Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group study

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The associations of cytogenetics with complete remission (CR) rates, overall survival (OS), and outcomes after CR were studied in 609 previously untreated AML patients younger than 56 years old in a clinical trial comparing 3 intensive postremission therapies: intensive chemotherapy, autologous transplantation (ABMT), or allogeneic bone marrow transplantation (alloBMT) from matched related donors. Patients were categorized into favorable, intermediate, unfavorable, and unknown cytogenetic risk groups based on pretreatment karyotypes. CR rates varied significantly ($P < .0001$) among the 4 groups: favorable, 84% (95% confidence interval [CI], 77%-90%); intermediate, 76% (CI, 71%-81%); unfavorable, 55% (CI, 48%-63%); and unknown, 54% (CI, 33%-74%). There was similar significant heterogeneity of OS ($P < .0001$), with the estimated relative risk of death from any cause being 1.50 (CI, 1.10-2.05), 3.33 (CI, 2.43-4.55), and 2.66 (CI, 1.59-4.45) for the intermediate, unfavorable, and unknown risk groups, respectively, compared with the favorable group. In multivariate analyses, the effects of cytogenetic risk status on CR rate and OS could not be explained by other patient or disease characteristics. Among postremission patients, survival from CR varied significantly among favorable, intermediate, and unfavorable groups ($P = .0003$), with significant evidence of interaction ($P = .017$) between the effects of treatment and cytogenetic risk status on survival. Patients with favorable cytogenetics did significantly better following ABMT and alloBMT than with chemotherapy alone, whereas patients with unfavorable cytogenetics did better with alloBMT. Cytogenetic risk status is a significant factor in predicting response of AML patients to therapy; however, to tighten treatment correlates within genetically defined AML subsets, a significantly larger leukemia cytogenetic database is warranted. (Blood. 2000; 96:4075-4083)

Introduction

Cytogenetic analysis performed at diagnosis is generally recognized as the single most valuable prognostic factor in acute myeloid leukemia (AML).[1,2] Characterization of adult patients with AML according to presentation karyotype provides an important basis for selection of therapy. For example, the outcome for patients with t(15;17) acute promyelocytic leukemia has substantially improved with the use of all-*trans*-retinoic acid in combination with chemotherapy, but the drug is without benefit for patients lacking this translocation.[3,4] A recent report categorizing patients to one of 3 cytogenetic groups, core binding factor (CBF) positive, normal, or all other karyotypic abnormalities, followed by randomization to either standard, intermediate, or high-dose cytarabine, suggested that the effect of cytarabine intensification varied significantly among the cytogenetic risk groups, with the major benefit of high-dose cytarabine restricted to patients with CBF karyotypes.[5] The German AML Cooperative recently reported improved complete remission (CR) rates for unfavorable cytogenetics using a double induction strategy of cytarabine/daunorubicin/6-thioguanine (TAD), followed by high-dose cytarabine with mitoxantrone (HAM).[6] Taken together, these data suggest that therapeutic strategies based on expected response of specific disease karyotype subsets may improve the outcome of therapy in AML.

Optimal postremission therapy for young patients with AML remains a topic of lively discussion. The postremission strategies of high-dose cytarabine and allogeneic and autologous stem cell transplantation all have contributed to improved outcome for adult patients with AML. To date, randomized studies comparing these therapies have led to inconsistent conclusions.[7-9] In most of these studies, outcome was not analyzed according to cytogenetic risk group. To investigate whether the impact of different postremission strategies might vary according to cytogenetic risk group, we analyzed the results of a large phase III trial (E3489/S9034) for young adult (< 56 years of age) AML patients who received idarubicin and cytarabine as induction therapy and allogeneic or autologous bone marrow transplantation or intensive chemotherapy as postremission therapy. The objectives of this analysis were (1) to examine the relationship of disease karyotype with CR rate, overall survival (OS), and postremission outcomes and (2) to

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examine the effect of cytogenetic risk groups within the 3 postremission arms. To allow comparison with the 10th United Kingdom Medical Research Council AML trial (MRC AML 10 trial), the cytogenetic data were also coded and analyzed according to published MRC criteria.[10]

Patients, materials, and methods

Patients and protocol

This study was based on patients registered by the Southwest Oncology Group (SWOG) or Eastern Cooperative Oncology Group (ECOG) to a single phase III intergroup study, E3489/S9034, a comparison of 3 intensive postremission therapies for adult patients (age 16-55) with previously untreated AML. The treatment regimens and clinical results for this trial have been described previously.[9] Briefly, all patients received 1 or 2 courses of induction therapy consisting of idarubicin, 12 mg/m^2 intravenous push daily for 3 days, and intravenous cytarabine, 25 mg/m^2; followed by 100 mg/m^2 per day continuously infused for 7 days. Patients achieving a CR received 2 and 5 days of idarubicin and cytarabine, respectively, at the induction doses and were then assigned or randomized to one of 3 postremission therapies. Patients with a histocompatible sibling donor were assigned to allogeneic bone marrow transplantation (alloBMT). Those without matched donors were randomized to either intensive consolidation chemotherapy or autologous bone marrow transplantation (ABMT). FAB morphologic classification was based on morphology and cytochemistry. Flow cytometry was used to confirm FAB M0 cases. Cytogenetic results were not known to morphologists and were not considered in assigning FAB morphologic type. The randomization was stratified by age (16-45 vs 46-55), FAB classification, whether 1 or 2 induction courses were required to achieve CR, and non–peer-reviewed karyotypic categorization (favorable vs intermediate vs unfavorable) as described.[9]

