Chemotherapy for Induction of Remission of Childhood Acute Myeloid Leukemia Followed by Marrow Transplantation or Multiagent Chemotherapy: A Report From the Childrens Cancer Group

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Purpose: **In an effort to evaluate the usefulness of bone marrow transplantation, the Childrens Cancer Group (CCG) initiated a multiinstitutional study comparing bone marrow transplantation versus chemotherapy after successful induction of remission for previously untreated children and young adults with acute myeloid leukemia.**

Patients and Methods: **From 1979 to 1983, 508 patients were entered onto this study and 490 were treated. After induction, patients with an HLA mixed leukocyte culture (MLC)-compatible sibling underwent bone marrow transplantation. Patients not eligible for bone marrow transplantation were eligible for randomization to two chemotherapy maintenance regimens. All patients undergoing bone marrow transplantation were conditioned with cyclophosphamide and total-body irradiation (TBI). Methotrexate was used to prevent or modify graft-versus-host disease (GVHD).**

Results: **Three hundred eighty-one patients achieved bone marrow remission (78%). Eighty-nine patients had an HLA/MLC-compatible sibling donor and were eligible for bone marrow transplantation, and 252 had no match. Comparison of survival estimates for patients eligible for transplantation versus not eligible at 3 years (52% *v* 41%), 5 years (50% *v* 36%), and 8 years (47% *v* 34%) showed a significant difference in favor of bone marrow transplantation ($P < .05$). Disease-free survival (DFS) demonstrated similar results. Application of a cure model to the results showed a better outcome for those eligible for transplantation ($P = .04$). Patients randomized between the two chemotherapy regimens did not show any significant difference between those treated with a continuous maintenance versus a cyclic regimen ($P = .16$).**

Conclusion: **Children and young adults who successfully achieved a remission with multiple-agent chemotherapy who had an HLA/MLC-compatible donor and were thus eligible for an allogeneic bone marrow transplant had better survival than those not eligible for transplantation.**

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THE CHILDRENS Cancer Group (CCG) initiated a multiinstitutional study (CCG-251) to evaluate the usefulness of marrow transplantation. Comparable results had been reported using combination induction chemotherapy followed by maintenance chemotherapy using alternate drugs in both single-institutional studies[1] and cooperative group studies.[2] The study reported here was the first phase III, multiinstitutional study of bone marrow transplantation in newly diagnosed children and young adults with acute myeloid leukemia (AML). We have previously published the induction results from CCG-251,[3] the correlation of outcome with cytogenetic analyses,[4] and an analysis of the patients who underwent bone marrow transplantation.[5] This report presents the long-term results of the comparison of marrow transplantation to maintenance chemotherapy and the comparison of two maintenance chemotherapeutic regimens. The use of bone marrow transplantation as an alternative method for maintenance of remission in adults with acute myeloid leukemia with an appropriate sibling donor had been pioneered in Seattle by Dr E. Donnall Thomas and associates.[6-8]

PATIENTS AND METHODS

Between September 1979 and October 1983, 508 previously untreated children and young adults (0 to 21 years of age) were entered onto a CCG study (CCG-251) for the treatment of AML. The diagnosis was made in the treatment institutions, based on bone marrow aspirates stained with Wrights or Giemsa, periodic acid–Schiff (PAS), esterase and peroxidase, or Sudan Black stains. Informed consent in accordance with institutional policies approved by the Department of Health and Human Services was obtained on all patients.

Therapy

For induction, all patients were initially treated with 14-day courses of doxorubicin 30 mg/m^2/d intravenously (IV) for 3 days

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and cytarabine (Ara-C) 100 mg/m^2/d by continuous IV infusion for 7 days. A minimum of two courses were administered, with the second course reduced to 5 days of Ara-C and 2 days of doxorubicin if less than 15% blasts were seen in the day-14 marrow sample. Bone marrow aspirations and biopsies were performed on day 14 of each course of therapy. The marrow status at the end of each course was classified as follows: M-1, ≤ 5% blasts; M-2A, 6% to 15% blasts; M-2B, 16% to 39% blasts; and M-3, ≥ 40% blasts.

A final marrow rating was not given to any patient with severe marrow hypocellularity on biopsy or with an absolute neutrophil count (ANC) less than 750/μL or a platelet count less than 75,000/μL. The aspirate and biopsy were repeated at weekly intervals until the cellularity and blood counts recovered.

