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CHEMOTHERAPY COMPARED WITH AUTOLOGOUS OR ALLOGENEIC BONE MARROW TRANSPLANTATION IN THE MANAGEMENT OF ACUTE MYELOID LEUKEMIA IN FIRST REMISSION

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ABSTRACT

Background In young adults with acute myeloid leukemia, intensive chemotherapy during the initial remission improves the long-term outcome, but the role of bone marrow transplantation is uncertain. We compared high-dose cytarabine with autologous or allogeneic marrow transplantation during the first remission of acute myeloid leukemia.

Methods Previously untreated adolescents and adults 16 to 55 years of age who had acute myeloid leukemia received standard induction chemotherapy. After complete remission had been achieved, idarubicin (two days) and cytarabine (five days) were administered. Patients with histocompatible siblings were offered allogeneic marrow transplantation, whereas the remaining patients were randomly assigned to receive a single course of high-dose cytarabine or transplantation of autologous marrow treated with perfosfamide (4-hydroperoxycyclophosphamide). Oral busulfan and intravenous cyclophosphamide were used as preparative regimens for both allogeneic and autologous marrow transplantation. The end points were survival from the time of complete remission and disease-free survival.

Results In an intention-to-treat analysis, we found no significant differences in disease-free survival among patients receiving high-dose chemotherapy, those undergoing autologous bone marrow transplantation, and those undergoing allogeneic marrow transplantation. The median follow-up was four years. Survival after complete remission was somewhat better after chemotherapy than after autologous marrow transplantation ($P=0.05$). There was a marginal advantage in terms of overall survival with chemotherapy as compared with allogeneic marrow transplantation ($P=0.04$).

Conclusions A postinduction course of high-dose cytarabine can provide equivalent disease-free survival and somewhat better overall survival than autologous marrow transplantation in adults with acute myeloid leukemia. (N Engl J Med 1998;339:1649-56.)

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THE rate of complete remission for adults with acute myeloid leukemia is approximately 65 percent overall and decreases with increasing age and the presence of unfavorable cytogenetic abnormalities.^{1,2} With postremission therapy, disease-free survival at five years ranges from 10 to 15 percent with low-dose maintenance therapy^{2,3} to 25 to 35 percent with intensive courses of chemotherapy, usually incorporating high-dose cytarabine.⁴⁻⁶ In young patients, further escalation of postremission therapy is feasible, provided autologous or allogeneic hematopoietic stem cells can be transplanted to repopulate the ablated bone marrow. Despite the complications of graft-versus-host disease, a number of studies suggest that long-term outcome is improved by allogeneic marrow transplantation during the first complete remission.⁷⁻¹⁰ Similarly, despite the potential risk of reinfusing leukemic cells during autologous marrow transplantation, both nonrandomized¹¹⁻¹⁴ and randomized^{15,16} studies have reported better long-term disease-free survival after autologous transplantation than after conventional chemotherapy. Other studies of adults^{10,17} and children,^{18,19} however, have failed to confirm improvement with autologous marrow transplantation. The unresolved question of what constitutes optimal therapy in adults

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with acute myeloid leukemia in the first complete remission led the Eastern Cooperative Oncology Group (ECOG), the Southwest Oncology Group (SWOG), and the Cancer and Leukemia Group B (CALGB) to conduct an intergroup study of postremission therapy. We assigned patients with histocompatible siblings to allogeneic marrow transplantation and randomly assigned the remaining patients to high-dose cytarabine or autologous marrow transplantation.

