

Influence of Cytogenetic Abnormalities on Outcome after Allogeneic Bone Marrow Transplantation for Acute Myeloid Leukemia in First Complete Remission

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ABSTRACT

Cytogenetic abnormalities detected at diagnosis are recognized as important in predicting response to chemotherapy in acute myeloid leukemia (AML). However, there is controversy concerning the prognostic significance of karyotype for outcome after allogeneic bone marrow transplantation (allo-BMT) performed in first complete remission (CR1). This single-institution report describes allo-BMT for AML in CR1 and the effect of diagnostic cytogenetic findings on the results of that treatment. Between August 1981 and December 1999, 93 patients underwent related donor (n = 82) or unrelated donor (n = 11) BMT. Conditioning and GVHD prophylaxis were achieved predominantly with busulfan and cyclophosphamide and with cyclosporine and methotrexate, respectively. Seventy-nine (85%) of 93 patients had successful marrow karyotyping at diagnosis, and the patients were categorized into 3 prognostic groups based on the British Medical Research Council AML 10 trial classification: 15 patients (19%) were classified as having favorable risk [inv(16), t(8;21), t(15;17)]; 55 (70%) as having intermediate risk [no abnormality, +8, +21, +22, del(7q), del(9q), 11q23 rearrangement, and other numerical or structural abnormalities]; and 9 (11%) as having adverse risk [-5, del(5q), -7, 3q rearrangements, ≥5 abnormalities, t(6;9), t(9;22)]. The median follow-up was 93 months (range, 16-241 months). The overall survival (OS) rate, event-free survival (EFS) rate, relapse rate, and treatment-related mortality (TRM) were not statistically different between the groups. The 5-year actuarial EFS rates for favorable, intermediate, and adverse risk groups were 58% (95% confidence interval [CI], 29%-79%), 58% (95% CI, 43%-70%), and 67% (95% CI 28%-88%), respectively. Reclassification of patients into cytogenetic prognostic subgroups according to Southwest Oncology Group criteria did not change these results. In univariate analysis, the only variable found to have a prognostic influence on OS ($P = .04$) and TRM ($P = .03$) was the type of donor (unrelated donor was linked to a worse prognosis), which was confirmed in multivariate analysis. Our study suggests that presentation karyotype has less prognostic significance for outcome following allo-BMT than for outcome following conventional chemotherapy. In particular, AML patients with poor prognostic cytogenetic changes in CR1 who are unlikely to be cured with chemotherapy alone may benefit from allo-BMT.

KEY WORDS

Cytogenetics • Karyotype • Allogeneic • BMT • Prognostic • AML in CR1

INTRODUCTION

In a variety of studies, chromosomal abnormalities detected in bone marrow cytogenetic analysis at the time of diagnosis have been shown to be key prognostic indicators

in acute myeloid leukemia (AML) [1-12]. In particular, the response to standard induction and consolidation chemotherapy is heavily influenced by the specific karyotypic abnormalities identified [1,8,12,13]. Several chromosomal

Table 1. Patient Characteristics (n = 79)

Age, median (range), y	38 (17-55)
Sex, M/F	37/42
WBC, median (range), $\times 10^9/L$	11.2 (0.8-252)
FAB classification, no. of patients	
M0	3
M1	16
M2	13
M3	9
M4	21
M5	12
M6	2
Unclassifiable	3
No. of patients with 1 cycle of chemotherapy to enter CR1	65
No. of patients with >1 cycle of chemotherapy to enter CR1	14
Time from diagnosis to BMT, median (range), mo	3.3 (1.8-9.0)

changes, ie, t(8;21), t(15;17), and inv(16), have consistently predicted a relatively favorable outcome following chemotherapy, whereas others, eg, -5, -7, or complex karyotypic changes, have been associated with a poor outcome. However, studies with large numbers of patients in which cytogenetic analysis was consistently and successfully performed have only recently begun to clarify the prognostic significance of other aberrant karyotypes and their variants in AML [1,2]. The importance of cytogenetic analysis as a predictive variable in AML has been recognized by the World Health Organization in their recent proposal for a revised classification of subtypes of this disorder [14]. The results of cooperative group studies in which cytogenetic analysis was included in multivariate analyses suggested that postremission therapy can reasonably be tailored to individual patients based on the prognosis predicted by their diagnostic bone marrow karyotype [1,2,8,15].

