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## AUTOLOGOUS OR ALLOGENEIC BONE MARROW TRANSPLANTATION COMPARED WITH INTENSIVE CHEMOTHERAPY IN ACUTE MYELOGENOUS LEUKEMIA

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**Abstract Background.** Allogeneic or autologous bone marrow transplantation and intensive consolidation chemotherapy are used to treat acute myelogenous leukemia in a first complete remission.

**Methods.** After induction treatment with daunorubicin and cytarabine, patients who had a complete remission received a first course of intensive consolidation chemotherapy, combining intermediate-dose cytarabine and amsacrine. Patients with an HLA-identical sibling were assigned to undergo allogeneic bone marrow transplantation; the others were randomly assigned to undergo autologous bone marrow transplantation (with unpurged bone marrow) or a second course of intensive chemotherapy, combining high-dose cytarabine and daunorubicin. Comparisons were made on the basis of the intention to treat.

**Results.** A total of 623 patients had a complete remission; 168 were assigned to undergo allogeneic bone marrow transplantation, and 254 were randomly assigned to one of the other two groups. Of these patients, 343 completed the treatment assignment: 144 in the allogeneic-transplantation group, 95 in the autologous-transplantation group, and 104 in the intensive-chemotherapy group. The relapse rate was highest in the intensive-chemother-

apy group and lowest in the allogeneic-transplantation group, whereas the mortality rate was highest after allogeneic transplantation and lowest after intensive chemotherapy. The projected rate of disease-free survival at four years was 55 percent for allogeneic transplantation, 48 percent for autologous transplantation, and 30 percent for intensive chemotherapy. However, the overall survival after complete remission was similar in the three groups, since more patients who relapsed after a second course of intensive chemotherapy had a response to subsequent autologous bone marrow transplantation. Other differences were also observed, especially with regard to hematopoietic recovery (it occurred later after autologous transplantation) and the duration of hospitalization (it was longer with bone marrow transplantation).

**Conclusions.** During first complete remission in acute myelogenous leukemia, autologous as well as allogeneic bone marrow transplantation results in better disease-free survival than intensive consolidation chemotherapy with high-dose cytarabine and daunorubicin. Transplantation soon after a relapse or during a second complete remission might also be appropriate. (N Engl J Med 1995; 332:217-23.)

**M**OST patients with primary acute myelogenous leukemia (AML) enter complete remission after induction therapy.<sup>1</sup> The majority, however, relapse despite various types of consolidation and maintenance chemotherapy.<sup>2,3</sup> Therefore, in adult patients less than 60 years of age, treatment after the initial induction of remission has been progressively intensified.<sup>4-8</sup>

An increasing number of patients who enter a complete remission are being treated with allogeneic bone marrow transplantation or, more recently, with autologous bone marrow transplantation. Most reports of results with bone marrow transplantation have been from

single institutions<sup>9-12</sup> or registries<sup>13-15</sup> and thus may reflect a selection bias.<sup>16,17</sup> The need for prospective studies comparing the treatment options for acute myelogenous leukemia has frequently been emphasized; however, the results of the initial controlled trials comparing allogeneic bone marrow transplantation and chemotherapy<sup>18-20</sup> were the subject of controversy.<sup>21,22</sup>

Autologous bone marrow transplantation using conditioning regimens similar to those first adopted for allogeneic bone marrow transplantation lacks the graft-versus-leukemia effect of the latter method.<sup>23</sup> It also carries the risk of reinjecting occult residual leukemic cells. Attempts to avoid this hazard have been made by purging the bone marrow before reinfusion.<sup>24</sup> Nevertheless, pilot studies have reported good outcomes at four to five years despite the use of unpurged bone marrow.<sup>10,25,26</sup>

In 1986 the European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups decided to conduct a prospective trial of three postremission treatments to examine disease-free survival and overall survival. All patients received an intensive course of consolidation therapy combining intermediate-dose cytarabine and amsacrine. Only patients who had an HLA-identical sibling were allowed to undergo alloge-

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†Members of each group who participated in the study are listed in the Appendix.

neic bone marrow transplantation.<sup>18,19</sup> The remaining patients were randomly assigned to receive either autologous bone marrow transplantation or a second course of intensified chemotherapy consisting of high-dose cytarabine and daunorubicin.

## METHODS

### Patients

Patients with previously untreated acute myelogenous leukemia were eligible for entry into the trial. The diagnosis was made by the participating centers according to the criteria of the French-American-British (FAB) classification system<sup>27</sup>; it was confirmed by the data center on the basis of the reported cytologic features, especially the presence of Auer bodies, positive staining for myeloperoxidase, or both. A cytology committee reviewed the smears from 66 percent of patients. Patients who were 10 to 45 years of age were eligible, but very few who were younger than 15 years of age were enrolled. Some centers were allowed to include patients 46 to 59 years of age, according to a policy established at the beginning of the trial. Informed consent was obtained according to the regulations of each institution. Patients with chronic myeloid leukemia or other myeloproliferative diseases in blast crisis were excluded, as were patients who had had a myelodysplastic syndrome for more than six months.

The median age of the patients was 33 years (range, 11 to 59), with a ratio of male to female patients of 1.08. The distribution of the morphologic types of AML according to the FAB classification was similar to that in other reports (M0, 0.1 percent; M1, 16.4 percent; M2, 33.3 percent; M3, 7.1 percent; M4, 20 percent; M5, 18.7 percent; M6, 3.9 percent; and M7, 0.6 percent). Some centers from the GIMEMA group excluded patients with acute promyelocytic (M3) leukemia.