METHODS

Patients and Therapies

The study opened in February 1990 and closed in February 1995. The data were analyzed as of August 1997. Eligible patients were 16 to 55 years old and had untreated acute myeloid leukemia of French–American–British (FAB) types M0 to M7,^{20,21} confirmed by centralized review of the bone marrow morphology and cytochemistry, immunophenotyping, and karyotype analysis. Eligibility required the absence of any illness that would preclude the possibility of subsequent marrow transplantation, adequate renal and hepatic function, no uncontrolled infection, a normal cardiac ejection fraction, and signed informed consent. Induction therapy consisted of idarubicin (12 mg per square meter of body-surface area per day given intravenously for three days) and intravenous cytarabine (25 mg per square meter, followed by 100 mg per square meter per day, infused continuously for seven days). Bone marrow obtained by aspiration and biopsy was evaluated on day 14; if residual leukemic blasts were seen, a second identical course of chemotherapy was administered. Patients in whom complete remission did not occur after one or two courses of therapy were withdrawn from the study. After recovery from the toxic effects of induction therapy and before randomization, all patients in complete remission received another course of induction therapy at the same daily doses, but with only two days of idarubicin and five days of cytarabine. To proceed with scheduled therapy or randomization, patients had to be in complete remission and have no lingering complications of prior chemotherapy, a normal cardiac ejection fraction, good performance status, adequate hepatic and renal function, no persistent infection requiring treatment with antibiotics, and no evidence of central nervous system leukemia. After complete remission, and during or after the consolidation phase, the availability of histocompatible donors was evaluated. Patients with a genotypically or phenotypically HLA-matched or single-antigen–mismatched family member who was available to serve as a donor were offered allogeneic marrow transplantation. Randomization to autologous marrow transplantation or high-dose cytarabine therapy was stratified according to age (≤ 45 vs. > 45 years), FAB type (M1, M2, M3, or M4 vs. M0, M5, M6, or M7), the number of courses of induction therapy administered to achieve complete remission (one vs. two), and karyotype category — favorable: t(8;21), t(15;17), or inv(16); intermediate: normal or having a single numerical abnormality other than those classified as unfavorable; or unfavorable: 5q-, -5, 7q-, -7, abnormalities of chromosome 9 or 11, or three or more clonal abnormalities.²² The randomization scheme was based on permuted blocks within strata and additional balancing within institutional sites.

For patients who were to receive autologous marrow transplantation, harvesting of bone marrow stem cells and perfosfamide (4-hydroperoxycyclophosphamide) treatment before cryopreservation were accomplished with published techniques.^{14,23,24} The protocol specified that high-dose cytarabine or marrow transplantation was to begin within three months after the beginning of complete remission, but longer delays were permitted to allow patients to fulfill eligibility requirements for this step. These criteria were applied uniformly in all postremission therapy groups. Patients randomly assigned to high-dose cytarabine received a single course of cytarabine consisting of 3 g per square meter infused intravenously over a 3-hour period every 12 hours for 12 doses.

The preparative regimen for both autologous and allogeneic marrow transplantation consisted of busulfan at a dose of 1 mg per kilogram of body weight given orally every six hours over four days (16 doses) on days -9 through -6 and cyclophosphamide at a dose of 50 mg per kilogram given intravenously over a one-hour period daily for four days on days -5 through -2. Bone marrow cells were reinfused on day 0. Prophylaxis against graft-versus-host disease was not specified, but a limited range of permissible options was defined. Complete remission and relapse were defined according to standard criteria.²⁵

Statistical Analysis

Disease-free survival was defined as the time between documented complete remission and relapse or death from any cause. Assignment to allogeneic marrow transplantation was made at the study site when a suitable donor was available. The time from the assignment of a patient to notification of the coordinating center varied widely, as compared with the timely reporting of patients to be randomly assigned to high-dose cytarabine or autologous marrow transplantation. To avoid any bias that this difference might introduce in comparing the three postremission therapies, survival was measured from the time of documented complete remission for all patients. Although data on allogeneic marrow transplantation are presented and analyzed, patients were assigned to this treatment on the basis of donor availability rather than by randomization. Therefore, the primary comparison of interest, defined at the outset of the trial, was that between the two randomly assigned postremission therapies, autologous marrow transplantation and high-dose cytarabine.