In contrast to the consistent predictive value that cytogenetic analysis has had for chemotherapy response and survival in AML, the prognostic value of chromosomal analysis for patients in first complete remission (CR1) who receive allogeneic bone marrow transplantation (allo-BMT) as consolidation therapy is less clear. Some studies have demonstrated a similar value for karyotypic studies in predicting outcome after allo-BMT [16-18], whereas others have failed to observe this effect [4,19-22]. Several of the larger studies that suggested a prognostic value for chromosome abnormalities in this situation were cooperative group or registry analyses in which the proportion of patients with evaluable cytogenetic analysis was relatively small [17] or the treatment protocols were variable [16-18]. On the other hand, in cases in which no predictive value was seen, the number of patients available for analysis was often small [4,20,21], or the way in which the chromosomal changes were assigned to various prognostic groups was different from what might now be accepted [4,19,20].

As part of the analysis of the British Medical Research Council (MRC) experience in the treatment of more than 1500 patients with AML, prognostic categories for cytogenetic abnormalities were recently published [1]. In this

report, the numbers of patients with specific karyotype alterations associated with AML were sufficient for the event-free survival (EFS) and overall survival (OS) rates associated with individual abnormalities to be determined with confidence and compared to each other. Three categories of chromosomal changes associated with a good, intermediate, or poor prognosis were identified. The Southwest Oncology Group (SWOG) has adopted a somewhat different prognostic categorization of cytogenetic abnormalities for AML. Certain frequent cytogenetic abnormalities judged as conferring an intermediate prognosis by the MRC were considered by the SWOG to confer a poor risk, resulting in changes in category assignment for a substantial number of patients. In the current study, we have used both the MRC and the SWOG classifications to evaluate retrospectively the prognostic effect of diagnostic karyotype on the outcome of 93 consecutive allo-BMTs performed in adults with AML in CR1 at the Vancouver Hospital and Health Sciences Center (VHHSC). In addition, the influence of other known prognostic clinical variables was considered for the 79 patients in whom cytogenetic analysis was successful.

MATERIALS AND METHODS

Patient Characteristics

Between November 1981 and December 1999, 93 patients with de novo AML in CR1 underwent allogeneic BMT (Table 1). Except in unusual circumstances, consolidation chemotherapy was not given prior to BMT. All patients provided informed consent, and all research studies were approved by the University and Institutional Review Boards. Bone marrow histopathology was centrally reviewed at VHHSC with diagnoses based on standard French-American-British (FAB) criteria [23].

Cytogenetic Analysis

Cytogenetic analyses were performed on unstimulated cultured marrow specimens at 4 regional laboratories and reviewed at VHHSC. The karyotypes were assessed according to the International System for (Human) Cytogenetic Nomenclature (ISCN) 1995 criteria [24]. Patients were divided into 3 prognostic subgroups according to cytogenetic category based on the MRC AML 10 trial [1]. The following criteria were used: favorable, t(8;21), t(15;17), inv(16); intermediate, no abnormality, +8, +21, +22, del(7q), del(9q), 11q23 rearrangement, and other numerical or structural abnormalities; and adverse, -5, del(5q), -7, 3q rearrangements, complex (≥ 5 abnormalities). In the MRC AML 10 trial, the presence of additional cytogenetic abnormalities did not modify the outcome of patients within the favorable category, and therefore additional cytogenetic abnormalities were not taken into account when classifying patients in the favorable group. Eleven of 15 patients in the favorable group had such additional changes (Table 2). The same group of patients was also divided into the 4 cytogenetic prognostic subgroups adopted by the SWOG [15]: favorable, inv(16)/t(16;16)/del(16q), t(15;17) with or without secondary aberrations or t(8;21) lacking del(9q) or being part of a complex karyotype; intermediate, normal, +8, +6, -Y, del(12p); adverse, del(5q)/-5, -7/del(7q), abnormalities of 3q, 9q, 11q, 20q, 21q, or 17p, t(6;9), t(9;22) and complex