### Treatment

Figure 1 shows the design of the study. The induction treatment consisted of one course, or in the case of a partial response, two courses, of daunorubicin, at a dose of 45 mg per square meter of body-surface area, given intravenously on days 1, 2, and 3, and cytarabine, at a dose of 200 mg per square meter, given as a continuous intravenous infusion on days 1 through 7.

All patients who had a complete remission were scheduled to receive a course of intensive consolidation chemotherapy consisting of intermediate-dose cytarabine (1000 mg per square meter), given as a continuous intravenous infusion over a period of 2 hours every 12 hours on days 1 through 6, and amsacrine, given intravenously at a dose of 120 mg per square meter on days 5, 6, and 7. After the first year of the study, the dose of cytarabine was decreased to 500 mg per square meter; this adjustment reduced the incidence of lethal infections from 8 percent in the first 75 patients to 4.5 percent in the subsequent patients.

Patients with a confirmed complete remission and an HLA-identical sibling willing to act as a donor were scheduled for allogeneic bone marrow transplantation. All remaining patients in complete remission were randomly assigned to undergo autologous bone marrow transplantation or a second course of intensive consolidation chemotherapy. The standard conditioning regimen for both allogeneic and autologous bone marrow transplantation consisted of cyclophosphamide, at a daily dose of 60 mg per kilogram of body weight on two consecutive days, and total-body irradiation, in a single fraction of 10 Gy or in four to six fractions (total, 12 Gy) given over a period of two to three days. In 34 percent of the patients who received an allogeneic transplant and in 55 percent of those who received an autologous transplant, the conditioning regimen combined busulfan at a daily dose of 4 mg per kilogram on days 6 to 3 before transplantation with cyclophosphamide at a daily dose of 60 mg per kilogram on days 2 and 1 before transplantation. Prophylaxis against graft-versus-host disease after allogeneic transplantation consisted mainly of cyclosporine alone or in combination with methotrexate. In 24 of 144 patients (17 percent) the allogeneic marrow was depleted of T cells before transplantation, mainly by elutriation. In patients randomly assigned to undergo autologous bone marrow transplantation, bone marrow was harvested after hematologic recovery from the first course of consolidation chemotherapy in amounts sufficient to collect

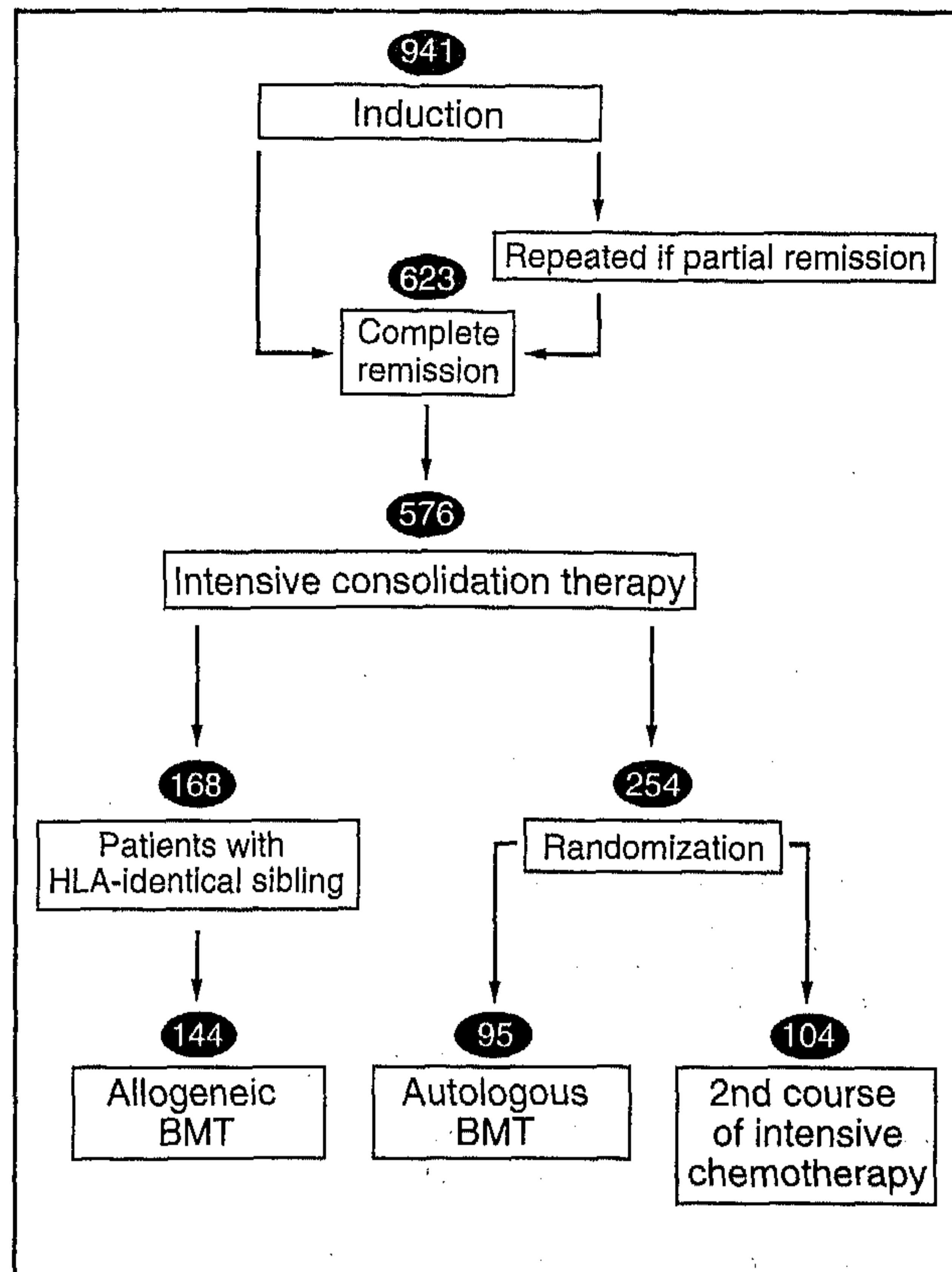


Figure 1. Design of the Study.