Cytogenetic analyses

Cytogenetic studies on bone marrow or unstimulated peripheral blood samples obtained prior to induction therapy were performed using standard G-banding with trypsin-Giemsa or trypsin-Wright's staining in ECOG- or SWOG-approved cytogenetics laboratories. Karyotypes were interpreted using International System for Cytogenetic Nomenclature (1995) criteria.[11] Studies were considered normal diploid if no clonal abnormalities were detected in a minimum of 20 mitotic cells examined. Central review of karyotypes for SWOG patients was performed by at least 3 members of the SWOG cytogenetics committee. Similarly, ECOG cytogenetic studies were performed and evaluated according to ECOG standards. In contrast to the data presented in the original report,[9] the cytogenetic data reported here were centrally reviewed to assess quality, processing, and final karyotypic interpretation. For this analysis, all studies deemed incomplete or inadequate were excluded.

Cytogenetic abnormalities were grouped according to published criteria adopted by SWOG.[2,5,10,12-16] Four cytogenetic categories were defined (Table 1). The *favorable* risk category included patients with abnormalities (abn) of inv(16)/t(16;16)/del(16q) or t(15;17) with any additional abnormalities, or t(8;21) without either a del(9q) or being part of a complex karyotype. The presence of a del(9q) in patients with t(8;21) leukemia has been reported as a poor risk indicator requiring more aggressive treatment.[15] The *intermediate* risk category included patients characterized by +8, −Y, +6, del(12p), or normal karyotype. The *unfavorable* risk category was defined by the presence of one or more of −5/del(5q), −7/del(7q), inv(3q), abn 11q, 20q, or 21q, del(9q), t(6;9), t(9;22), abn 17p, and complex karyotype defined as 3 or more abnormalities. Twenty-six patients had cytogenetic aberrations considered to have *unknown* prognostic significance because of their low frequency in AML.

To allow comparison with the MRC AML 10 trial, the cytogenetic data were also coded and analyzed according to published MRC criteria.[10] The major differences between these 2 systems are the definition of complex karyotypes (≥ 3 unrelated karyotypic differences in SWOG vs ≥ 5 aberrations by MRC); the classification by MRC of all t(8;21) studies as favorable, despite the presence of del(9q) or complex karyotypes; and the classification of 11q aberrations as intermediate by MRC but unfavorable by SWOG. In addition, all SWOG karyotypes of unknown prognostic significance are designated as intermediate risk by MRC.

Criteria for treatment outcomes

Complete response and relapse were defined according to standard criteria.[17] OS was measured from the day of registration on study until death from any cause, censored for patients known to be alive at last contact. Survival from CR was defined similarly but from the date CR was achieved. Disease-free survival (DFS) was measured from the date of CR until either relapse or death from any cause, censored at last contact for patients last known to be alive without report of relapse.

Statistical analysis

Collection and quality control of patient pretreatment and outcome data were performed according to standard ECOG procedures. Analyses involving postremission therapy were based on intention to treat, with all patients analyzed according to their postremission treatment arms irrespective of whether they actually received the designated treatment. Distributions of OS and DFS were estimated by the method of Kaplan and Meier.[18] Prognostic significance of cytogenetic categories, treatment assignments, and other pretreatment factors (age, sex, performance status, FAB classification, marrow and peripheral counts, disease signs and symptoms, and extramedullary involvement) were investigated in logistic regression models for CR and proportional hazards regression models for OS, survival from CR, and DFS. Quantitative factors such as age, blood or marrow cell counts, or percentages were treated as continuous variables in these regression models. The prognostic effects of the SWOG and MRC cytogenetic classification systems were compared indirectly, as follows. In regression models, collapsing categories of a qualitative predictor variable restricts the model's ability to fit the data. Measures of the resulting "loss of fit" provide formal statistical tests of whether the collapsed categorization

Table 1. Southwest Oncology Group and Medical Research Council cytogenetic risk category definitions

Risk status	SWOG coding	No. of patients (n = 609)	MRC coding	No. of patients (n = 609)
Favorable	inv(16)/t(16;16)/del(16q), t(15;17) with/without secondary aberrations; t(8;21) lacking del(9q) or complex karyotypes	121 (20%)	inv(16)/t(16;16)/del(16q), t(15;17), t(8;21) with/without secondary abn	130 (21%)
Intermediate	Normal, +8, +6, −Y, del(12p)	278 (46%)*	Normal, 11q23 abn, +8, del(9q), del(7q), +21, +22, all others	375 (62%)
Unfavorable	del(5q)/−5, −7/del(7q), abn 3q, 9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22) and complex karyotypes (≥ 3 unrelated abn)	184 (30%)	del(5q)/−5, −7, abn (3q), complex karyotypes (≥ 5 unrelated abn) t(9;22) and t(6;9)†	104 (17%)
Unknown	All other abnormalities	26 (4%)	Category not recognized	—

SWOG indicates Southwest Oncology Group; MRC, Medical Research Council (United Kingdom); abn, abnormality.
*The intermediate group contains 244 patients with normal karyotypes.
†Risk status for t(6;9) or t(9;22) is not defined by MRC criteria, presumably due to a lack of these low-frequency aberrations in their cohort.

fits the data significantly worse than the original, finer categorization. Such tests are not available if, like the SWOG and MRC schemes, one categorization cannot be obtained by collapsing categories of the other. Therefore, the relative prognostic values of the 2 schemes were examined by testing the loss of fit associated with each one compared with a model with categories defined by the combination of both. If the resulting loss of fit was statistically significant for one scheme but not the other, the latter scheme could be viewed as having greater prognostic value. All *P* values are 2-tailed. Analyses were based on data available as of July 7, 1998.