Because long-term cure occurs in a small subgroup of patients with this disease, the study was designed according to a Berkson–Gage cure-rate model.²⁶ Accrual and follow-up goals were set to provide the study with at least 80 percent power to detect a 50 percent increase in the cure rate and a 50 percent increase in median disease-free survival among the patients destined to relapse, with the use of a generalized Wilcoxon 5 percent two-sided test.²⁷ The study design called for a total of approximately 130 patients randomly assigned to each of the two therapies — autologous marrow transplantation and high-dose cytarabine — with 180 relapses expected in order to achieve the desired power. The protocol provided for interim analyses after every 45 relapses, or at 25 percent increments in the available data on the end point of disease-free survival. Interim analyses used an O'Brien–Fleming boundary²⁸ to determine critical values for interim significance tests. The study was unblinded at the third interim analysis, when it became apparent that the anticipated differences in disease-free survival would not emerge, and that significant differences in survival existed between the groups.

For time-to-event comparisons for outcomes other than the main end point, the log-rank statistic²⁹ was used for purposes of comparability with the literature. In survival and disease-free survival curves, all patients who were eligible for initial study entry who had a documented complete remission were analyzed on an intention-to-treat basis, according to the treatment assigned after remission, regardless of whether they received the intended therapy. Survival and disease-free survival curves were estimated by the method of Kaplan and Meier.³⁰ The independence of row and column effects in contingency tables was tested with either Fisher's exact test or exact methods for ordered categorical data.³¹

RESULTS

Accrual of Patients

Of the 808 patients who entered the study, 36 were ineligible because they were given the wrong diagnosis, the cardiac ejection fraction was low or unmeasured, slides were not submitted for central review, or follow-up data were missing. Of the remaining 772 patients, 32 could not be evaluated: 19 because com-

plete remission was not documented, 7 because of missing follow-up data, 5 because the patient withdrew before completing therapy, and 1 because central nervous system leukemia was detected shortly after entry. Thus, 740 of the 808 patients (92 percent) were eligible for induction therapy.

Induction Therapy

Of the 740 patients who were eligible for induction therapy, 518 (70 percent) had a complete remission, with no significant differences among the various FAB subtypes. Eighty percent of the remissions occurred after a single course of induction therapy, and the frequency of deaths related to the induction therapy was 7 percent. Centralized review yielded data on karyotypes that could be evaluated for 572 patients (77 percent). The three karyotype subgroups correlated with the likelihood of complete remission: 83 percent for the favorable types, 74 percent for the intermediate category, and 56 percent for unfavorable karyotypes ($P < 0.001$). The rate of complete remission was essentially the same for all patients whose karyotypes were successfully determined and for those whose karyotypes were unknown, suggesting no selection bias due to unidentified karyotypes.

Initial postremission therapy (two days of idarubicin plus five days of cytarabine) was associated with neutropenia (defined as < 500 granulocytes per cubic millimeter) lasting three weeks; patients with this complication virtually always required hospitalization for febrile neutropenia, but there were no deaths.

Of the 518 patients who entered a complete remission, 172 were removed from the study before randomization or assignment to postremission therapy. The principal causes were refusal to continue in the study, persistent medical problems after induction therapy, and relapse before randomization. This group did not differ in the distribution of karyotype categories from the 346 patients who remained in the analysis of postremission therapy (data not shown).

Postremission Therapy

The 4-year survival rate, estimated from study entry, among all 740 eligible patients who could be evaluated was 35 percent; the median survival was 19 months. The number of patients randomly assigned to each therapy (high-dose cytarabine or autologous marrow transplantation) was approximately the same as the number assigned to allogeneic marrow transplantation (Table 1). No significant differences among

TABLE 1. CHARACTERISTICS OF PATIENTS ASSIGNED TO POSTREMISSION THERAPY.

CHARACTERISTIC	HIGH-DOSE CYTARABINE*	AUTOLOGOUS BONE MARROW TRANSPLANTATION*	ALLOGENEIC BONE MARROW TRANSPLANTATION†
No. of patients	117	116	113
Time from complete remission to postremission therapy — wk‡			
Median	12.4	14.6	14.1
Range	1.3–20.7	4–27	4–44
Removed from study or data missing — no.	3	4§	6
Refused postremission therapy — no.	5	21	3
Relapsed before receiving postremission therapy — no.¶	2	15	9
Inadequate marrow stem-cell harvest — no.		9	
Insurance coverage refused — no.		3	2
Medical complications prevented postremission therapy — no.	1	1	1
Received intended postremission therapy — no. (%)	106 (91)	63 (54)	92 (81)
Karyotype category according to prognosis — no. (%)			
Favorable (n=67)	23 (20)	27 (23)	17 (15)
Intermediate (n=132)	42 (36)	38 (33)	52 (46)
Unfavorable (n=64)	21 (18)	21 (18)	22 (19)
Unknown (n=83)	31 (26)	30 (26)	22 (19)

*Patients were randomly assigned to therapy.