The numbers are the numbers of patients at each treatment step. Details of the treatment are given in the Methods section. BMT denotes bone marrow transplantation.

at least  $1 \times 10^8$  nucleated cells per kilogram and at least  $1 \times 10^4$  granulocyte-macrophage colony-forming units per kilogram; this bone marrow was cryopreserved without purging in all but six patients from three centers.

Patients who were randomly assigned to a second course of intensive consolidation chemotherapy received high-dose cytarabine (2 g per square meter), given as a continuous infusion over a 2-hour period every 12 hours on days 1, 2, 3, and 4, and daunorubicin, at a dose of 45 mg per square meter on days 5, 6, and 7. The dose of cytarabine was limited to 2 g per square meter to decrease the risk of cerebellar toxicity.<sup>20</sup> No hematopoietic growth factor was used.

### Statistical Analysis

All patients were prospectively registered at the EORTC Data Center, in Brussels, Belgium. Patients who had a confirmed complete remission after a first course of intensive consolidation chemotherapy and who did not have an HLA-identical sibling were randomly assigned to treatment groups according to the minimization technique,<sup>29</sup> in which they were prospectively stratified according to age and center. A total of 243 randomized patients was required to detect a difference of 20 percentage points (30 percent vs. 50 percent) in disease-free survival at three years between patients undergoing autologous bone marrow transplantation and those who received a second course of intensive consolidation chemotherapy. The homogeneity of the treatment groups was tested with the Kruskal-Wallis<sup>30</sup> and chi-square<sup>29</sup> tests.

Disease-free survival was calculated from the date of the first complete remission until the date of the first relapse or the date of death in first complete remission. The duration of survival after complete remission corresponds to the length of time from the first complete remission to the date of death. Actuarial curves were calculated according to the Kaplan-Meier technique, and the standard error was computed with Greenwood's formula.<sup>29</sup> The differences between

curves were tested for statistical significance with the two-tailed log-rank test.<sup>29</sup> For ordered prognostic factors, the log-rank test for linear trend was used.<sup>29</sup> The instantaneous relative risk of an event per unit of time in one treatment group as compared with that in another and its corresponding 95 percent confidence interval were computed with calculations of the log-rank type.<sup>31</sup>

Even though some patients received treatments other than their assigned ones, all randomized patients and the patients considered eligible for allogeneic bone marrow transplantation were analyzed only in their respective treatment groups in order to adhere to the intention-to-treat principle.

## RESULTS

Between November 1986 and April 1993, 990 patients were registered in the study by 59 institutions. Thirty-six patients were ruled ineligible (19 because of an inadequate diagnosis and 17 because they met other exclusion criteria), and 13 patients could not be evaluated because of missing data. Thus, a total of 941 patients were evaluated. As of November 1993 the median follow-up was 3.3 years.

A complete remission was achieved in 623 patients (66 percent), 576 of whom received the first course of intensive consolidation chemotherapy. An HLA-matched sibling was identified for 230 of the 623 patients who entered complete remission, and 168 of those patients were assigned to undergo allogeneic bone marrow transplantation, 4 directly after entering a complete remission and 164 after the first course of consolidation chemotherapy. Of the remaining patients, 254 underwent randomization: 128 to autologous bone marrow transplantation and 126 to a second course of intensive consolidation chemotherapy. The number of patients who completed their assigned treatment was 144 in the group assigned to allogeneic transplantation, 95 in the group assigned to autologous transplantation, and 104 in the group assigned to intensive chemotherapy. Table 1 shows the main reasons for not carrying out allogeneic bone marrow transplantation or randomization or completing the treatment. Toxicity was a notable cause of exclusion, especially after the first course of intensive chemotherapy. Refusal to receive the assigned treatment was less common among patients assigned to allogeneic transplantation than among those randomly assigned to autologous transplantation or intensive chemotherapy.

Protocol violations also occurred, whether instituted by a physician or a patient. Thus, in addition to early relapses or deaths and 2 patients lost to follow-up, 39 patients who were assigned to one of the three treatment groups did not complete the protocol as scheduled. Some of them completed a treatment different from the one planned: of the patients randomly assigned to a second course of intensive consolidation chemotherapy, five underwent autologous bone marrow transplantation and one allogeneic transplantation. Of the patients randomly assigned to undergo autologous

Table 1. Reasons for Not Completing the Protocol as Scheduled at Each Step among Patients Who Entered a First Complete Remission.\*

CATEGORY	INDUCTION ONLY	IC1 ONLY	RANDOMIZED PATIENTS		PATIENTS ASSIGNED TO ALLOGENEIC BMT	ALL PATIENTS
			IC2	AUTOLOGOUS BMT		
No. completing assigned treatment	0	0	104	95	144	343
Reason for not completing treatment						
Early relapse	5	12	5	12	18	52
Lethal toxic effect	3	27	2	1	0	33
Nonlethal toxic effect	20	41	5	10†	2	78
Refusal to undergo treatment	7	64	10	8	1	90
Protocol violation	4	9	0	2	1	16
Loss to follow-up or other reason	4	5	0	0	2	11
Total	43	158	126	128	168	623

\*IC1 denotes a first course of intensive consolidation chemotherapy, IC2 a second course of intensive consolidation chemotherapy, and BMT bone marrow transplantation.

