochester Medical Center, Rochester, N.Y. — R. Duerst; University of South Alabama, Mobile — Y.-M. Yang; University of South Florida, Tampa — E. Hvizdala; University of Texas, San Antonio — P.J. Thomas; University of Texas at Galveston, Galveston — M. Haggard; University of Texas, Southwestern Medical School, Dallas — G. Buchanan; University of Vermont College of Medicine, Burlington — J. Dickerman; University of Virginia, Charlottesville — P. de Alarcon; Walter Reed Army Medical Center, Washington, D.C. — D. Maybee; Warren Clinics, Tulsa, Okla. — G. Kirkpatrick; Washington University School of

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REFERENCES

- Weinstein HJ, Mayer RJ, Rosenthal DS, Coral FS, Camitta BM, Gelber RD. Chemotherapy for acute myelogenous leukemia in children and adults: VAPA update. *Blood* 1983;62:315-9.
- Grier HE, Gelber RD, Camitta BM, et al. Prognostic factors in childhood acute myelogenous leukemia. *J Clin Oncol* 1987;5:1026-32.
- Creutzig U, Ritter J, Riehm H, et al. Improved treatment results in childhood acute myelogenous leukemia: a report of the German cooperative study AML-BFM-78. *Blood* 1985;65:298-304.
- Steuber CP, Civin C, Krischer J, et al. A comparison of induction and maintenance therapy for acute nonlymphocytic leukemia in childhood: results of a Pediatric Oncology Group study. *J Clin Oncol* 1991;9:247-58.
- Nesbit ME Jr, Buckley JD, Feig SA, et al. Chemotherapy for induction of remission of childhood acute myeloid leukemia followed by marrow transplantation or multiagent chemotherapy: a report from the Childrens Cancer Group. *J Clin Oncol* 1994;12:127-35.
- Woods WG, Ruymann FB, Lampkin BC, et al. The role of timing high-dose cytosine arabinoside intensification and of maintenance therapy in the treatment of children with acute nonlymphocytic leukemia. *Cancer* 1990;66:1106-13.
- Ravindranath Y, Steuber CP, Krischer J, et al. High-dose cytarabine for intensification of early therapy of childhood acute myeloid leukemia: a Pediatric Oncology Group study. *J Clin Oncol* 1991;9:572-80.
- Sanders JE, Thomas ED, Buckner CD, et al. Marrow transplantation for children in first remission of acute nonlymphoblastic leukemia: an update. *Blood* 1985;66:460-2.
- Bostrom B, Brunning RD, McGlave P, et al. Bone marrow transplantation for acute nonlymphocytic leukemia in first remission: analysis of prognostic factors. *Blood* 1985;65:1191-6.
- Graham-Pole J. Treating acute lymphoblastic leukaemia after relapse: bone marrow transplantation or not? *Lancet* 1989;2:1517-8.
- Yeager AM, Kaizer H, Santos GW, et al. Autologous bone marrow transplantation in patients with acute nonlymphocytic leukemia, using ex vivo marrow treatment with 4-hydroperoxycyclophosphamide. *N Engl J Med* 1986;315:141-7.
- Appelbaum FR, Clift RA, Buckner CD, et al. Allogeneic marrow transplantation for acute nonlymphoblastic leukemia after first relapse. *Blood* 1983; 61:949-53.
- Gorin NC, Aegerter P, Auvert B, et al. Autologous bone marrow transplantation for acute myelocytic leukemia in first remission: a European survey of the role of marrow purging. *Blood* 1990;75:1606-14.
- McMillan AK, Goldstone AH, Linch DC, et al. High-dose chemotherapy and autologous bone marrow transplantation in acute myeloid leukemia. *Blood* 1990;76:480-8.
- Löwenberg B, Verdonck LJ, Dekker AW, et al. Autologous bone marrow transplantation in acute myeloid leukemia in first remission: results of a Dutch prospective study. *J Clin Oncol* 1990;8:287-94.
- Hakami N, Look AT, Steuber PC, et al. Combined etoposide and 5-azacitidine in children and adolescents with refractory or relapsed acute nonlymphocytic leukemia: a Pediatric Oncology Group study. *J Clin Oncol* 1987; 5:1022-5.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:475-81.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc [A]* 1972;135:185-206.
- Ravindranath Y, Abella E, Krischer JP, et al. Acute myeloid leukemia (AML) in Down's syndrome is highly responsive to chemotherapy: experience on Pediatric Oncology Group AML Study 8498. *Blood* 1992;80:2210-4.
- Cassileth PA, Andersen J, Lazarus HM, et al. Autologous bone marrow transplant in acute myeloid leukemia in first remission. *J Clin Oncol* 1993; 11:314-9.
- Burnett AK, Tansey P, Watkins R, et al. Transplantation of unpurged autologous bone-marrow in acute myeloid leukaemia in first remission. *Lancet* 1984;2:1068-70.
- Appelbaum FR, Fisher LD, Thomas ED. Chemotherapy v marrow transplantation for adults with acute nonlymphocytic leukemia: a five-year follow-up. *Blood* 1988;72:179-84.

24. Reiffers J, Gaspard MH, Maraninchi D, et al. Comparison of allogeneic or autologous bone marrow transplantation and chemotherapy in patients with acute myeloid leukaemia in first remission: a prospective controlled trial. *Br J Haematol* 1989;72:57-63.
 25. Schiller GJ, Nimer SD, Territo MC, Ho WG, Champlin RE, Gajewski JL. Bone marrow transplantation versus high-dose cytarabine-based consolidation chemotherapy for acute myelogenous leukemia in first remission. *J Clin Oncol* 1992;10:41-6.
 26. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. *N Engl J Med* 1995;332:217-23.
 27. Stevens RF, Hann IM, Burnett AK, Goldstone AH, Wheatley K, Gray RG. Improved outcome in paediatric acute myeloid leukemia: results of the MRC AML 10 trial. *Med Pediatr Oncol* 1994;23:172. abstract.
 28. Amadori S, Testi AM, Arico M, et al. Prospective comparative study of bone marrow transplantation and postremission chemotherapy for childhood acute myelogenous leukemia. *J Clin Oncol* 1993;11:1046-54.
 29. Woods WG, Koblinsky N, Buckley J, et al. Intensively timed induction therapy followed by autologous or allogeneic bone marrow transplantation for children with acute myeloid leukemia or myelodysplastic syndrome: a Childrens Cancer Group pilot study. *J Clin Oncol* 1993;11:1448-57.
 30. Creutzig U, Harbott J, Sperling C, et al. Clinical significance of surface antigen expression in children with acute myeloid leukemia: results of study AML-BFM-87. *Blood* 1995;86:3097-108.
 31. Woods WG, Koblinsky N, Buckley J, et al. Timing intensive induction therapy improves post-remission outcome in acute myeloid leukemia (AML) irrespective of the use of bone marrow transplantation (BMT). *Blood* 1994; 84:Suppl 1:232a. abstract.
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