Results

Between March 1990 and February 1995, a total of 808 patients entered study E3489/S9034, including 293 from SWOG and 492 from ECOG (Figure 1). The remaining 23 patients from a third cooperative group were omitted from this study. Eighteen of the SWOG and ECOG patients were ineligible for study E3489/S9034, and 4 other patients never began protocol therapy. Of the 763 SWOG and ECOG patients eligible for this prospective study, 609 (80%) had acceptable karyotypic studies at the time of central review for this study. Reasons for exclusion included no specimen submitted (n = 30), no growth (n = 62), and inadequate number of cells analyzed, inadequate specimen processing, or poor unevaluable morphology (n = 62). The 609 evaluable patients (284F, 325M) had median age of 39 (range 16-55).

The ECOG and SWOG patients were similar with respect to the proportion with normal studies (40% for both groups) and the ratios of favorable, intermediate, unfavorable, and unknown risk groups (Table 2). They were also similar in the prevalence of specific clonal abnormalities, with the exception of inv(3q), for which 11 of 12 cases were from ECOG, most likely reflecting a random chance imbalance. However, the prevalence of "complex" and miscellaneous "other" abnormalities was higher in the SWOG cohort (14% and 24%, respectively) than the ECOG cohort (10% and 17%, respectively). Characteristics of included patients and leukemic specimens, by SWOG cytogenetic risk assessment, are given in Table 3.

Response to induction therapy

A total of 584 of the 609 patients had sufficient data to confirm their responses to remission induction therapy. Of these, 412 (71%) achieved CR. The CR rate varied significantly ($P < .0001$) among the 3 groups with known cytogenetic risk status, ranging from 84% (98 of 117; 95% confidence interval [CI], 77%-90%) for favorable to 76% (205 of 270; CI, 71%-81%) for intermediate to 55% (96 of 173; CI, 48%-63%) for unfavorable (Table 4). This heterogeneity was largely due to the lower CR rate in the unfavorable group compared with the other 2 combined ($P < .0001$); the difference between intermediate and favorable groups was not significant ($P = .080$). The CR rates were similar in the 2 Groups: 242 of 348 (70%) for ECOG and 170 of 236 (72%) for SWOG, and there was no significant interaction between the effects of Group and the 3 cytogenetic risk categories ($P = .64$). Thus, the prognostic significance of cytogenetic category was similar in the 2 Groups despite differences in the proportions of patients with complex or miscellaneous "other" abnormalities.

Multiple logistic regression analyses that explored the prognostic effects of the available pretreatment variables, including all of those listed in Table 3, along with cytogenetic risk status were performed for the 560 patients with known risk status and response. These analyses suggested that only cytogenetic risk status and either performance status (PS) ($P = .0059$) or fever at presentation

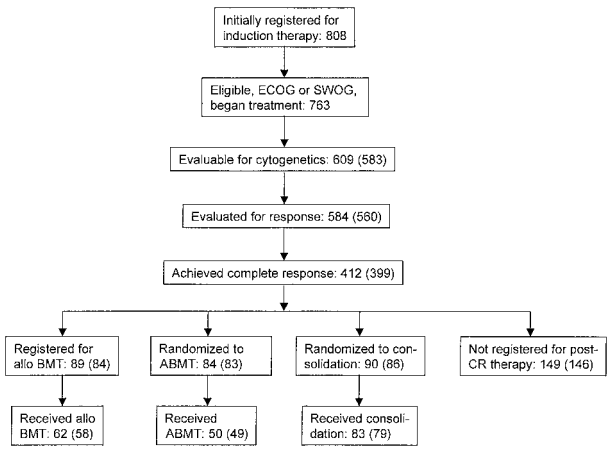

Figure 1. Schematic diagram of treatment plan and numbers of patients assigned or randomized to treatment arms and treated at each step. Numbers in parentheses refer to patients with known SWOG cytogenetic risk status.

Table 2. Frequencies of cytogenetic risk categories and specific clonal abnormalities, by cooperative group

	ECOG (n = 355)		SWOG (n = 254)		Total (n = 609)	
	No.	%	No.	%	No.	%
Favorable	71	20	50	20	121	20
Intermediate	163	46	115	45	278	46
Unfavorable	106	30	78	31	184	30
Unknown	15	4	11	4	26	4
−5/5q−*	23	6	13	5	36	6
−7/7q−†	29	8	23	9	52	9
+8‡	30	8	23	9	53	9
inv(3)/t(3;3)	11	3	1	0.4	12	2
Abnormality of 11q	22	6	20	8	42	7
Abnormality of 13q	5	1	3	1	8	1
i(17q)	2	1	1	0.4	3	0.5
Abnormality of 17p	5	1	4	2	9	1
Abnormality of 20q	2	1	4	2	6	1
Abnormality of 21q§	3	1	3	1	6	1
t(9;22)	7	2	1	0.4	8	1
t(8;21)‖	31	9	19	7	50	8
t(15;17)¶	13	4	14	6	27	4
inv(16)/t(16;16)#	30	8	23	9	53	9
t(6;9)	4	1	7	3	11	2
del(9q)	7	2	10	4	17	3
Other trisomy	34	10	28	11	62	10
−X	7	2	2	1	9	1
−Y**	15	8	5	4	20	6
Complex abnormalities††	36	10	35	14	71	12
Other abnormality(ies)	59	17	61	24	120	20

ECOG indicates Eastern Cooperative Oncology Group; SWOG, Southwest Oncology Group.