†Including four patients with insufficient colony growth of the bone marrow sample in vitro.

bone marrow transplantation, five received a second course of intensive consolidation chemotherapy and two underwent allogeneic transplantation. One of the patients scheduled for allogeneic bone marrow transplantation instead received intensive chemotherapy. Nevertheless, patients were kept in their assigned groups for the analysis of results.

The median length of time between the achievement of complete remission and the initiation of the last treatment step differed significantly among the three treatment groups: 10 weeks in the intensive-chemotherapy group, 14 weeks in the autologous-transplantation group, and 15 weeks in the allogeneic-transplantation group ( $P < 0.001$ ). The number of early relapses consequently differed between the three groups: 5 in the intensive-chemotherapy group, 12 in the autologous-transplantation group, and 18 in the allogeneic-transplantation group. The delays in treatment were principally due to delays at the transplantation centers and to the time required to assess colony growth in vitro in the case of autologous transplantation. Four patients randomly assigned to autologous transplantation and 10 assigned to allogeneic transplantation had an early relapse and were treated at relapse or after entering a second complete remission.

Table 2 shows the characteristics of the patients in the three groups. Univariate analyses of disease-free survival revealed several adverse prognostic factors: an FAB class other than M2 or M3 ( $P < 0.001$ ), a longer interval from diagnosis to complete remission ( $P < 0.001$ ), the need for more than one course of induction chemotherapy to achieve a complete remission ( $P = 0.003$ ), a poor or intermediate prognosis according to the cytogenetic classification of Keating et al.<sup>32</sup> ( $P = 0.002$ ), a high white-cell count ( $P = 0.002$ ), and an elevated serum lactate dehydrogenase concentration ( $P = 0.03$ ). These prognostic factors were evenly distributed among the three groups. All patients scheduled for allogeneic transplantation were 45 years of age or younger, whereas 10 patients assigned to intensive chemo-

therapy and 9 patients assigned to undergo autologous transplantation were 46 to 59 years of age. In this study, age (10 to 59 years) was not a prognostic factor for disease-free survival.

Table 3 shows the incidence of death or relapse of AML as a first event for all patients who entered complete remission. Most relapses occurred in bone marrow, but 10.5 percent were extramedullary (central nervous system or cutaneous), occurring either alone or in combination with a relapse affecting bone marrow. The crude relapse rate was higher in the intensive-chemotherapy group (57.1 percent) than in the autologous-transplantation group (40.6 percent) or the allogeneic-transplantation group (24.4 percent). The respective death rates in the three groups were 7.1 percent, 9.4 percent, and 17.3 percent. The crude death rates among patients who were in a first complete remission, classified according to the treatment actually received, were 5.8 percent in the intensive-chemotherapy group (6 of 104 patients), 10.4 percent in the autologous-transplantation group

(10 of 96 patients), and 20 percent in the allogeneic-transplantation group (29 of 145 patients).

Figure 2 shows the probability of disease-free survival in the three groups and the projected rates ( $\pm$ SE) at four years for intensive chemotherapy ( $30 \pm 4$  percent), autologous transplantation ( $48 \pm 5$  percent), and allogeneic transplantation ( $55 \pm 4$  percent). A comparison of disease-free survival in the autologous-transplantation group with that in the intensive-chemotherapy group yielded a relative risk of death or relapse of 0.73 (95 percent confidence interval, 0.52 to 1.00) and a P value of 0.05 (by the log-rank test). Restricting the analysis to the 235 randomized patients who were 45 years of age or younger yielded similar results ( $P = 0.04$ ). For exploratory purposes, additional analyses were made, with an appreciation for potential sources of bias (especially with respect to the regimen of bone marrow transplantation preferred by the various centers). Disease-free survival was not influenced by the type of conditioning regimen used (with or without total-body irradiation) for engraftment. The influence of the method of preventing graft-versus-host disease after allografting (methotrexate plus cyclosporine vs. cyclosporine alone) was almost significant ( $P = 0.06$ ).

Figure 3 shows overall survival after a complete remission according to the intended treatment. There were no significant differences among the three groups. A higher incidence of early mortality after allogeneic transplantation was counterbalanced by a lower incidence of late mortality in that group. At four years the estimated rate of overall survival was  $46 \pm 5$  percent for the intensive-chemotherapy group,  $56 \pm 5$  percent for the autologous-transplantation group, and  $59 \pm 4$  percent for the allogeneic-transplantation group. The difference in survival between the two randomized groups was not significant ( $P = 0.43$  by the log-rank test; relative risk, 0.86; 95 percent confidence interval, 0.59 to 1.25).

Among the patients who relapsed after completing the assigned treatment and received reinduction chemotherapy, those given a second course of intensive consolidation chemotherapy had the highest proportion of second complete remissions (Table 4). Many of them (22 of 36) subsequently underwent autologous bone marrow transplantation, frequently with bone marrow

Table 3. Incidence of Death or Relapse of AML among 623 Patients with a First Complete Remission.\*

CATEGORY	RANDOMIZED PATIENTS		PATIENTS ASSIGNED TO ALLOGENEIC BMT (N = 168)	OTHER PATIENTS† (N = 201)
	IC2 (N = 126)	AUTOLOGOUS BMT (N = 128)	no. of patients (%)	
Total events	81 (64.3)	64 (50.0)	70 (41.7)	128 (63.7)
Relapse of leukemia	72 (57.1)	52 (40.6)	41 (24.4)	93 (46.3)
Death during first complete remission	9 (7.1)	12 (9.4)	29 (17.3)	35 (17.4)
Alive in first complete remission	45 (35.7)	64 (50.0)	98 (58.3)	73 (36.3)

\*IC2 denotes a second course of intensive consolidation chemotherapy, and BMT bone marrow transplantation.