After two courses of induction therapy, patients with an M-1 marrow were considered to be in remission and moved to maintenance therapy; those with an M-3 marrow were taken off study, and the remainder were given a third course of induction treatment. At day 43, patients with an M-1 marrow proceeded to maintenance; M-2B or M-3 marrow patients were classified as treatment failures; and M-2A patients received a fourth course of induction therapy. After the fourth course, patients with M-1 or M-2A marrows were considered in remission and proceeded to maintenance; all other patients were considered induction failures and were taken off protocol.

Bone Marrow Transplantation

Patients with siblings were HLA-typed, as were the patients' mother, father and all siblings. Mixed leukocyte cultures (MLC) were performed after the patient was in remission and there were adequate lymphocytes in the peripheral blood. Patients were considered eligible for transplantation if a sibling was genotypically HLA-A and -B identical and MLC nonreactive with the patient. Patients not eligible for bone marrow transplantation because an appropriately matched donor marrow was unavailable, but who achieved a bone marrow remission (M-1 or M-2A), were eligible for randomization to two chemotherapeutic maintenance regimens (see Chemotherapy Randomization and Table 1). Once eligible for bone marrow transplantation, patients were to be immediately referred to a bone marrow transplantation center. If a bed was not immediately available, patients were treated with an interim therapy of Ara-C 50 mg/m^2 subcutaneously (SC) on days 5, 12, and 19, and thioguanine 60 mg/m^2/d orally on days 1 through 4 and 8 through 11.

All patients undergoing bone marrow transplantation were conditioned with cyclophosphamide (60 mg/kg/d) IV for 2 days, followed by total-body irradiation (TBI), either 8 to 10 Gy delivered at .05 to 0.1 Gy per minute or 7.5 Gy delivered at .26 Gy per minute. For TBI, the prescription point was the midpoint of the body at the level of the umbilicus. The prescribed dose was to fall within the range of 7.5 to 10 Gy. The dose inhomogeneity relative to the selected prescription dose and for points along the patient axis was not to deviate by greater than ± 10%. Methotrexate was used to prevent or modify the development of acute graft-versus-host disease (GVHD): 15 mg/m^2 IV on day +1 and 10 mg/m^2 IV on days +3, +6, +11, +18, and then weekly from day 18 through day 102.

Supportive care, including patient isolation procedures, methods of enteric decontamination, use of systemic antimicrobial therapy, use of central venous catheters, indications for blood product support, and treatment of GVHD, was performed according to institutional preference, and was not prescribed in the protocol. All blood products were irradiated using a minimum of 15 Gy.

Chemotherapy Randomization

All patients who achieved a bone marrow remission but did not have an HLA/MLC-compatible sibling donor or who for other reasons did not participate in the bone marrow transplant regimen were first given a course of CNS prophylaxis. This consisted of 18 Gy cranial irradiation combined with intrathecal (IT) methotrexate on days 1, 8, and 15. Concurrent with the CNS radiation, patients received chemotherapy consisting of oral thioguanine 60 mg/m^2 on days 1 through 5 and Ara-C SC on days 5, 12, and 19. IT methotrexate was administered on day 1 of the first four courses of maintenance regimen no. 1 and in the cyclic regimen on the first day of the first four cycles.

Table 1. Maintenance Regimen

Regimen No.	Drug Dosage and Rate	Days Given	Course Length (days)
1 (continuous)	Vincristine 1.5 mg/m^2	1	28
	Thioguanine 75 mg/m^2 orally	1-28	
	Ara-C 75 mg/m^2 IV	1-4	
	Azacitidine 50 mg/m^2 IV every 12 hours	1-4	
	Cyclophosphamide 25 mg/m^2 IV every 8 hours	1-4	
2 (cyclic)	Ara-C 100 mg/m^2 IV	1-5	21
	Doxorubicin 30 mg/m^2 IV*	1	
	Vincristine 2 mg/m^2 IV	1	21
	Methotrexate 7.5 mg/m^2 IV	1-4	
	Mercaptopurine 500 mg/m^2 orally	1-4	
	Prednisolone 1 g/m^2 IV	1-4	
	Azacitidine 150 mg/m^2 IV	1-5	28
	Doxorubicin 30 mg/m^2 IV*	1	
	Cyclophosphamide 1 g/m^2 IV	1	21
	BCNU 200 mg/m^2 IV	1	
	Ara-C 50 mg/m^2 SC	5	7
	Thioguanine 60 mg/m^2 orally	1-4	

*Daunorubicin substituted in March 1981.