*35 cases coded as unfavorable; one inv(16) case with −5 coded as favorable.

†Sole abnormality in 10 cases; 49 of 52 coded as unfavorable. Three cases coded as favorable due to presence of t(8;21) or inv(16).

‡Sole abnormality in 25 cases; 19 cases coded as unfavorable and 6 cases coded as favorable because of the presence of other abnormalities.

§Other than t(8;21).

‖Sole abnormality in 18 cases; 41 coded as favorable; 9 cases coded as unfavorable: 7 with del(9q) and 2 cases with complex karyotypes.

¶All coded as favorable. Sole abnormality in 18 cases. Three cases with complex abnormalities.

#All coded as favorable. Sole abnormality in 40 cases. Three cases with −7/7q− or −5/5q− (2 with complex karyotypes).

**Percentages for −Y are based on the 325 males only.

††Complex abnormalities per MRC criteria for 609 patients accounted for 31 patients (9%) in the ECOG cohort and 22 patients (9%) in SWOG for a total of 53 patients (9%).

Table 3. Patient and disease characteristics, by cytogenetic risk status

Characteristic	Favorable (n = 121)	Intermediate (n = 278)	Unfavorable (n = 184)	Unknown (n = 26)
Age, y				
Median	34	40	39	44
Range	17-54	16-55	17-54	18-54
Female	43%	54%	40%	35%
Median WBC ($\times 10^9$/L)	15.1	18.0	9.5	21.5
Median marrow blast*	56%	64%	69%	83%
Median blood blast*	38%	37%	30%	52%
Median hemoglobin (g/dL)*	8.7	9.3	8.7	9.0
Median platelets ($\times 10^9$/L)*	37	61	56	41
Hepatomegaly*	8%	8%	6%	0%
Splenomegaly*	9%	9%	10%	4%
Extramedullary leukemia*	42%	49%	44%	41%
Fever > 38° at presentation*	47%	44%	51%	26%
Zubrod performance status*				
0	36%	33%	38%	35%
1	51%	54%	43%	46%
2-4	12%	13%	18%	19%
Fab class (central morphology review)				
M1	7%	27%	21%	31%
M2	42%	27%	27%	31%
M3†	17%	3%	1%	8%
M4	21%	14%	10%	0%
M5	1%	12%	11%	12%
M6	0%	3%	5%	0%
Other‡	3%	8%	18%	15%
Unknown§	9%	7%	7%	4%

*Results are based on fewer than 609 patients with data available.

†Of 33 morphologic M3 cases, all 21 with t(15;17) were coded as favorable; 9 karyotypically normal cases were coded as intermediate; one 11q23 case was coded as unfavorable [t(11;17)(q2?3;q2?5)]; and 2 were coded as unknown [add(1)(q22) and add(13)(q1?4)].

‡Other includes M0, M7, AML (not otherwise specified), and miscellaneous other.

§Patients with no or inadequate materials submitted for central morphology review.

($P = .0080$) were highly significant prognostic factors for response. After adjusting for either or both PS and fever, the heterogeneity of CR rates among the 3 cytogenetic categories remained highly significant ($P < .0001$). These analyses suggested that the effects of cytogenetics on CR rate could not be explained by any of the other patient or disease characteristics considered.

Overall survival by cytogenetic risk status

Of the 609 patients with evaluable cytogenetics, 403 have died. The other 206 have survived a median of 58 months (range 8 to 94 months). Among the 583 patients with known cytogenetic risk status, OS varied significantly according to cytogenetic risk status ($P < .0001$) (Figure 2). Comparisons of OS within cytogenetic risk groups are summarized in Table 4. The estimated relative risk (RR) of death compared with the favorable group was 1.50 (CI, 1.10-2.05) for the intermediate group and 3.33 (CI, 2.43-4.55) for the unfavorable group.

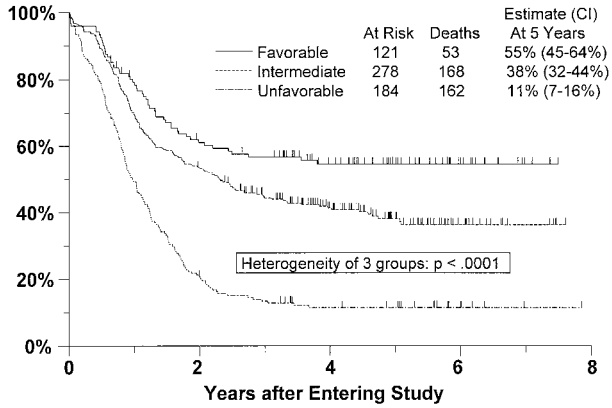

Figure 2. Estimated distributions of OS by cytogenetic risk status. OS was measured from date of entry into the study until death from any cause. Tick marks indicate censored observations, and 95% CIs are shown in parentheses.

Multiple proportional hazards regression analyses were performed to investigate whether the apparent effect of cytogenetic risk status on OS might be explained by the effects of other prognostic factors. After adjusting for the effect of cytogenetic risk status, 3 variables had significant prognostic effects: OS decreased with increasing age ($P < .0001$) and white blood count (WBC) ($P = .0072$) and with worsening PS ($P = .0002$). The effect of cytogenetic risk status remained highly significant ($P < .0001$) after adjusting for the effects of these 3 factors. None of the other factors considered were significantly associated with OS after accounting for the effects of risk status, age, WBC, and PS. Thus, it did not appear that the effect of risk status on survival could be attributed to the other factors.