†This category includes patients who were not included in any of the treatment groups for the reasons listed in Table 1.

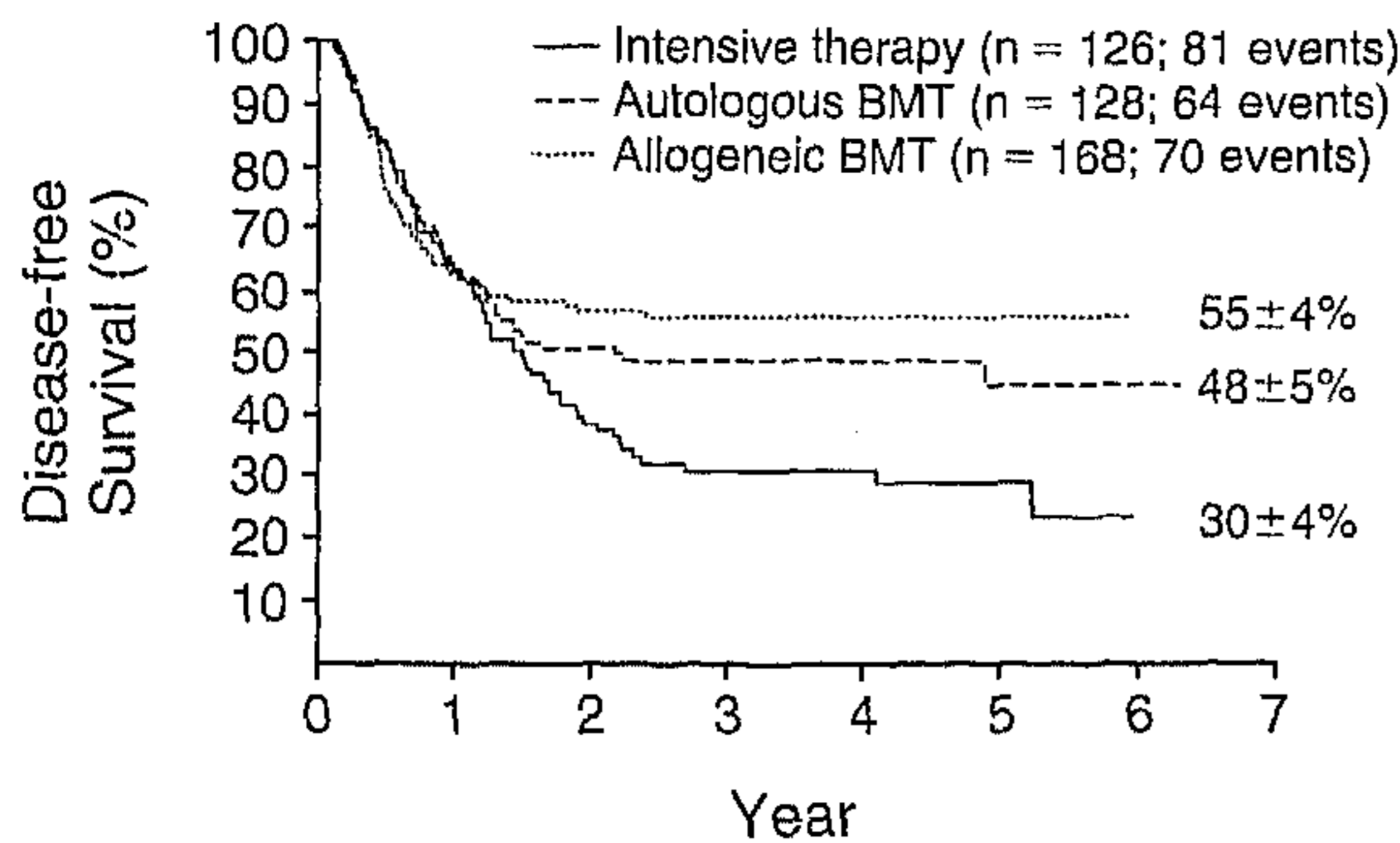
Table 2. Characteristics of the Patients in Each Treatment Group.\*

CHARACTERISTIC	RANDOMIZED PATIENTS		PATIENTS ASSIGNED TO ALLOGENEIC BMT (N = 168)	P VALUE†
	IC2 (N = 126)	AUTOLOGOUS BMT (N = 128)		
	percent			
Age				0.71
$\leq 25$ yr	35.7	32.8	25.0	
26–45 yr	56.3	60.2	75.0	
46–59 yr	7.9	7.0	0	
White-cell count				0.90
$< 5000/\text{mm}^3$	26.4	30.5	22.0	
5000–49,000/ $\text{mm}^3$	46.4	42.2	58.3	
$\geq 50,000/\text{mm}^3$	27.2	27.3	19.6	
FAB classification				0.99
M1	17	11	14	
M2	40	41	39	
M3	6	5	5	
M4	20	24	20	
M5	13	16	18	
M6	2	2	2	
M7	1	1	1	
No. of cycles needed for complete remission				0.07
1	88.1	86.7	79.2	
2	11.9	13.3	20.8	
Cytogenetic group‡				0.34
Good	12.5	18.6	25.3	
Intermediate	30.3	39.0	33.8	
Poor	19.6	20.3	18.3	
Inconclusive	37.5	22.0	22.5	

\*The characteristics of sex, World Health Organization performance status, and the presence of fever at diagnosis were evenly distributed. Because of rounding, not all categories total 100 percent. IC2 denotes a second course of intensive consolidation chemotherapy, and BMT bone marrow transplantation.