Following CNS prophylaxis, patients were eligible for randomization between two maintenance programs (regimens no. 1 and 2; see Table 1 for doses and schedules). Regimen no. 1 (continuous) consisted of continuous thioguanine with monthly courses of cyclophosphamide, vincristine, azacitidine, and Ara-C. This regimen was taken from the best arm of the CCG's prior reported experience with maintenance therapy for AML.[9] Regimen no. 2 (cyclic) consisted of repeated cycles of thioguanine and Ara-C; doxorubicin and Ara-C; prednisolone, vincristine, methotrexate, and mercaptopurine; azacitidine and doxorubicin; and carmustine (BCNU) and cyclophosphamide. This maintenance regimen was derived from non-CCG studies and was patterned in part after the vincristine, doxorubicin, prednisone, and Ara-C (VAPA) protocol used at the Dana-Farber Cancer Center.[10]

Therapy Modifications

Induction. In November 1980, as a result of greater than expected induction mortality for children less than 3 years of age, drug doses for these children were reduced and changed from a surface-area basis to a dose based on body weight: Ara-C 3.3 mg/kg and doxorubicin 1.0 mg/kg. This modification reduced doses of all drugs by a factor of 1.3 to 2.0 for children under age 3. In March 1981, daunorubicin was substituted for doxorubicin because of concerns over a high incidence of gastrointestinal toxicity. One hundred fifty-two assessable patients received doxorubicin, including seven who received daunorubicin as well, and 338 received daunorubicin. Of the 141 children under the age of 3 years, 35 received doxorubicin

(30 mg/m^2), nine received doxorubicin (1 mg/kg), and 97 received daunorubicin (1 mg/kg). Children aged 3 years and older received 30 mg/m^2 of daunomycin.

Maintenance therapy. In July 1982, a decision was made to change the length of therapy for all patients randomized to receive maintenance chemotherapy from 3 years to 2 years from the beginning of maintenance therapy. Patients who experienced an isolated extramedullary relapse were eligible for discontinuation of therapy as long as they had achieved 2 years of continuous complete remission after their isolated extramedullary relapse.

Observations and Quality Control

Pretreatment evaluation included chromosomal analysis using an unstimulated bone marrow specimen, lumbar puncture to detect CNS involvement, blood urea nitrogen, uric acid, AST, ALT, and alkaline phosphatase, urinalysis, and cardiac evaluation including chest x-ray, ECG, and echocardiogram. Bone marrow aspirations and biopsies were performed every 112 days for those on chemotherapy and at day 100 and every 3 months for the first 2 years for those receiving bone marrow transplantation.

Statistical Methods

The significance of observed differences in proportions was tested using the χ^2 statistic and, when appropriate for small sample size, Fisher's exact test. Survival comparisons were based on the log-rank statistic.[11] Survival, disease-free survival (DFS), and time to relapse were measured from the day of transplant, and estimates were calculated using the product-limit method. Standard errors for these estimates were calculated using Greenwood's formula, and 95% confidence intervals (CIs) were calculated as the point estimate plus and minus 1.96 times the standard error. DFS was defined as the time to relapse or death from any cause. Time to relapse, which was used to estimate the relapse rate, was defined as the time from transplant or onset of maintenance therapy to a marrow relapse, censoring at time of death for patients who did not relapse.

Initial comparisons between groups for time-related outcomes were based on the log-rank statistic. Since death in the bone marrow transplantation arm tended to occur soon after the transplant, the hazard functions for the transplant and chemotherapy regimens were not proportional and the log-rank statistic may not be the best way to measure outcome differences. For these comparisons, we used a cure model[12] that estimates and compares the proportion that remain free of adverse events after prolonged follow-up (ie, a plateau value).

Assessment of the potential benefit for bone marrow transplantation was made by comparing all patients eligible for bone marrow transplant (because they had an HLA/MLC-compatible sibling donor) whether they received a transplant or not. This generated a form of biologic randomization, since allocation to a treatment group was dependent on the random segregation of HLA alleles into siblings of the patient. The only potential confounder was sibship size, which obviously influenced the probability of finding a match, but since sibship size has never been suggested as a prognostic factor for acute myeloid leukemia, we felt that the potential for bias from this source would be minimal.

RESULTS

Figure 1 outlines the number of patients on this study who reached the major end points of the study design. By October 1983, 508 previously untreated children and young adults, age 21 or younger with acute myeloid leukemia, were entered onto the study. Of the 508 eligible patients, 490 were assessable. Characteristics of these 490 patients are listed in Table 2. Three hundred eighty-one patients achieved a bone marrow remission (78%). Eighty-nine patients (23%) were determined shortly after diagnosis to have an HLA/MLC-compatible sibling donor, and 252 patients had no match. In 40 patients, the match status was either not determined or the data are unknown. The overall survival rate for the 490 eligible patients entered onto the study was 33% (95% CI, 29% to 37%) at 5 years and 31% (95% CI, 27% to 35%) at 8 years.