Further analyses of the unfavorable group

Further investigation of the unfavorable group examined the role of complex abnormalities in the presence or absence of −5/5q− and/or −7/7q−. There was significant heterogeneity of outcomes in the 4 resulting groups ($P = .0068$ for CR, $P = .0018$ for survival) (Table 5). In particular, the patients with aberrations of chromosome 5 and/or 7 in a complex karyotype had a particularly low CR rate (37%), and all died within 2.5 years. Patients in the unfavorable risk group without −5/5q−, −7/7q−, or complex karyotype had a 68% CR rate, although this did not result in markedly superior long-term survival compared with the remaining unfavorable subgroups.

Table 4. Complete remission and overall survival, by cytogenetic risk status

		Complete remission			Overall survival		
Risk status	Total no. of patients	CRs/Pts*	CR rate (%)	95% CI	Died	RR	95% CI
Favorable	121	98/117	84	77-90	53	1.00	—
Intermediate	278	205/270	76	71-81	168	1.50	1.10-2.05
Unfavorable	184	96/173	55	48-63	162	3.33	2.43-4.55
Unknown	26	13/24	54	33-74	20	2.66	1.59-4.45

CR indicates complete remission; CI, confidence interval; Pts, patients; RR, relative risk.

*Denominator is the number of patients who were evaluated for response.

Table 5. Comparison of treatment outcomes among subgroups of unfavorable risk category

−5/5q− and/or −7/7q−	Complex karyotype	No. of patients	CR rate		Overall survival			
					Probability of surviving 2 years		Relative risk	
			CR(%)*	95% CI	Probability (%)	95% CI	RR	95% CI
No	No	90	68	58-78	27	19-37	1.00	—
	Yes	30	50	31-69	20	8-39	1.29	0.83-2.00
Yes	No	31	43	26-61	19	7-37	1.27	0.81-1.98
	Yes	33	37	19-54	3	0-16	2.40	1.58-3.64

CR indicates complete remission; CI, confidence interval; RR, relative risk.
*Response was unknown for 11 patients: 1 with −5/5q− and/or −7/7q− only, 2 with complex only, 5 with neither, and 3 with both.

Postremission therapy

Of the 412 patients who achieved CR, 149 (36%) were not registered for postremission therapy. Reasons for failure to register have been previously published.[9] The remaining 263 were assigned to alloBMT (n = 89, 34%) or randomized between ABMT (n = 84, 32%) and consolidation (n = 90, 34%). The distributions of cytogenetic categories are shown by treatment arm in Table 6. These distributions, based on centrally reviewed karyotypes, differ slightly from those reported in Table 1 of the original report of clinical results from this study.[9] For the 399 patients with known cytogenetic risk status who achieved CR, the distribution of cytogenetic categories did not vary significantly among the 4 postremission treatment groups (3 treatment arms and nonregistered; $P = .68$).

The proportions of patients who received their assigned postremission treatments varied widely among the treatment arms and cytogenetic groups (Table 7). Among the 86 consolidation patients, at least 90% received their study therapy regardless of cytogenetic group. However, among the 84 allogeneic and 83 autologous transplant patients, the proportions receiving transplants on study were lower overall and decreased sharply with worsening risk status. In the unfavorable risk group, only 61% and 50% of the alloBMT and ABMT patients, respectively, received their transplants on study.

A total of 140 of the 263 patients registered for postremission therapy have died, and the remaining have survived between 8 months and 7.5 years (median 4.8 years) after achieving CR. Survival from CR did not vary significantly among the 3 treatment arms ($P = .50$) (Figure 3A). However, among the 253 patients with known cytogenetic risk status, there was significant heterogeneity of survival among the 3 cytogenetic groups ($P = .0003$) (Figure 3B). The estimated probability of surviving 5 years after achieving CR was 57% (CI, 44%-69%) for patients with favorable karyotypes, compared with 48% (CI, 39%-58%) for the intermediate group and 23% (CI, 12%-35%) for the unfavorable group. Compared with the favorable group, the RRs of death were 1.13 (CI, 0.72-1.77) and 2.37 (CI, 1.47-3.82) for the intermediate and unfavorable groups, respectively. Thus, the intermediate and favorable groups did not differ significantly ($P = .58$), and the heterogeneity was almost entirely due to relatively poor survival of patients in the unfavorable group (RR = 2.18 compared with favorable and intermediate combined [CI, 1.51-3.14; $P = .0001$]). Too few complete responders in the unknown cytogenetic risk group were registered for postremission therapy (n = 10) to evaluate their post-CR survival reliably.

Exploratory analyses were performed to investigate whether treatment effects might vary among the cytogenetic groups, based on the 253 patients with known cytogenetic risk status who were registered for postremission therapy. There was significant heterogeneity of survival after CR among the 9 subgroups defined by treatment arm and risk group ($P = .0001$) (Table 8). This heterogeneity was largely due to the differences mentioned above; however, after accounting for the differences between cytogenetics groups, the heterogeneity remaining among the 9 groups was marginally significant ($P = .017$). This suggests that differences between the treatment arms may vary according to cytogenetic group. As shown in Table 8, among patients with favorable karyotypes, those in the ABMT arm had the best (RR = 0.70 compared with the alloBMT arm) survival from CR, whereas the chemotherapy arm had the worst (RR = 2.04) survival from CR ($P = .051$ for heterogeneity among the 3 treatment arms) (Figure 3C). In the intermediate group, in contrast, ABMT patients had the worst survival from CR (RR = 1.43) and chemotherapy the best (RR = 0.70) outcomes ($P = .076$) (Figure 3D). Finally, in the unfavorable group both ABMT (RR = 2.22) and chemotherapy patients (RR = 1.82) had poorer outcomes than alloBMT patients ($P = .11$) (Figure 3E). Of particular interest was the possibility that alloBMT might be more beneficial than ABMT or further chemotherapy for patients with unfavorable cytogenetics. Combining the latter 2 treatment arms yielded an RR of 2.00 (CI, 0.98-4.06) compared with alloBMT. This difference, although only marginally significant ($P = .043$), is consistent with the hypothesis that alloBMT is more effective than ABMT or chemotherapy in overcoming the detrimental impact of unfavorable cytogenetics.