†All P values were calculated with the Kruskal–Wallis test, except that for FAB classification, which was calculated with the chi-square test.

‡The prognosis was based on cytogenetic analysis according to the classification of Keating et al.<sup>12</sup> and was determined in 56 patients in the group assigned to a second course of intensive consolidation chemotherapy, 59 patients assigned to autologous bone marrow transplantation, and 71 patients assigned to allogeneic bone marrow transplantation.



Intensive therapy	126	74	37	24	17	7	1
Autologous BMT	128	76	49	38	26	10	4
Allogeneic BMT	168	87	63	48	29	15	0

Figure 2. Kaplan-Meier Plots of Disease-free Survival, According to Whether Patients Were Assigned to Autologous or Allogeneic Bone Marrow Transplantation (BMT) or a Second Course of Intensive Consolidation Therapy.

The number of patients at risk is shown below each time point. Plus-minus values are the projected disease-free survival rates ( $\pm$ SE) at four years. The events considered were relapse or death during a first complete remission.

harvested during the first complete remission. By contrast, the rate at which a second bone marrow transplantation was performed after a relapse in the groups that underwent either allogeneic or autologous transplantation was low.

Table 5 shows pairwise comparisons of the estimates of the relative risk of relapse after treatment allocation and of death after the completion of the assigned treatment. The risk of relapse was highest in the intensive-chemotherapy group, followed by autologous transplantation and then by allogeneic transplantation, despite the higher number of early relapses in patients assigned to transplantation. When the relative risk of death after the completion of treatment was ranked, allogeneic transplantation was first, followed by autologous transplantation and then by intensive chemotherapy.

Other differences were observed among the three groups. The length of time to hematopoietic recovery was significantly longer after autologous transplantation than after allogeneic transplantation or intensive chemotherapy; the median time for the absolute granulocyte count to return to at least 1000 per cubic millimeter was 6, 3, and 3 weeks after autologous transplantation, allogeneic transplantation, and intensive chemotherapy, respectively, and the median time for the platelet count to return to at least 100,000 per cubic millimeter was more than 20, 7, and 6 weeks, respectively ( $P < 0.001$ ). The duration of hospitalization was longer ( $P < 0.001$ ) for autologous and allogeneic transplantation than for consolidation chemotherapy (median days of hospitalization, 45, 40, and 28, respectively;  $P < 0.001$ ).

**DISCUSSION**

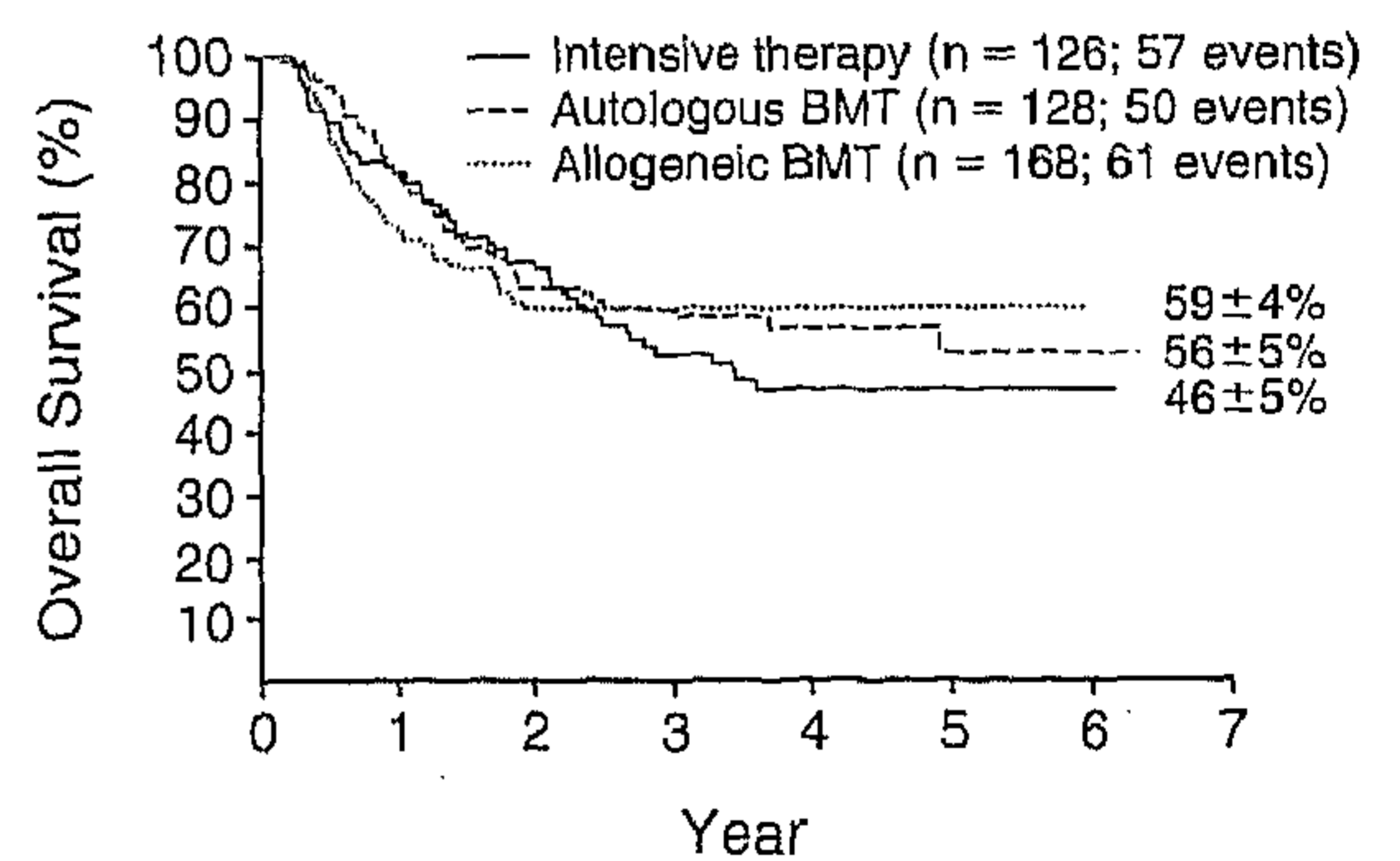
Our study confirms reports from single centers or registries<sup>10,14,33</sup> that autologous bone marrow transplantation, performed during a first complete remission of