†Patients were assigned to therapy on the basis of the availability of a suitable donor.

‡Times were calculated only for patients who started therapy.

§Although they were in complete remission after induction therapy as defined by the study criteria, two of these four patients were removed from the study because a clonal karyotype abnormality was detected, and two others underwent autologous bone marrow transplantation at a nonparticipating facility.

¶All of these relapses occurred within one to five months after complete remission (median, three months).

these three groups were found regarding age, sex, number of courses of therapy required to achieve complete remission, FAB type, or karyotype classification. Among the patients assigned to autologous marrow transplantation or high-dose cytarabine, the median time from study entry to randomization was 15.6 weeks (range, 5.6 to 28.0). The median time from complete remission to the initiation of postremission therapy was 14.6 weeks for autologous marrow transplantation and 14.1 weeks for allogeneic marrow transplantation, as compared with 12.4 weeks for high-dose cytarabine. The times to marrow transplantation were significantly longer than the times to chemotherapy ($P=0.001$), regardless of whether the differences were calculated on the basis of the date of transplantation or by censoring data on patients scheduled for autologous or allogeneic marrow transplantation at the time they were withdrawn from the study.

Of 116 patients assigned to autologous marrow transplantation, only 63 (54 percent) received the intended therapy, for the reasons shown in Table 1.

In comparison, nearly all patients assigned to high-dose cytarabine (91 percent) and 81 percent of those given allogeneic marrow received the intended therapy. Follow-up data were analyzed on an intention-to-treat basis, including all patients in their assigned groups. At the time of this analysis (August 1997), the median follow-up of the 135 patients remaining in continuous complete remission was approximately 4 years (minimum, 10 months; maximum, 7.1 years). By August 1998, one year after the analysis of these data, no additional relapses had occurred. Two patients died while in complete remission (one patient had refused autologous marrow transplantation, and the other died of severe graft-versus-host disease after allogeneic marrow transplantation).

The distribution of karyotypes (Table 1) did not differ significantly among treatment groups ($P=0.38$). Failure to receive the assigned therapy did not cause an imbalance in the distribution of karyotypic abnormalities (data not shown) among the remaining patients who received treatment as scheduled. Long-

TABLE 2. RESULTS OF POSTREMISSION THERAPY.

RESULT	HIGH-DOSE CYTARABINE*	AUTOLOGOUS BONE MARROW TRANSPLANTATION*	ALLOGENEIC BONE MARROW TRANSPLANTATION*
Death within 100 days of postremission therapy — no. of deaths/no. of patients treated (%)	3/106 (3)	9/63 (14)	19/92 (21)
Cause of death — % of treated patients			
Venooclusive disease	0	2	6
Bacterial infection	2	4	1
Fungal infection	1	2	3
Cytomegalovirus infection	0	0	4
Acute graft-versus-host disease	0	0	5
Graft failure	0	1	0
Time from bone marrow transplantation until granulocyte count $>500/\text{mm}^3$ — days			
Median	—	32	19
Range	—	14–86	8–50
Time from bone marrow transplantation until self-sustaining platelet count — days			
Median	—	64	24
Range	—	26–339	11–932
Disease-free survival of patients assigned to therapy			
Median — mo	18	14	32
95% confidence interval†	12–24	11–28	15–NR
At 4 yr — %	35±9	35±9	43±10
Survival of patients assigned to therapy			
Median — mo	60	27	35
95% confidence interval†	30–NR	18–NR	23–NR
At 4 yr — %	52±9	43±9	46±10
Treatment failure — no. of failures/no. of patients assigned to therapy (%)			
Relapse	71/117 (61)	56/116 (48)	33/113 (29)
Death during complete remission	4/117 (3)	16/116 (14)	28/113 (25)

*Patients were randomly assigned to therapy.