Table 6. Cytogenetic risk status by postremission treatment arm

Risk status	Allogeneic BMT		Autologous BMT		Consolidation		No postremission treatment on study		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Favorable	19	23	26	31	22	23	31	21	98	25
Intermediate	47	56	37	45	44	51	77	53	205	51
Unfavorable	18	21	20	24	20	26	38	26	96	24
Total Known	84	100	83	100	86	100	146	100	399	100
Unknown	5	—	1	—	4	—	3	—	13	—
Total	89	—	84	—	90	—	149	—	412	—

BMT indicates bone marrow transplantation.

Table 7. Delivery of postremission treatment, by cytogenetic risk status and treatment arm

	Allogeneic BMT		Autologous BMT		Consolidation		Total	
Risk status	Treated/Pts	%	Treated/Pts	%	Treated/Pts	%	Treated/Pts	%
Favorable	16/19	84	17/26	65	21/22	95	54/67	81
Intermediate	31/47	66	22/37	59	40/44	91	93/128	73
Unfavorable	11/18	61	10/20	50	18/20	90	39/58	67
Total	58/84	69	49/83	59	79/86	92	186/253	74

BMT indicates bone marrow transplantation; Pts, patients.

After accounting for the effect of cytogenetic risk status, increasing age was also a significant prognostic factor for survival ($P = .0038$). In age-adjusted analyses, the heterogeneity of survival from CR remained significant ($P = .0002$), with estimated RRs (0.97 [CI, 0.62-1.54] and 2.20 [CI, 1.36-3.56] for intermediate and unfavorable, respectively) only slightly less than from those of the unadjusted comparisons (1.13 [CI, 0.72-1.77] and 2.37 [CI, 1.47-3.82]). After accounting for the effects of age and cytogenetic risk group, none of the other factors contributed significantly to the prognosis for survival from CR, suggesting that the effect of risk status could not be attributed to other factors.

Disease-free survival

The analysis of DFS gave essentially the same results as the analysis of survival from CR, with no significant heterogeneity of DFS among the treatment arms ($P = .079$), highly significant heterogeneity among cytogenetic risk groups ($P < .0001$), and an interaction between the effects of risk status and treatment assignment ($P = .017$ after accounting for differences between risk groups).

Comparison of SWOG and MRC cytogenetic classifications

The SWOG and MRC cytogenetic risk classifications were identical for 503 patients but differed for 106 patients (Table 9). Eighty patients coded as unfavorable by SWOG were coded as favorable (9 patients) or intermediate (71 patients) by MRC criteria. Consequently, the proportion of patients with unfavorable karyotypes was markedly smaller according to the MRC criteria (17%, compared with 30% using SWOG criteria). All 26 patients who were not classified in the SWOG scheme were coded intermediate in the MRC scheme. Analyses similar to those described above were performed with the patients classified according to the MRC rather than SWOG criteria. Results of the 2 sets of analyses were generally similar (results not shown).

As shown in Table 9, patients were classified into 6 of the 12 possible combinations of SWOG and MRC categories. In logistic regression analysis of CR rates, the loss of fit associated with collapsing the 6 combined categories into the 4 SWOG categories was highly significant ($P = .0001$), but that associated with the MRC classification was only marginally significant ($P = .030$). This comparatively poor fit of the SWOG system occurred largely because it classified as unfavorable 67 patients in the MRC intermediate group with a CR rate of 67% and classified 8 in the MRC favorable group with a CR rate of 100%.

Proportional hazards regression models for survival and DFS were examined in an analogous manner. For OS, significant loss of fit was observed for both the SWOG ($P = .0067$) and MRC ($P = .0004$) classification schemes (results not shown). In similar analyses of survival from CR, there was no significant loss of fit for the SWOG classification ($P = .29$) but significant loss of fit for the MRC scheme ($P = .0020$). In summary, the MRC scheme provided a better prognostic model for CR, and the SWOG scheme provided a better model for survival from CR. Both schemes were deficient at predicting OS.