AML, results in a disease-free survival of approximately 50 percent at four years. This result was obtained even though the bone marrow was not purged in most cases. Either autologous or allogeneic bone marrow transplantation resulted in an apparently longer disease-free survival than a short course of consolidation chemotherapy. However, the estimated overall survival at four years was similar in the three treatment groups.

Studies intended to assess these types of postremission treatment in AML<sup>19,34-36</sup> are frequently criticized for having limited numbers of patients or selection biases or for failing to use intention-to-treat analysis. Like a few other prospective studies, the present one was designed in an attempt to avoid such limitations or biases.<sup>19,37</sup> It included a large number of centers and patients, thus allowing a systematic comparison of the three treatment options despite the unavoidable heterogeneity of the transplantation regimens. No patient relapsed more than two years after allogeneic bone marrow transplantation; although the results of autologous bone marrow transplantation appear to be similar, only longer follow-up can reveal the risk of late relapses.

We observed real differences between the groups that underwent allogeneic and autologous bone marrow transplantation: relapses were more frequent among those who underwent autologous transplantation, but the mortality rate was higher among those who underwent allogeneic transplantation. Another consideration is that the conditioning regimens for bone marrow transplantation cause infertility, thus leading some young patients to choose chemotherapy instead.

It has frequently been suggested that patients selected for allogeneic transplantation are young people with good prognostic factors.<sup>16,18</sup> In our study, the timing of assignment to allogeneic transplantation varied and depended on the identification of donors and the length of time needed for the patients to recover from the tox-



Intensive therapy	126	95	67	40	25	9	2
Autologous BMT	128	94	60	45	29	12	4
Allogeneic BMT	168	100	67	50	31	16	0

Figure 3. Kaplan-Meier Plots of Overall Survival after a First Complete Remission, According to Whether Patients Were Assigned to an Autologous or Allogeneic Bone Marrow Transplantation (BMT) or a Second Course of Intensive Consolidation Therapy.

The number of patients at risk is shown below each time point. Plus-minus values are the projected survival rates ( $\pm$ SE) at four years. The event considered was death at any time.

Table 4. Number of Patients Completing Their Assigned Treatment Who, after Relapse and Reinduction, Had a Second Complete Remission and Subsequently Underwent Allogeneic or Autologous Bone Marrow Transplantation.\*

CATEGORY	IC2 (N = 58)	AUTOLOGOUS BMT	ALLOGENEIC BMT
		(N = 29)	(N = 20)
		<i>no. of patients (%)</i>	
2nd complete remission	36 (62)	11 (38)	8 (40)
Subsequent allogeneic BMT	2	0	2
Subsequent autologous BMT	22	2	0

\*IC2 denotes a second course of intensive consolidation chemotherapy, and BMT bone marrow transplantation.

ic effects of previous treatments. The number of patients who did not complete their assigned treatments was also considerable. Nevertheless, the three groups are comparable and seem to be representative of the typical population of patients with AML in a first complete remission. This conclusion is supported by the number of patients assigned to allogeneic bone marrow transplantation, which is close to the number expected on the basis of genetic chance, and by the even distribution of the main characteristics of the patients who entered the study, particularly features of prognostic value. It is therefore likely that either transplantation regimen was superior to intensive consolidation chemotherapy. However, the advantage of bone marrow transplantation may depend on the type of consolidation chemotherapy selected. Our chemotherapy regimen, which is currently being assessed in a parallel prospective study of patients 46 to 60 years of age,<sup>38</sup> could have been suboptimal. In other prospective studies, different regimens of intensive consolidation chemotherapy were superior to conventional regimens<sup>37,39</sup> or were equivalent to bone marrow transplantation.<sup>37,40,41</sup>

In our study the advantage of allogeneic and autologous transplantation over intensive chemotherapy was limited to disease-free survival; neither transplantation regimen significantly improved overall survival. Although a lower rate of death during complete remission in the intensive-chemotherapy group might explain this discrepancy, the difference seems due mainly to the better salvage rates with secondary autologous transplantation in patients who relapsed after chemotherapy. Some authors have therefore suggested restricting transplantation to patients in a first relapse or second

complete remission.<sup>19,42,43</sup> Only randomized studies can reliably assess the value of this strategy.