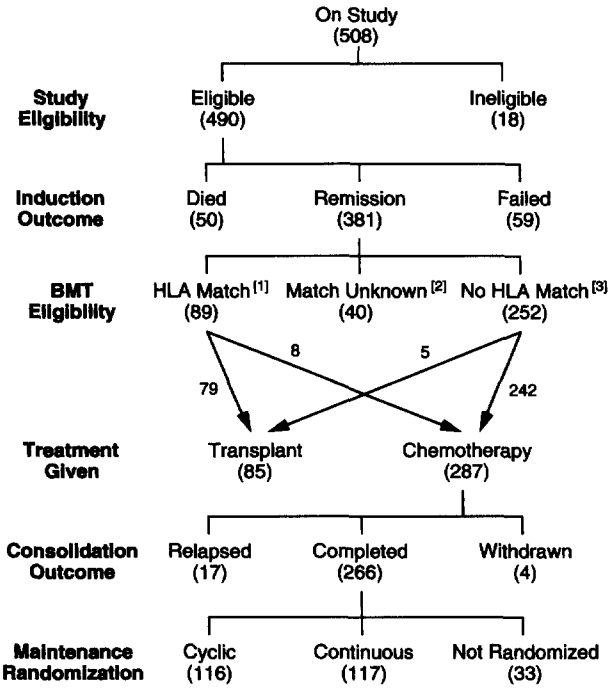

Fig 1. Flow chart shows the number of cases reaching major milestones or end points in the study. [1] Two patients were withdrawn from study; [2] 1 patient was transplanted, 37 received chemotherapy, and 2 were withdrawn; [3] 5 patients were withdrawn from study.

Induction

Of 490 assessable patients, 381 (78%) achieved a bone marrow remission. These results were previously reported.[8] Three hundred twenty-eight (67%) obtained an M-1 marrow after a minimum of two induction courses. A further 44 went into remission after a third course and nine after a fourth course.

For children under 3 years of age at diagnosis, the change from doxorubicin to daunorubicin combined with dose reduction improved the induction success (66% *v* 88%; $P = .05$) and reduced the death rate from 29% to

Table 2. Comparison of Patient Characteristics Enrolled in CCG-251

Presenting Characteristic	Induction		Postinduction			
	Doxorubicin (n = 152)	Daunorubicin (n = 338)	Matched (n = 89)	Unmatched (n = 252)	Continuous (n = 117)	Cyclic (n = 116)
Sex						
Male	83	169	50	124	55	57
Female	69	169	39	128	62	59
Age, years						
< 8	85	192	43	151	66	71
> 8	67	146	46	101	51	45
Initial WBC count ($\times 10^9$/L)						
< 20	94	186	61	149	74	58
> 20	58	152	28	103	43	58
Pathology						
AML/AGL	94	173	48	147	77	61
AMMOL	31	87	30	52	21	30
AEL	0	7	0	6	1	4
AMOL	18	49	6	38	13	17
APL	9	22	5	9	5	4

Abbreviations: AGL, acute granulocytic leukemia; AMMOL, acute myelomonocytic leukemia; AEL, acute erythroleukemia; AMOL, acute monocytic leukemia; APL, acute promyelocytic leukemia.

1% ($P < .0001$). For the older children (> 3 years), the change to daunorubicin from doxorubicin did not change remission success (78% *v* 76%), but did reduce the death rate from 15% to 8% ($P = .09$). Comparison of long-term follow-up by the type of anthracycline shows the superiority of daunorubicin over doxorubicin ($P = .06$) (Fig 2). The difference is entirely explained by the difference in the death rates in the first 3 months of treatment.