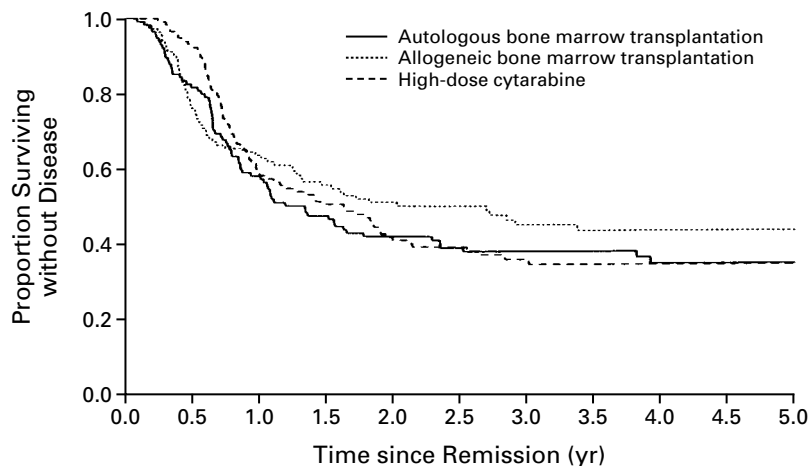
†Patients were assigned to therapy on the basis of the availability of a suitable donor.

‡NR denotes that the upper limit of the confidence interval for the median has not yet been reached.

term and disease-free survival (data not shown) for all randomly and directly assigned patients correlated with the prognostic grouping of the karyotypes. No firm conclusions can be drawn, however, about the relation between karyotype groupings and the long-

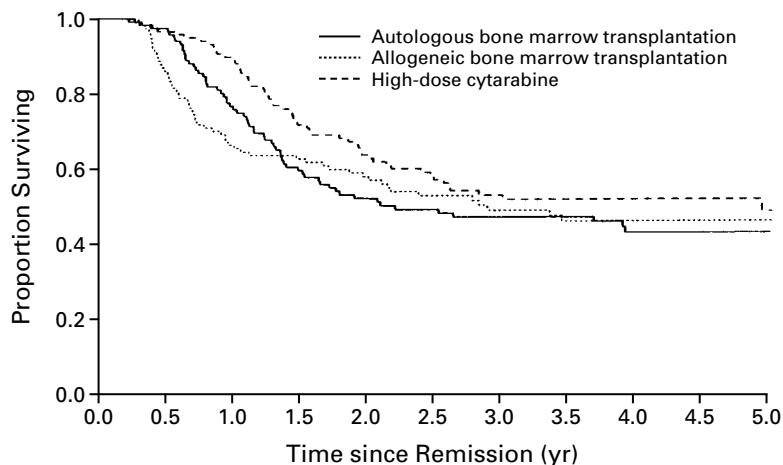
term results of the three postremission therapies, because this study was not designed to measure this correlation.

Table 2 and Figure 1 show disease-free survival rates in the three postremission treatment groups. The



GROUP	NO. OF EVENTS/NO. AT RISK				
Autologous transplantation	48/116	18/66	4/45	2/34	0/22
Allogeneic transplantation	41/113	14/71	5/55	1/32	0/22
Cytarabine	48/117	21/69	5/47	1/29	0/18

Figure 1. Probability of Disease-free Survival According to Postremission Therapy.