Table 2. Cytogenetic Abnormalities and Prognostic Groups*

MRC Classification	No. of Patients (% of Total)	SWOG Classification	No. of Patients (% of Total)
Favorable	15 (19)	Favorable	15 (19)
t(8;21) + additional changes	3	t(8;21) + additional changes	3
t(15;17) alone	3	t(15;17) alone	3
t(15;17) + additional changes	3	t(15;17) + additional changes	3
inv(16) alone	1	inv(16) alone	1
inv(16) + additional changes	5	inv(16) + additional changes	5
Intermediate	55 (70)	Intermediate	40 (51)
Normal karyotype	36	Normal karyotype	36
+8	4	+8	4
+21	1		
del(7q)	1		
del(9q)	1		
11q23 rearrangement	6		
Other numerical or structural abnormalities	6		
Adverse	9 (11)	Adverse	18 (23)
3q rearrangement	5	3q rearrangement	5
Complex (≥ 5 unrelated abnormalities)	2	Complex (≥ 3 unrelated abnormalities)	3
t(6;9)†	1	t(6;9)	1
t(9;22)†	1	t(9;22)	1
		11q23 rearrangement	6
		del(7q)	1
		del(9q)	1
		Unknown or other	6 (7)
Total	79	Total	79

*As described in "Materials and Methods."

†Risk status for t(6;9) or t(9;22) is not defined by MRC criteria, possibly because of a lack of these low-frequency aberrations in their cohort.

karyotypes (≥ 3 unrelated abnormalities); and unknown, all other abnormalities. Thus, the major differences between the 2 classifications are the definition of complex karyotype (≥ 5 abnormalities in MRC versus ≥ 3 unrelated abnormalities in SWOG); the classification of 11q abnormalities as intermediate by MRC and adverse by SWOG; and the classification by MRC of all t(8;21) as favorable, despite the presence of either del(9q) or complex karyotypes. In addition, all SWOG karyotypes of unknown prognostic significance are designated as intermediate risk by MRC criteria.

Conditioning Regimens

Details of the conditioning regimens are shown in Table 3. A diagnostic lumbar puncture was performed at the beginning of conditioning with intrathecal injection of cytosine arabinoside 30 mg/m² or methotrexate 12 mg. In general, cyclophosphamide (Cy) with fractionated total body irradiation (TBI) was used before unrelated donor BMT (Cy: 50 mg/kg intravenously [IV] daily, days -6 to -4; TBI: 200 cGy twice a day, days -3 to -1), and a busulfan (Bu)-based regimen, primarily BuCy-2 [25], was used for related donor BMT patients (Bu: 1 mg/kg by mouth every 6 hours daily, days -7 to -4; Cy: 60 mg/kg IV daily, days -3 and -2). Patients receiving Bu were given phenytoin as seizure prophylaxis [26]. Uroepithelial prophylaxis was with hyperhydration.

Bone Marrow Transplantation

Seventy patients received marrow from a histocompatible sibling, 5 from a 1-antigen mismatched sibling, and 2 from matched relatives. Three patients received peripheral blood

stem cells from a histocompatible sibling, 1 patient received peripheral blood stem cells from a 1-antigen mismatched sibling, and 1 patient received marrow and peripheral blood from a sibling. Eleven patients received marrow from an unrelated donor; 9 pairs were matched, 1 pair was 1-antigen mismatched, and 1 pair was 2-antigen mismatched. Bone marrow was plasma- and/or erythrocyte-depleted when necessitated by ABO incompatibility [27].

Graft-versus-Host Disease Prophylaxis

Details of the different graft-versus-host disease (GVHD) prophylaxis regimens used are outlined in Table 3. The majority of patients received cyclosporine (CSP) and short-course methotrexate with or without other agents [28-31]. One patient received unrelated donor bone marrow that was T-cell depleted by an immunomagnetic cell separation technique using iron-dextran particles cross-linked to anti-CD3 antibodies [32]. Treatment of established acute GVHD was with high-dose methylprednisolone (MP); those with GVHD resistant to MP received an anti-T-cell antibody, either anti-CD5/ricin immunotoxin (XomaZyme; XOMA, Berkeley, CA) [29], interleukin-2 receptor antibody (BT563 or B-B10; Biotest, Dreieich, Germany), or antithymocyte globulin (either ATGAM [Upjohn, Kalamazoo, MI] or thymoglobulin [Sangstat Medical, Menlo Park, CA]). GVHD was graded according to standard criteria [33].