Our analysis confirms the prognostic value, in terms of disease-free survival, of some clinical and biologic variables such as the cytogenetic risk group and the time needed to achieve a complete remission. The cytogenetic group has an especially important effect on the outcome of treatment in AML.<sup>32</sup> Some authors have suggested adapting treatment to the cytologic and karyotypic pattern of the leukemic cells, but such a specific approach is currently applied only to the promyelocytic subtype of AML, for which tretinoin (all-trans-retinoic acid) is used.<sup>44</sup>

In our study and in other trials,<sup>7,35,40</sup> the large number of patients who did not complete the treatment protocol for various reasons, especially because of a physician's decision or their own wishes, is notable. Such decisions are usually made because of concern about the expected toxicity of the various treatments, which may counterbalance hopes for a cure. Ongoing analyses of the cost effectiveness and quality of life during and after the completion of treatment will have an important bearing on the decision-making process. Together with results regarding the comparative risk of relapse, toxicity, and treatment-related mortality, they will help patients and physicians to choose the best postremission treatment.

#### APPENDIX

The following centers and investigators from the EORTC Leukemia Cooperative Group participated in this study: *Austria*: Innsbruck, Universitätsklinik (J. Thaler); *Belgium*: Antwerpen, University of Antwerpen (M.E. Peetermans); Brugge, Hôpital St. Jan (A. Louwagie); Bruxelles, Institut Bordet (P. Stryckmans), Hôpital Saint Pierre (C. Cauchie), and Hôpital Erasme (W. Ferremans); Verviers, Hôpital Civil (R. Paulus); *Croatia*: Zagreb, Hospital Rebro (B. Labar), and Novosel School (B. Jaksic); *France*: Nice, Centre Antoine Lacassagne (A. Thyss); Paris, Hôtel-Dieu (R.A. Zittoun); Suresnes, Centre Foch (E. Baumelou); Villejuif, Institut Gustave Roussy (M. Hayat); *the Netherlands*: Amsterdam, Onze Lieve Vrouw Gasthuis (K. Roozendaal); Eindhoven, Catharina Ziekenhuis (H. Hillen); Enschede, Vereniging Ziekenzorg (W. Van Berkel); Hertogenbosch, Groot Ziekenhuis (J. Burghouts); Leiden, Leiden University (R. Willemze); Nijmegen, St. Radboud Hospital (T. de Witte); *Portugal*: Coimbra, Universidade de Coimbra (G. Teixeira); Porto, San Joan (M. Ribeiro); and *Turkey*: Ankara, Ibnui Sina Hospital (M.D. Beksac).

The following centers and investigators from the GIMEMA group participated in this study: *Italy*: Ancona, Università di Ancona (P. Leoni); Avellino, Ospedale Civile (E. Volpe); Aviano, Centro di Riferimento Oncologico (S. Monfardini); Bari, Università di Bari (V. Liso); Bologna, Istituto L.A. Scagnoli (S. Tura, G. Visani, and A. Zaccaria); Cagliari, Ospedale Businco (G. Broccia); Catania, Ospedale Ferrarotto (E. Cacciola); Catanzaro, Ospedale Pugliese (A. Alberti); Cremona, Ospedale Civile 51 (A. Porcellini); Cuneo, Ospedale S. Croce (A. Gallamini); Ferrara, Arcispedale S. Anna (G.L. Castoldi); Firenze, Università di Firenze (P. Rossi Ferrini and F. Leoni); Foggia, Ospedale Riuniti (M. Monaco); Genova, Ospedale S. Martino (E. Damasio); Latina, Ospedale S. Maria Goretti (L. Deriu); Milano, Ospedale Niguarda (F. De Cataldo); Napoli, Ospedale N. Pelligrini (R. De Biasi), II Università (B.

Table 5. Pairwise Comparisons of the Estimates of Relative Risk with Respect to the Time to First Relapse and Time to Death in First Complete Remission.\*

END POINT	AUTOLOGOUS BMT	ALLOGENEIC BMT	ALLOGENEIC BMT VS.
	vs. IC2	vs. IC2	AUTOLOGOUS BMT
	<i>relative risk (95% CI)</i>		
Relapse after allocation to treatment group	0.66 (0.47-0.94)	0.43 (0.29-0.62)	0.64 (0.43-0.96)
Death after completion of treatment	1.66 (0.62-4.45)	2.78 (1.42-5.44)	1.89 (1.00-3.59)

\*BMT denotes bone marrow transplantation, IC2 a second course of intensive consolidation chemotherapy, and CI confidence interval.

Rotoli), and Ospedale Cardarelli (R. Cimino); Nuoro, Ospedale S. Francesco (A. Gabbas); Palermo, Università Policlinico (P. Citarrella), Ospedale Cervello (F. Caronia), and Università di Palermo (A. Cajozzo); Parma, Università (V. Rizzoli); Pavia, Policlinico S. Matteo (C. Bernasconi); Perugia, Università Clinica Medica (F. Grignani), and Università Istituto di Ematologia (M. Martelli); Pesaro, Ospedale S. Salvatore (G. Lucarelli); Pescara, Ospedale Civile (G. Torlontano); Potenza, Ospedale S. Carlo (F. Ricciuti); Reggio Calabria, Ospedale Riuniti (F. Nobile); Roma, II Università Tor Vergata (G. Papa\*), I Università La Sapienza (F. Mandelli, W. Arcese, and G. Meloni), Università Cattolica del Sacro Cuore (G. Leone), and Ospedale S. Camillo (A. De Laurenzi); San Giovanni Rotondo, Ospedale Casa Sollievo della Sofferenza (M. Carotenuto); and Torino, Ospedale Maggiore S. Giovanni Battista (L. Resegotti), and Università di Torino (A. Pileri).

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*Cytogenetic committee:* A. Hagemeyer, G. Alimena, A. Bernheim, and A. Zaccaria.

\*Deceased.

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