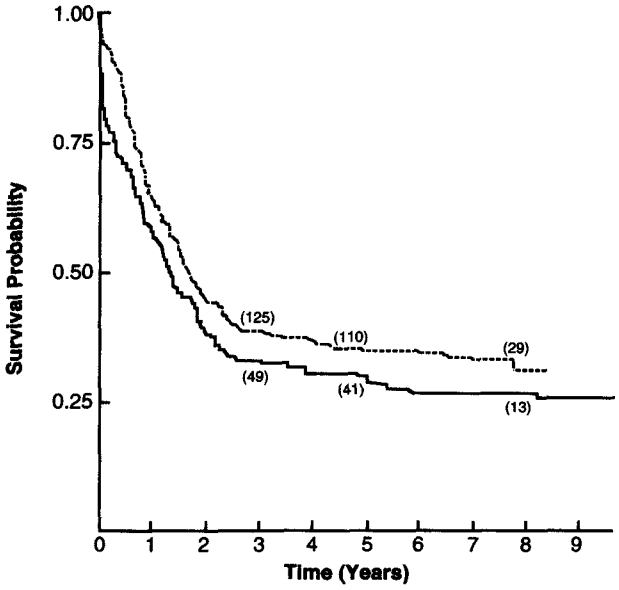

Fig 2. Kaplan-Meier estimates of the probability of survival of patients who achieve a remission given doxorubicin (——, N = 152), compared with those patients given daunorubicin (– – –, N = 338). $P = .06$.

The overall survival rate for the 381 patients who were successfully induced was 40% (95% CI, 35% to 45%) at 5 years and 38% (95% CI, 33% to 43%) at 8 years.

Survival According to Bone Marrow Transplant Eligibility

Characteristics of the patients eligible for marrow transplant (matched) and not eligible (unmatched) are listed in Table 2. No significant differences in patient characteristics were observed between these two groups. Forty-two of the 89 patients with a match and eligible for bone marrow transplantation remain alive with a median follow-up duration of 5 years. Eighty-eight of the 252 without an HLA match remain alive (Fig 3).

Long-term outcome for patients eligible for bone marrow transplantation is superior to that for those without a matched sibling donor, although the difference was not significant by the log-rank test ($P = .25$). This reflects the fact that the hazard was very high during the first year of the intensive transplant arm and then dropped sharply, leading to a crossing over of the survival curves (Fig 3). This pattern of failures substantially reduces the power of the log-rank test to detect differences in overall survival. Examination of the timing of events in the two groups shows a striking difference. Thirty-six of the 89 children (40%) at risk in the matched group had a relapse or died in the first year, and 110 of 252 of the unmatched group (44%) experienced such events. However, in year 2, seven of 53 of the matched group (13%) and 43 of the unmatched 142 (30%) experienced an adverse event.

Comparison of survival estimates at single time points for patients eligible for transplant versus not eligible at

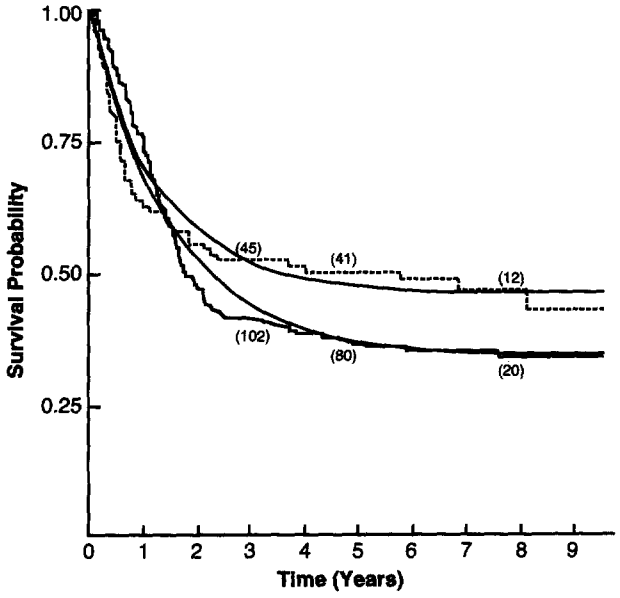

Fig 3. Survival from end of induction, for those achieving a complete remission, comparing patients eligible for transplant (- - -, N = 89) with those who were not (——, N = 252). Fitted cure-model curves are plotted for each group. P = .04.

3 years (52% *v* 41%), 5 years (50% *v* 36%), and 8 years (47% *v* 34%) showed significant differences ($P < .05$).

A potentially more powerful method of comparing the long-term results of bone marrow transplantation to maintenance chemotherapy is to use a cure-model statistical analysis. Application of this method of analysis showed a significantly better outcome ($P = .04$) for those children with a matched sibling donor (Figure 3).

DFS results (Fig 4) comparing patients eligible for bone marrow transplant versus chemotherapy demonstrate a similar superiority of bone marrow transplantation over chemotherapy. An estimated 48% (95% CI, 37% to 58%) of patients eligible for bone marrow transplantation were disease-free at 3 years, compared with 36% (95% CI, 30% to 42%) for those on chemotherapy ($P < .05$). Similar estimation at 5 and 8 years showed DFS rates of 45% versus 33% and 45% versus 32%, respectively ($P < .05$ for both comparisons). Application of the cure model to these data also showed a better outcome for bone marrow transplantation patients ($P = .04$). When these analyses were repeated comparing bone marrow transplantation with the best of the two maintenance regimens, there was no change in the overall results.