Supportive Care

Patients were treated on the Leukemia and Bone Marrow Transplant Unit at the VHHSC in rooms equipped

Table 3. *Transplantation Details**

	No. of Patients (% of Total)
Conditioning regimen	
BuCy	63 (80)
Cy/TBI	11 (14)
AraC/Cy/TBI	3 (4)
Other	2 (2)
Stem cell source	
Related donor	68 (86)
Unrelated donor	11 (14)
GVHD prophylaxis	
CSP/MTX	56 (71)
CSP/MTX + other	13 (16)
CSP/MP	4 (5)
MTX and/or MP	3 (4)
Other	3 (4)
Unknown	0 (0)

*AraC indicates cytosine arabinoside; MTX, methotrexate.

with high-efficiency particulate air (HEPA) filtration. Hickman catheters were used routinely. Empiric IV antibiotics, amphotericin B, acyclovir, cytomegalovirus (CMV)-negative blood products, high-titer anti-CMV immunoglobulin, and total parenteral nutrition were given as required. Low-dose heparin (100 U/kg per day) for veno-occlusive disease prophylaxis was given routinely after November 1992 [34]. From June 1992, fungal prophylaxis was with fluconazole IV at 200 to 400 mg per day or amphotericin B IV at 10 mg/m² per day. From September 1992, if the donor or recipient was CMV antibody positive, gancyclovir was given from engraftment until day 100 at a dose of 5 mg/kg IV twice a day for 5 days and then 5 mg/kg daily from Mondays to Fridays or as adjusted for renal impairment. Growth factors were used for graft failure, drug-induced neutropenia, and, from October 1995 to September 1997, in patients receiving postengraftment gancyclovir as part of a separate study [35].

Statistical Analysis

The actuarial OS, EFS, treatment-related mortality (TRM), and relapse probabilities were calculated using the product limit estimates of Kaplan and Meier [36], with surviving patients being censored on January 30, 2002. The following factors were analyzed with respect to OS, EFS, TRM, and relapse rates: recipient age, white blood cell count (WBC) at diagnosis, FAB classification, cytogenetic prognostic group (favorable, intermediate, or adverse according to MRC criteria), number of chemotherapy cycles to enter CR1 (1 or >1 cycle), time from diagnosis to BMT, donor type (related/unrelated), and year of BMT. Univariate and multivariate analyses of prognostic factors were performed using Cox's proportional hazard regression model [37].

RESULTS

Seventy-nine (85%) of 93 patients had successful marrow karyotyping at diagnosis. In 3 patients, karyotyping was attempted but no analyzable metaphases were obtained, and in 11 patients, cytogenetic analysis was not performed at diagnosis (patients were diagnosed and treated with

induction chemotherapy before referral to VHHSC for BMT). Because there were no differences in OS, EFS, TRM, or risk of relapse between the patients who had successful marrow karyotyping and those who did not, the analysis included only patients with available karyotype at diagnosis (79 patients). The patients were divided into the 3 prognostic karyotype groups according to MRC criteria as defined in "Materials and Methods". Fifteen patients (19%) were in the favorable-prognosis group, 55 patients (70%) were in the intermediate-prognosis group, and 9 patients (11%) were in the adverse-prognosis group (Table 2). In the favorable-prognosis group, 11 of 15 patients had chromosomal abnormalities in addition to the favorable change. In 4 patients, these abnormalities were numerical chromosomal abnormalities commonly seen with such changes [-Y in 2 patients with t(8;21) and +22 in 2 patients with inv(16)]. None of these 11 cases had poor prognostic karyotypic changes in association with the good prognostic chromosomal abnormality. In the intermediate-prognosis group, 36 of 55 patients had a normal karyotype, which is 46% of the total group, a proportion very similar to that reported by others [1,2,6]. The adverse-prognosis group consisted of 9 patients, 5 of whom had a 3q rearrangement and 2 of whom had complex cytogenetic changes, 1 patient a t(6;9) and another a t(9;22).

With a median follow-up of 93 months (range, 16-241 months), the 5-year OS rates were not statistically significantly different between the 3 cytogenetic risk groups: 65% (95% confidence interval [CI], 35%-84%) for the favorable-prognosis group, 57% (95% CI, 42%-70%) for the intermediate group, and 67% (95% CI, 28%-8%) for the adverse group ($P = .76$). There was also no difference in the 5-year EFS rates among the 3 groups: 58% (95% CI, 29%-79%) for the favorable-prognosis group, 58% (95% CI, 43%-70%) for the intermediate group, and 67% (95% CI, 28%-88%) for the adverse group ($P = .90$; Figure 1A). The TRM rates were similar among the 3 groups: 14% (95% CI, 4%-45%) in the favorable, 23% (95% CI, 12%-39%) in the intermediate, and 0% in the adverse group ($P = .37$). The 5-year relapse rates were also not significantly different: 32% (95% CI, 13%-66%) in the favorable, 25% (95% CI, 15%-40%) in the intermediate, and 33% (95% CI, 12%-72%) in the adverse risk group ($P = .80$; Figure 2A).