Analyses of the joint effects of MRC risk classification and postremission treatment were not pursued, because only 23 of the

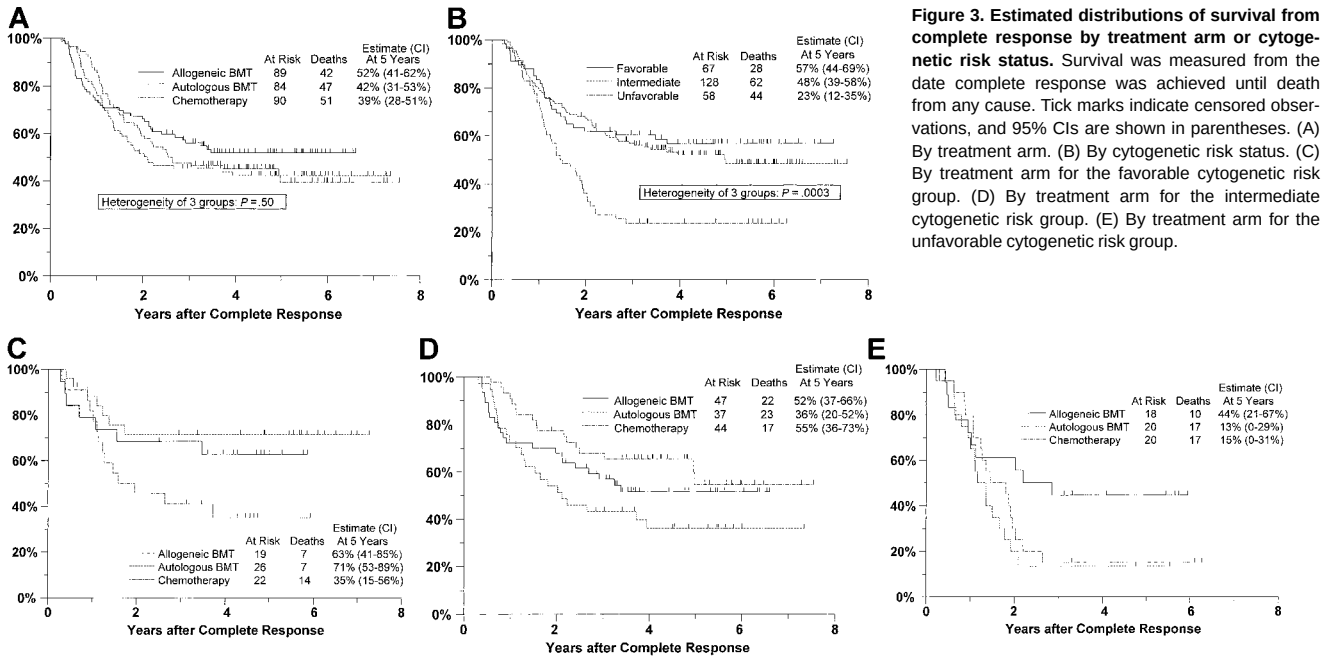

Figure 3. Estimated distributions of survival from complete response by treatment arm or cytogenetic risk status. Survival was measured from the date complete response was achieved until death from any cause. Tick marks indicate censored observations, and 95% CIs are shown in parentheses. (A) By treatment arm. (B) By cytogenetic risk status. (C) By treatment arm for the favorable cytogenetic risk group. (D) By treatment arm for the intermediate cytogenetic risk group. (E) By treatment arm for the unfavorable cytogenetic risk group.

Table 8. Estimated relative risk of death from any cause after complete remission, by postremission treatment arm and SWOG cytogenetic risk status

	All treatment arms combined (n = 253)		Allo-BMT (n = 84)	Autologous BMT (n = 83)		Consolidation (n = 86)	
Risk status	RR*	CI	RR†	RR†	CI	RR†	CI
Favorable	1.00	—	1.00	0.70	0.25-2.01	2.04	0.82-5.05
Intermediate	1.34	0.57-3.14	1.00	1.43	0.80-2.57	0.70	0.37-1.31
Unfavorable	1.73	0.66-4.55	1.00	2.22	1.01-4.87	1.82	0.83-3.98

AlloBMT indicates allogeneic bone marrow transplantation; RR, relative risk; CI, confidence interval.
*Estimated RRs for risk status groups, all treatment arms combined.
†Estimated RRs for postremission treatment arms within risk status group.

43 remitting patients in the MRC unfavorable group were registered for postremission therapy (9 alloBMT, 6 ABMT, and 8 chemotherapy).

Discussion

The results described above suggest that cytogenetic characteristics present at diagnosis are associated not only with response to induction therapy for adult AML but also with outcomes of postremission therapy. This analysis was based on information obtained in a large multicenter trial for adult patients with previously untreated AML. The strengths of this trial included its large number of patients, well-defined eligibility criteria (including pretreatment cytogenetic studies), uniform treatment regimens for induction and postremission therapies, and stratification by karyotype category in the randomization between ABMT and chemotherapy. However, this trial also presented some key limitations for analysis. Many remitting patients (36%) were not registered for postremission therapy on study, and the number registered (263 patients) was rather small for comparisons involving 3 treatment arms and 3 or 4 cytogenetic groups. Other disadvantages were the relatively high proportion (26%) of patients who were registered for postremission therapy but did not receive their assigned treatments and, also, the fact that this proportion varied among treatment arms and cytogenetic groups. As reported previously, compared with chemotherapy patients, relatively fewer transplant patients received their protocol postremission therapy, and their times to initiation of posttransplantation therapy were significantly longer in the transplant arms.[9] The present analysis showed that the proportion receiving protocol postremission therapy also decreased with worsening cytogenetic risk status. These differences may reflect greater caution by physicians awaiting the patient's complete recovery from induction therapy before starting intensive transplant regimens and may reflect greater risk of early relapse (before starting postremission therapy) among patients with unfavorable cytogenetics. As a result, differences in postremission outcomes between treatment arms cannot be attributed with certainty to the treatment regimens. Instead, in this intent-to-treat analysis, the differences reflect the combined effects of treatment and the likelihood that assigned treatment will be received.