Survival by Treatment Received

When treatment results were compared using the therapy patients actually received, the estimates of survival and DFS and *P* values (log-rank) were similar to those presented comparing matched versus unmatched patients. Of the 85 patients who actually received a bone marrow transplant, 39 are alive, compared with 106 of 287 who received CNS prophylaxis (log-rank $P = .42$). Comparing survival estimates at single time points for those transplanted versus not transplanted at 3 years (52% *v* 43%), 5 years (49% *v* 38%), and 8 years (46% *v* 35%) demonstrated a significant superiority for transplanted patients ($P < .05$). However, the cure-model comparison was not significant, as was the case with the log-rank method.

GVHD and Relapse After Bone Marrow Transplantation

Thirty-eight of 82 patients (46%) who received a bone marrow transplant and had data available on GVHD developed acute GVHD. Survival was clearly superior for those without GVHD (Fig 5). The risk of relapse was estimated as 33% (95% CI, 20% to 48%) at 8 years (Fig 6). Although most of the relapses occurred before 4 years, there was one relapse at 8 years. A more detailed analysis of transplant factors for these patients has been reported previously.[8]

Maintenance Randomization

Two hundred eighty-seven children and young adults who achieved a bone marrow remission and did not have an HLA/MLC-compatible sibling donor or agree to the bone marrow transplantation underwent CNS prophylaxis consisting of cranial radiation and IT methotrexate. Two

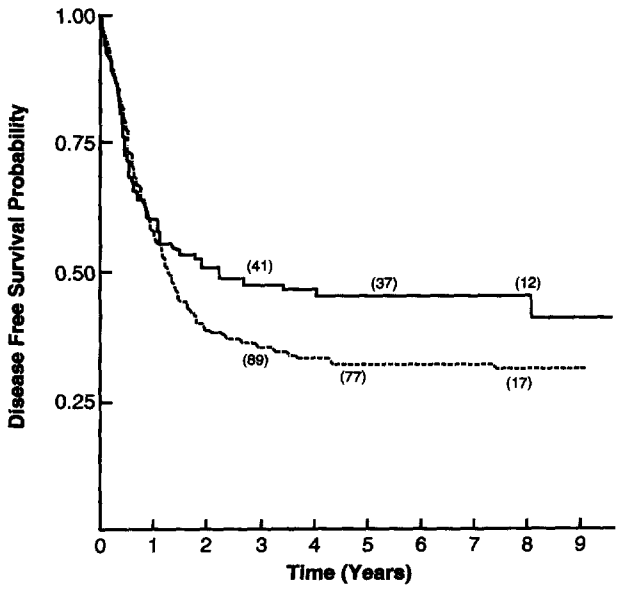

Fig 4. DFS from end of induction, for those achieving a complete remission, comparing patients given transplant (N = 85) with those not transplanted (N = 287). P = .12 (log-rank).

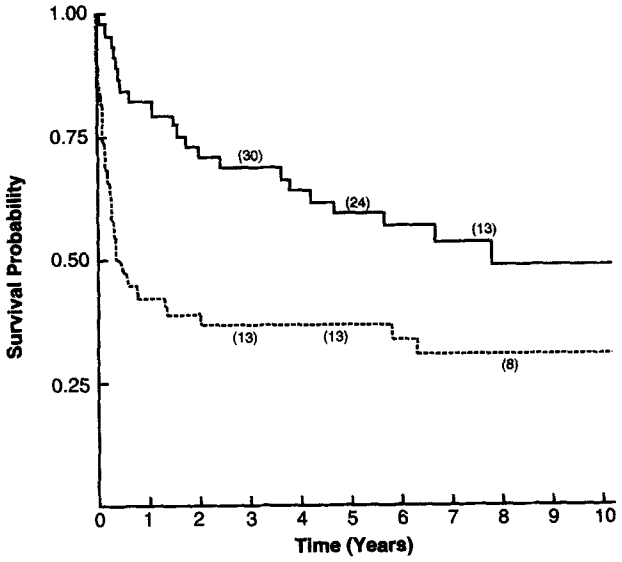

Fig 5. Comparison of survival following transplantation for those with (——, N = 39) and without (– – –, N = 42) acute GVHD.