When the 79 patients were reclassified using the SWOG criteria for cytogenetic prognostic subgroups, 9 patients' cytogenetic changes that were coded as intermediate by MRC criteria were assessed as adverse by SWOG criteria. Consequently, the proportion of patients with adverse karyotype increased (24% for SWOG criteria compared to 11% for MRC criteria). Six patients whose abnormalities were coded as intermediate by MRC criteria had their abnormalities categorized as unknown or other by the SWOG classification. Using the SWOG strategy, the 5-year OS rates were 65% (95% CI, 35%-84%) in the favorable group, 62% (95% CI, 44%-76%) in the intermediate group, 54% (95% CI, 29%-74%) in the adverse group, and 50% (95% CI, 11%-80%) in the unknown category ($P = .69$). EFS rates were 58% (95% CI, 29%-79%) in the favorable group, 62% (95% CI, 45%-76%) in the intermediate group, 56% (95% CI, 31%-75%) in the adverse group, and 50% (95% CI, 11%-80%) in the unknown category ($P = .82$; Figure 1B). The TRM rates were 14% (95% CI, 4%-45%) in the favor-

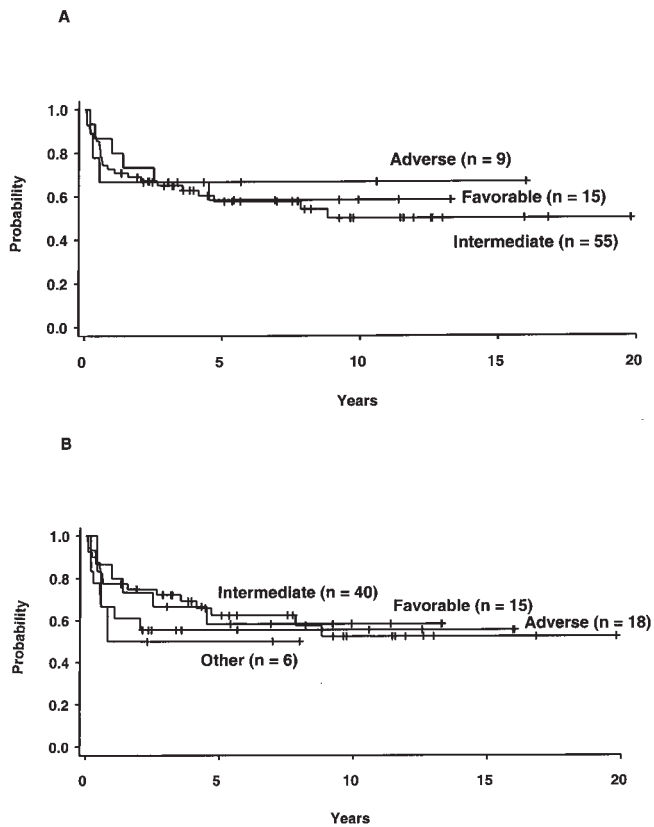


Figure 1. A, EFS after allo-BMT by cytogenetic prognostic group at diagnosis using MRC criteria. B, EFS after allo-BMT by cytogenetic prognostic group at diagnosis using SWOG criteria.

able group, 24% (95% CI, 13%-44%) in the intermediate group, 11% (95% CI, 3%-38%) in the adverse group, and 0% in the unknown category ($P = .60$). Similarly, the 5-year relapse rates were 32% (95% CI, 13%-66%) in the favorable group, 17% (95% CI, 8%-35%) in the intermediate group, 38% (95% CI, 19%-65%) in the adverse group, and 50% (95% CI, 20%-89%) in the other group ($P = .19$; Figure 2B). Thus, the use of this alternative cytogenetic classification did not change the significance of the different prognostic subgroups after allo-BMT for AML in first CR.