GROUP	NO. OF EVENTS/NO. AT RISK				
Autologous transplantation	27/116	27/87	5/56	3/43	0/30
Allogeneic transplantation	38/113	9/74	8/61	2/36	0/25
Cytarabine	12/117	30/104	11/72	1/47	1/29

Figure 2. Probability of Survival According to Postremission Therapy.

median disease-free survival in the group treated with autologous marrow transplantation was 14 months; a life-table estimate of disease-free survival (± 2 SD) at 4 years was 35 ± 9 percent. The respective figures in the high-dose cytarabine group were 18 months and 35 ± 9 percent ($P=0.77$). Neither result differed significantly from the results with allogeneic marrow transplantation (median disease-free survival, 32 months; life-table estimate, 43 ± 10 percent at 4 years). Delays in the period from remission to transplantation (during which there were 2 relapses in the chemotherapy group, 15 in the autologous marrow group, and 9 in the allogeneic marrow group) could have decreased disease-free survival among patients scheduled for marrow transplantation (Table 1). Alternatively, this difference in the number of relapses before the scheduled procedure could have been due to the study design, which allowed patients in complete remission to begin high-dose cytarabine without the bone marrow evaluation that was mandated before allogeneic or autologous marrow transplantation. As shown in Table 2 and Figure 2, survival was better after high-dose cytarabine than after autologous marrow transplantation ($P=0.05$). In comparison with the group given allogeneic marrow, the group given chemotherapy had marginally better survival ($P=0.04$), and there were no significant differences in survival between patients receiving allogeneic marrow and those receiving autologous marrow.

DISCUSSION

With the regimens used in this study of adolescents and adults in a first complete remission of acute myeloid leukemia, the results with autologous marrow transplantation were no better than those with postremission high-dose chemotherapy alone, when the data were analyzed on an intention-to-treat basis. Relapses were most frequent among patients assigned to high-dose cytarabine (61 percent), less common among those assigned to autologous marrow transplantation (48 percent), and least common among those assigned to allogeneic marrow transplantation (29 percent) (Table 2). Conversely, the treatment-related mortality (i.e., mortality less than 100 days after the beginning of therapy) among patients remaining in complete remission was highest for allogeneic marrow transplantation (21 percent), lowest for high-dose cytarabine (3 percent), and intermediate for autologous marrow transplantation (14 percent). The inverse relation of these outcomes neutralized the competing effects of the three regimens, which explains the lack of difference in disease-free survival. Nevertheless, survival was better after high-dose cytarabine than after autologous marrow transplantation ($P=0.05$). In contrast, two large, randomized trials of autologous marrow transplantation in similar patients found a significant improvement in disease-free survival with marrow transplantation. Zittoun et

al.¹⁵ reported an estimated disease-free survival of 48 ± 5 percent at four years with autologous transplantation, as compared with 30 ± 4 percent with chemotherapy ($P=0.04$). In the study by Burnett et al.,¹⁶ disease-free survival seven years after autologous marrow transplantation was 53 percent, as compared with 40 percent after chemotherapy ($P=0.04$). Like the current study, both these studies included a relatively large number of patients and analyzed data on an intention-to-treat basis. Unlike the patients in our study, however, the patients in these two studies received at least one cycle of intensive postremission chemotherapy before randomization, and the pretransplantation regimen included total-body irradiation instead of busulfan. Autologous marrow transplantation may be less effective in patients with greater burdens of undetected disease and therefore might best be used after intensive postremission chemotherapy rather than as a substitute for it.

Like us, others have found that autologous marrow transplantation does not substantially improve survival in comparison with chemotherapy.^{15,16} The lack of consistency between the results for disease-free survival and overall survival may reflect, in part, the benefit of marrow transplantation after an initial relapse. Substantially more patients who had relapses after chemotherapy underwent salvage autologous or allogeneic marrow transplantation than patients who relapsed after receiving autologous or allogeneic marrow transplantation as postremission therapy (Table 3). Moreover, for each postremission-therapy group, approximately the same percentage of patients who were treated with marrow transplantation after an initial relapse are currently alive. Since the follow-up of these patients after salvage transplantation is relatively short, continued follow-up is important to determine whether the survival curves remain stable.

The failure of a substantial fraction of patients to remain in the study and receive the assigned treatment is problematic for any study of postremission therapy¹⁵⁻¹⁹; in published series, 33 to 50 percent of patients in initial complete remission were removed from the study (Table 4). Although 83 to 97 percent of patients randomly assigned to chemotherapy received the scheduled therapy, only 54 to 87 percent received the intended autologous marrow transplantation (Table 4).