hundred thirty-three were then randomized to receive one of the two maintenance chemotherapeutic programs. One hundred sixteen were randomized to receive the cyclic regimen consisting of the cyclic reinduction of daunorubicin and Ara-C; prednisone, vincristine, methotrexate, and mercaptopurine (POMP); azacitidine and daunorubicin; BCNU and cyclophosphamide; and thioguanine and Ara-C; 117 were randomized to continuation maintenance (Table 2). All of the patients were continued on

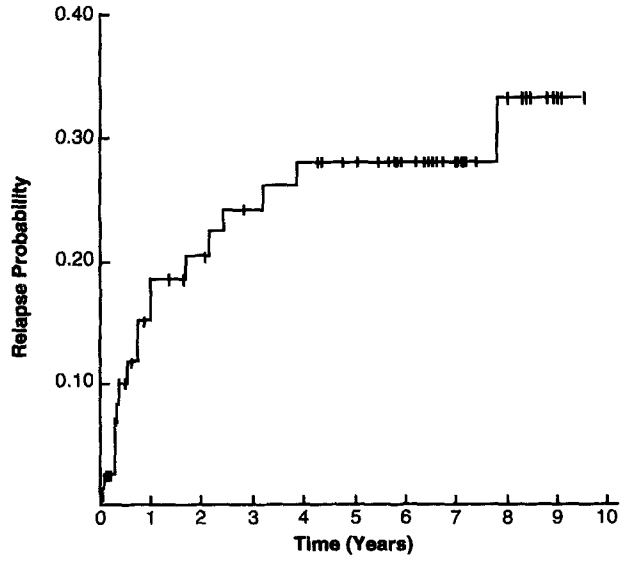

Fig 6. Probability of relapse for 85 patients who received a bone marrow transplantation.

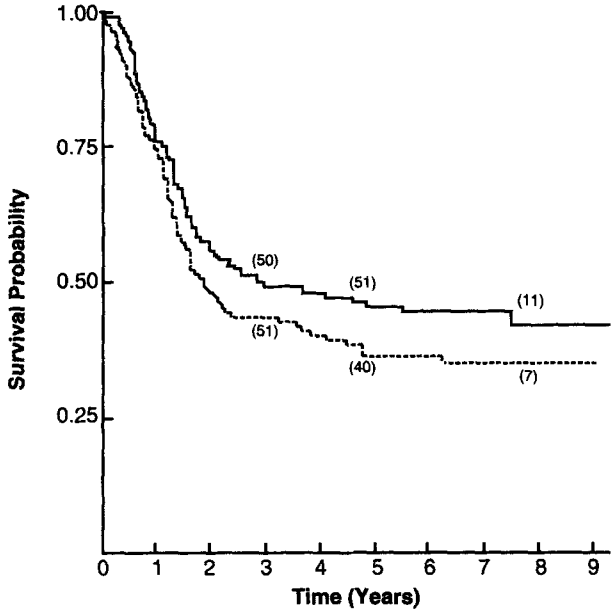

Fig 7. Comparison of survival from end of consolidation for those given cyclic (– – –, N = 116) and continuous (——, N = 117) maintenance chemotherapy. $P = .16$.

maintenance treatment for 2 years. Table 2 compares the maintenance chemotherapy treatment groups by sex, age at diagnosis, initial WBC count, and pathologic diagnosis. There were no significant differences observed between these two chemotherapy regimens. Although survival of patients randomized to the continuous regimen was somewhat superior to that on the cyclic regimen, this difference was not statistically significant ($P = .16$; Fig 7). At 5 years, the survival rate in the continuous regimen was 45% (95% CI, 36% to 54%) versus 37% (95% CI, 28% to 36%) in the cyclic regimen.

For DFS, the results were similar, showing a superiority for the continuous regimen that was not statistically significant ($P = .2$). At 3 and 5 years, patients on the continuous regimen had DFS rates of 44% (95% CI, 35% to 53%) and 42% (95% CI, 33% to 51%), respectively, as compared with 38% (95% CI, 29% to 47%) and 34% (95% CI, 25% to 43%) for those on the cyclic regimen.

The relapse rate was higher for chemotherapy-treated patients ($P < .0001$), but the mortality risk from causes other than relapse was higher among transplanted patients. Nonrelapse mortality among transplanted patients was almost entirely due to GVHD and its infectious complications. Mortality among transplant recipients was about equally due to relapse and other causes.[13]

DISCUSSION

At the time this study started in 1979, the appropriate strategy for the treatment of children with newly diag-

nosed acute myeloid leukemia had not been determined. This study was designed to assess the efficacy of an induction regimen and to test the role of marrow transplantation as compared with intensive chemotherapy after the achievement of a complete response.