The different cytogenetic subgroups (by MRC criteria) were also analyzed for the presence of other known prognostic variables. Although patients in the favorable-prognosis cytogenetic group were somewhat younger (67% were <36 years old) than those in the intermediate-prognosis (40%) and adverse-prognosis (44%) groups, the differences in age did not reach statistical significance ($P = .24$). More patients with favorable cytogenetic changes had a low WBC at diagnosis (66% of patients with WBC <10⁹/L) compared to patients in the intermediate group (45%) and the adverse group (11%) ($P = .018$). Also, more patients in the favorable- and intermediate-prognosis groups needed only 1 cycle of induction chemotherapy to enter CR (93% and 84%, respectively) than did patients in the adverse group (56%) ($P = .03$). No patients in the favorable cytogenetic group and only 15% of patients in the intermediate group received unrelated donor transplants compared to

33% of patients in the adverse group ($P = .023$). There were no differences between the groups with respect to the time from diagnosis to transplantation and the period when the transplantation was done (ie, 1981-1991 versus 1992 or later). The FAB subtypes of leukemias in the favorable-prognosis group were M2, M3, or M4, whereas in the intermediate group, all subtypes were represented and in the adverse group, AML M0, M1, M4 and M5 were seen.

Univariate analysis of noncytogenetic variables for the total group of 79 patients showed that only the use of unrelated donors had a prognostic influence on OS ($P = .04$) and TRM ($P = .03$) and also had a trend toward reduced EFS ($P = .06$). Unrelated donor transplants were also linked to a worse prognosis than were related donor transplants in multivariate analysis for OS ($P = .03$) and TRM ($P = .04$). No other variable was found to be a significant predictor of OS, EFS, TRM, or risk of relapse (Table 4).

DISCUSSION

This study analyzed the impact of diagnostic karyotype on outcome following allo-BMT in patients with AML in CR1 treated at a single institution. Although patient numbers are small, the data demonstrate no difference in TRM rates, relapse rates, disease-free survival (DFS) rates, or OS rates among patients with cytogenetic changes known to predict

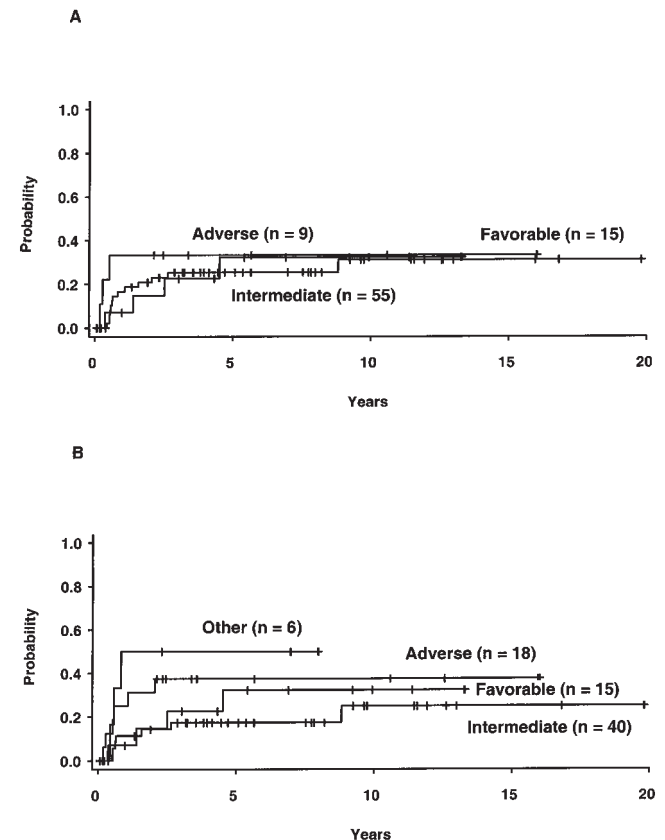


Figure 2. A, Risk of relapse after allo-BMT by cytogenetic prognostic group at diagnosis using MRC criteria. B, Risk of relapse after allo-BMT by cytogenetic prognostic group at diagnosis using SWOG criteria.