In our study, no significant differences in the distribution of known prognostic factors were found between those who continued in the study and those who refused to proceed to the next step in the treatment. To restrict the analysis to patients who actually received the intended therapy would have been misleading. Such patients had a median disease-free survival of 28 months and an estimated rate of disease-free survival of 45 percent 4 years after autologous marrow transplantation, with corresponding figures of 34 months and 47 percent for allogeneic

TABLE 3. FREQUENCY OF SALVAGE BONE MARROW TRANSPLANTATION AFTER RELAPSE, ACCORDING TO POSTREMISSION THERAPY.

VARIABLE	HIGH-DOSE CYTARABINE (N=117)*	AUTOLOGOUS BONE MARROW TRANSPLANTATION (N=116)*	ALLOGENEIC BONE MARROW TRANSPLANTATION (N=113)†
		number (percent)	
Relapse	71 (61)	56 (48)	33 (29)
Bone marrow transplantation after relapse	25 (35)	7 (12)	6 (18)
Autologous	14	4	1
Allogeneic	6	3	5
Matched unrelated donor	5	0	0
Patient currently alive	13 (52)	3 (43)	2 (33)
No bone marrow transplantation after relapse	46 (65)	49 (88)	27 (82)
Patient currently alive	6 (13)	5 (10)	4 (15)

*Patients were randomly assigned to therapy.

†Patients were assigned to therapy on the basis of the availability of a suitable donor.

TABLE 4. PATIENTS COMPLETING ASSIGNED THERAPY IN RANDOMIZED TRIALS OF BONE MARROW TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA.

STUDY	PATIENTS REMAINING IN THE STUDY AFTER COMPLETE REMISSION	PATIENTS ASSIGNED TO THERAPY WHO COMPLETED THE THERAPY		
		CHEMOTHERAPY*	AUTOLOGOUS BONE MARROW TRANSPLANTATION*	ALLOGENEIC BONE MARROW TRANSPLANTATION†
			number/total number (percent)	
Current study	346/518 (67)	106/117 (91)	63/116 (54)	92/113 (81)
Zittoun et al. ¹⁵	422/623 (68)	104/126 (83)	95/128 (74)	144/168 (86)
Burnett et al. ¹⁶	759/1509 (50)	186/191 (97)	126/190 (66)	NA/378
Harousseau et al. ¹⁷	252/367 (69)	71/78 (91)	75/86 (87)	73/88 (83)
Ravindranath et al. ¹⁸	321/552 (58)	113/117 (97)	71/115 (62)	79/89 (89)

*Patients were randomly assigned to therapy.

†Patients were assigned to therapy on the basis of the availability of a suitable donor. NA denotes not available.

marrow transplantation. For autologous marrow transplantation, the median survival has not yet been reached and the 4-year survival rate was 55 percent, as compared with a median survival of 41 months and a 48 percent rate of 4-year survival for allogeneic marrow transplantation.

These results resemble those reported in single-institution studies of marrow transplantation and may reflect selection bias when patients are excluded because of their refusal of therapy, relapse before marrow transplantation, or medical ineligibility. Conversely, the current and previous studies can be viewed as flawed assessments of the value of autologous mar-

row transplantation, because so many patients never received it. The intention-to-treat analysis does, however, provide a comparison between treatments offered to patients but not necessarily accepted by them, as can occur in clinical practice.

Our results indicate that autologous marrow transplantation early after the induction of a first remission with a preparatory regimen that does not include total-body irradiation was of no benefit. Chemotherapy with a single course of high-dose cytarabine was associated with the best survival after complete remission. This result may have been due to the benefits of salvage autologous or allogeneic marrow transplan-

tation in patients who relapsed after receiving high-dose cytarabine. Alternative strategies, including measures to ensure the completion of the assigned therapy, the postponement of transplantation until after intensive consolidation therapy, or different techniques, such as the use of peripheral blood rather than bone marrow stem cells in autologous transplantation,^{12,32,33} could alter the outcome of future trials.

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