Remission induction rates with Ara-C, an anthracycline, or azacitidine before this study had been in the range of 30% to 45% with the drugs administered singly.[14-16] Combinations of Ara-C plus an anthracycline had been tested in a large adult cooperative group, with 60% to 70% induction rates.[17] In the present study, 78% of patients achieved a complete remission. The timing and number of subsequent courses of induction were determined by the results of scheduled marrow biopsies; this strategy clearly improved the management of these patients during induction. Because of the unacceptable toxicity in the patients, especially under the age of 3 years, we replaced the doxorubicin with daunorubicin and changed the dosing in those under age 3 years from per square meter to per kilogram weight. The major improvement seen from these changes was a reduction of mortality from 29% to 10% for children younger than age 3 years and a reduction from 18% to 8% for children older than 3 years. This combination of 7-day infusion of Ara-C and 3 days of daunorubicin thus became the CCG standard induction regimen for children and young adults with newly diagnosed AML[18].

This study also compared two intensive maintenance regimens. The chemotherapy regimens used were designed to determine whether the use of a cyclic therapy patterned after the VAPA protocol of Dana-Farber Cancer Institute[10] using different antimetabolites was superior to a continuous maintenance regimen that was the best therapy from our previous studies.[9] The cycles used in cyclic maintenance were derived from the VAPA regimen and also from two adult studies using oral thioguanine and Ara-C[19] and BCNU and cyclophosphamide.[20] The data suggest that the cyclic regimen was slightly less effective than the continuous regimen. These maintenance results are similar to others reported recently for children with acute myeloid leukemia.[21,22] The results show that the continuous regimen compares favorably with other more intensive maintenance therapies or consolidation protocols. Although there are still some late relapses on both maintenance treatments, most relapses occur before 5 years. Only two relapses (one in each regimen) were seen after 5 years.

The major reason for undertaking this study was to determine whether survival for children and young adults undergoing an allogeneic bone marrow transplant from an HLA/MLC-compatible sibling was superior to that of patients receiving the best chemotherapy then available. Most studies that report results with bone marrow transplantation have inherent biases, because it is difficult to find an appropriate control group of chemotherapy-treated patients. These biases were eliminated in this study by comparing transplant-eligible patients (those with a sibling who was HLA-compatible) to those nontransplant-eligible (those without an HLA-compatible sibling). While the assignment to bone marrow therapy was not randomized, normal Mendelian inheritance ensures that the probability of an HLA match is dependent only on the number of available siblings and not on any patient characteristics. Thus, the strength of inference in comparing the results in the transplant (eligible versus nontransplant eligible) is much greater than for most observational data analyses. At 8 years, the percent surviving in the matched patient group is 47%, compared with 34% in the HLA-unmatched patient groups. Comparisons using log-rank statistics do not accurately reflect the differences, because of the early mortality due to GVHD and its sequelae in the bone marrow transplantation arm, and because the cure model, which indicated a significantly superior outcome ($P = .04$) for those in the transplant arm, is more powerful.

More recent studies have addressed the question of whether bone marrow transplantation is the treatment of choice for children and young adults in first remission.[22-24] The study reported here, which first introduced bone marrow transplantation into a pediatric cooperative clinical trial program, clearly demonstrates that those children and young adults in first remission who have an HLA/MLC-compatible donor for bone marrow transplantation have a better than 45% chance of long-term DFS. Studies reported by Appelbaum et al[22] from Seattle and Dahl et al[23] from St Jude, with median follow-up durations of 5 years or more, support the contention that bone marrow transplantation is superior to chemotherapy for patients with acute myeloid leukemia in first remission. A recent report, with shorter follow-up, by Blaise et al[25] confirms the advantage of bone marrow transplantation and points out the importance of prospective randomized trials. Different preparative regimens for bone marrow transplantation and better ways of decreasing GVHD will need to be evaluated in similar cooperative group trials and compared with optimal chemotherapeutic programs to determine the best approach to the treatment of these children and young adults.

APPENDIX: Participating Principal CCG Investigators

Institution	Investigator	Grant No.
Group Operations Office, University of Southern California Comprehensive Cancer Center, Los Angeles, CA	Denman Hammond, MD Harland Sather, PhD Mark Krailo, PhD Jonathan Buckley, MBBS, PhD Madeline Bauer, PhD Daniel Stram, PhD Jae Won Lee, PhD	CA 13539
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University of North Carolina, Chapel Hill, NC	Herbert Cooper, MD	—
University of Medicine and Dentistry of New Jersey, Camden, NJ	Milton Donaldson, MD	—
Children's Mercy Hospital, Kansas City, MO	Arnold Freeman, MD	—
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