Table 4. Univariate Analysis for Outcome at 5 Years

Characteristics	No. of Patients	OS		EFS		Relapse		TRM	
		%	P	%	P	%	P	%	P
Age at diagnosis, y									
17-25	17	52		52		41		12	
26-35	19	72	.29	67	.33	22	.28	14	.63
36-55	43	57		58		25		23	
WBC at diagnosis									
0-9 × 10 ⁹ /L	36	58		55		29		23	
10-50 × 10 ⁹ /L	28	59	.95	59	.88	26	.90	20	.60
>50 × 10 ⁹ /L	14	63		63		32		7	
FAB classification*									
M0	3	67		67		0		33	
M1	16	43		44		46		19	
M2	13	58		49		11		45	
M3	9	67	.45	67	.37	25	.63	11	.14
M4	21	66		66		30		6	
M5	12	64		64		25		14	
M6	2	100		100		0		0	
Karyotype (MRC criteria)									
Favorable	15	65		58		32		14	
Intermediate	55	57	.77	58	.90	25	.76	23	.37
Adverse	9	67		67		33		0	
No. of cycles to enter CR									
1 cycle	65	57		56		32		18	
>1 cycle	14	71	.96	71	.81	9	.16	21	.17
Time from diagnosis to BMT									
0-12 weeks	29	54		51		36		20	
13-24 weeks	42	55	.24	55	.41	29	.40	23	.75
>24 weeks	8	100		100		0		0	
Type of donor									
Related	68	62		60		27		17	
Unrelated	11	45	.04	45	.06	38	.56	27	.03
Year of BMT									
1981-1991	28	64		64		23		16	
>1991	51	58	.32	57	.30	30	.56	19	.35

*Unclassifiable in 3 patients.

different rates of successful remission induction, relapse, and overall survival following conventional chemotherapy [1].

Fifteen percent of AML patients referred to our center for allo-BMT during the period studied did not have cytogenetic analysis performed at diagnosis, reflecting the fact that this investigation was not routinely available in all referring centers before 1990. However, among those cases in which karyotype analysis was performed, cytogenetic abnormalities were detected in 52% overall, including failures and normal results. This rate is similar to the frequencies reported in large series of de novo AML patients [1,2,6].

Among the 15 patients with cytogenetic changes consistent with a favorable prognosis, 11 had additional changes. However, 2 large studies have found that such additional chromosomal abnormalities do not affect prognosis [1,17]. Thus, these changes were ignored when assigning patients to cytogenetic risk groups. The OS and DFS rates following allo-BMT of this patient group in our series were very similar to those reported by the MRC group and others [1,17]. Currently, most centers, including our own, would not perform transplantation for patients in the favorable cytogenetic prognostic group in CR1 because available data suggest

that this approach has no advantage over chemotherapy alone [1,8]. However, the majority of the 15 favorable-prognosis patients in our series received transplants before 1997, at which time these facts were not fully appreciated.

Of our 9 patients with adverse prognostic cytogenetic abnormalities, 7 were alive and free of disease 16 to 130 months following transplantation. These data contrast with our experience in patients receiving allografts for myelodysplastic syndrome (MDS), among whom adverse cytogenetic changes as defined by the International Prognostic Scoring System for MDS [38] predicted a substantially increased relapse rate and shorter survival following allo-BMT than seen in the standard- and good-risk cytogenetic subgroups [39]. However, different classifications of cytogenetic risk groups were used in the 2 studies, and the specific abnormalities seen in the patients included in the poor-prognosis groups also differed. Among 17 MDS patients in the poor-prognosis group, 7 patients had abnormalities of chromosome 7 and 10 patients had 3 or more chromosomal changes. In the current series, 5 of 9 AML patients had chromosome 3q rearrangement, with 1 of these patients having 2 additional chromosomal changes.

The poor-prognosis group of patients in the current study was 11% of the total group of allo-BMT patients studied. Although this proportion is similar to the frequency determined at diagnosis of AML in the MRC trial [1], it may also reflect the low CR1 rate and short remission duration in this group of patients. Thus, it is likely that some AML patients with high-risk chromosomal abnormalities failed to enter CR or relapsed before they could be referred to our center to undergo allo-BMT. The biology of disease among these 9 patients who received transplants was probably relatively favorable compared to that generally observed in AML patients in the unfavorable-prognosis karyotype group. Of note, none of the patients studied here had -5 , -7 , or $\text{del}(5q)$, cytogenetic abnormalities that are known to be associated with a particularly poor prognosis and whose frequency increases in older patients in whom allo-BMT cannot be considered [2,12]. The absence of such patients may have had a favorable impact on the OS and DFS of the group with adverse prognosis cytogenetic abnormalities in our series. However, when we further analyzed the 3 cytogenetic subgroups for the frequency of other prognostic variables, we found that among patients with adverse-prognosis cytogenetics compared to the other 2 groups there was a higher percentage of patients who were older, had higher presenting WBC counts, required more than 1 cycle of induction chemotherapy to enter CR, and more often had an unrelated donor as the stem cell source. These differences were statistically significant for the last 3 variables, demonstrating the generally unfavorable characteristics of this patient group. Nevertheless, these data indicate that long-term DFS is possible after allo-BMT for some patients in the poor-prognosis group if transplantation is carried out in CR1.

Our finding that there was no correlation between the cytogenetic prognostic risk group assigned at diagnosis in AML patients and OS, EFS, or TRM is consistent with several European studies in which the number of patients studied was similar [4,20,21]. Interestingly, 2 of these series [4,20] used the same classification of karyotype abnormalities as did Keating et al. [19] in a substantially larger study in which cytogenetic abnormalities showed a trend toward prediction of relapse rate after allo-BMT. The major difference between this classification and the MRC classification is that in the former classification, the intermediate-prognosis group included normal karyotype and $-Y$ only, with all other abnormalities (other than the 3 recognized good prognostic changes) included in the poor-prognosis group [19]. The more recent MRC study has reclassified a number of common abnormalities from the poor- to the intermediate-prognosis group, ie, $+8$, $11q23$ rearrangement, $+21$, $\text{del}(7q)$, $+22$, and other numerical and structural abnormalities that did not meet their criteria for adverse prognostic significance [1]. This difference might explain why the former studies observed less difference between the poor- and intermediate-prognosis subgroups than did the latter study. In addition to the MRC study, 2 other large cooperative group reports and an International Bone Marrow Transplant Registry (IBMTR) analysis have demonstrated a prognostic significance for karyotype on outcome after allo-BMT [16-18]. In each case, the cytogenetic risk-group classification was different from that of the MRC, with $11q23$ rearrangements and $\text{del}(7q)$ notably classified with the poor-

risk group and complex abnormalities that did not involve -5 or -7 [16] or $t(9;22)$ [17,18] classified with the intermediate-risk group. Although no specific mention is made of $3q$ rearrangements in these 3 studies, it appears that they would have been classified with the intermediate-risk group in 2 of the 3 studies [16,17]. Five of our 9 poor-prognosis patients had $3q$ rearrangements, and as of this report 4 of them were alive and free of disease after allo-BMT, suggesting that AML with $3q$ rearrangements may be more effectively treated with allo-BMT than are leukemias with other poor prognostic changes. Because the MRC study did not indicate how many of their allo-BMT patients carried the $3q$ rearrangement, a direct comparison of their poor-risk transplantation patients and ours cannot be made. To determine if our choice of the MRC cytogenetic classification had influenced our results, we reclassified the patients according to SWOG cytogenetic criteria. Although the SWOG reclassification increased the number of patients in the poor-prognosis category in our series, it had no impact on our finding that there was no significant difference in OS, DFS, relapse rate, and TRM between the different prognostic subgroups.

The primary aim of this study was to examine the relationship between karyotype and outcome after allo-BMT. However, we also evaluated the effects of other factors that have been shown to influence response to treatment and survival in AML, ie, age at diagnosis, WBC count at diagnosis, FAB classification, number of chemotherapy cycles to enter CR, time from diagnosis to BMT, the use of related or unrelated donors, and year of transplantation [8,19,40-42]. The only variable found to have an impact on OS and TRM was the use of an unrelated donor, which was associated with a worse prognosis.

In summary, although the small size of this study limits its power to identify subtle differences between prognostic groups, the data suggest that the diagnostic karyotype had a relatively minor impact on outcome after allo-BMT for AML in CR1. It is encouraging that long-term DFS is at least a possibility for patients with a poor prognostic karyotype. These results are consistent with those recently published by the SWOG/Eastern Cooperative Oncology Group (ECOG), in which AML patients with unfavorable cytogenetics who received allo-BMT obtained a significant survival advantage over those receiving an autologous transplant or conventional chemotherapy [15]. More recently, the European Organization for Research and Treatment of Cancer-Gruppo Italiano Malattie Ematologiche dell'Adulto (EORTC-GIMEMA) AML-10 trial, which included a larger number of patients in the poor-risk category than did the MRC trial and most other studies, demonstrated that patients with poor prognostic cytogenetics who proceeded to allo-BMT had a similar outcome to those in other prognostic subgroups and a significantly improved outcome compared to patients with poor prognostic cytogenetics in whom allo-BMT was not performed [22].

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