The proportion of favorable alloBMT patients who received their assigned treatment was 84%, almost as high as the proportion receiving chemotherapy (95%), with fewer patients receiving their planned treatment in the autologous setting (65%). Nevertheless, the transplant patients had better survival after CR, with 5-year estimates more than 60% for either transplant arm, compared with 35% for the chemotherapy arm. These differences must be interpreted with caution in view of their marginal statistical significance ($P = .05$) amid the large number of comparisons performed in this study. However, these data are consistent with the MRC AML 10 conclusion that the addition of autologous BMT as intensification provides superior DFS for patients with good risk or favorable cytogenetic patients.[19] Conversely, several randomized studies comparing these postremission therapies have failed to confirm improvement with ABMT,[7-9] including the intergroup treatment trial of this investigation.[9] Although a meta-analysis of these randomized trials might assist in defining the best postremission therapy in cytogenetically defined subgroups of AML, the lack of standardization among investigators may confound the analysis.

The cytogenetic risk classification defined all patients with inv(16)/t(16;16) or t(15;17) as favorable, regardless of additional abnormalities. As a result, 7 patients in the favorable group had complex abnormalities in addition to inv(16)/t(16;16) or t(15;17). Two of the 7 had inv(16)/t(16;16) along with −5/5q− or −7/7q−; both had resistant disease and short survival (< 8 months). None of the other 5 patients had −5/5q− or −7/7q−; all 5 achieved CR and are alive at 1146 to 2509 days. Although in general these results are

Table 9. Comparison of Southwest Oncology Group and Medical Research Council cytogenetic classifications

	MRC coding							
	Favorable CRs/Pts		Intermediate CRs/Pts		Unfavorable CRs/Pts		All categories CRs/Pts	
SWOG coding	%CR	95% CI	%CR	95% CI	%CR	95% CI	%CR	95% CI
Favorable	98/117 (121)		0/0 (0)		0/0 (0)		98/117 (121)	
	84	76-90	—	—	—	—	84	76-90
Intermediate	0/0 (0)		205/270 (278)		0/0 (0)		205/270 (278)	
	—	—	76	70-81	—	—	76	70-81
Unfavorable	8/8 (9)		45/67 (71)		43/98 (104)		96/173 (184)	
	100	63-100	67	55-78	44	34-54	55	48-63
Not stated	0/0 (0)		13/24 (26)		0/0 (0)		13/24 (26)	
	—	—	54	33-74	—	—	54	33-74
All categories	106/125 (130)		263/361 (375)		43/98 (104)		412/584 (609)	
	85	77-91	73	68-77	44	34-54	71	67-74

Ratios are based on patients evaluated for response. The total number of patients in each category is shown in parentheses.
SWOG indicates Southwest Oncology Group; MRC, Medical Research Council (United Kingdom); CR, complete remission; Pts, patients; CI, confidence interval.

consistent with the recently advanced hypothesis that secondary abnormalities are not necessarily associated with poor risk in patients with inv(16)/t(16;16) or t(15;17),[5,10] further analysis is warranted for patients presenting with inv(16)/t(16;16) or t(15;17) in association with chromosome 5 and 7 aberrations. With so few patients having this karyotypic profile, resolution of this issue will require intergroup and perhaps international clinical trials.

Although all-*trans*-retinoic acid was not available at the time this study was initiated, few patients with t(15;17) would currently be treated without its addition. Accordingly, we performed analyses of the good risk group (n = 121) with and without the inclusion of the 27 t(15;17) patients (results not shown). The results were quantitatively unchanged by their exclusion.

The pattern of outcomes in the intermediate risk group differed from that of the favorable group, with the ABMT arm having the poorest survival, with an estimated 36% probability 5 years after CR, compared with more than 50% for the alloBMT and chemotherapy arms ($P = .076$). The intermediate risk group is heterogeneous, including a large proportion of patients with normal karyotypes (88%), with the remainder having a variety of abnormalities, including loss of a sex chromosome without additional aberrations, or other uncommon karyotypic aberrations with unknown prognostic significance. More extensive molecular analyses may help to identify prognostic tumor markers for both stratification and detection of minimal residual disease in these patients.

Patients with karyotypically normal AML represent a heterogeneous population. Caligiuri et al detected submicroscopic duplications of the *MLL* gene in about 10% of karyotypically normal AML patients.[20] Newer molecular cytogenetic techniques have detected additional clonal aberrations not resolvable by classic cytogenetics, in both karyotypically normal and abnormal leukemia cases.[21-23] These techniques have revealed abnormalities that would, if detected by classical methods, have resulted in the reclassification of some patients from intermediate risk to the unfavorable risk category.[21,23] The prognostic significance of these abnormalities when they are present but undetectable by classical cytogenetics is currently unknown. Further molecular characterization may be useful in defining effective treatment modalities specific for the various patient subpopulations that compose the intermediate risk group.

In the unfavorable group, heterogeneity among the 3 postremission treatment arms was not statistically significant ($P = .11$), although patients appeared to benefit when treated with alloBMT, ($P = .043$ compared with ABMT and chemotherapy arms combined). The alloBMT arm had an estimated 44% probability of surviving 5 years after CR, compared with 15% or less in the chemotherapy and ABMT arms. This difference was observed even though the proportion of patients actually receiving their assigned postremission treatment was much higher in the chemotherapy arm (90%) than the transplant arms (52% for ABMT, 58% for alloBMT). The observation that patients with poor-risk cytogenetics appear to have a better OS and DFS after HLA-matched sibling transplants suggests that alloBMT using alternative donors might be considered for such patients without matched siblings.

Additional investigation of the unfavorable risk group suggested that further prognostic subdivision of this group may be possible. In particular, only 37% of the 33 patients with chromosome 5 or 7 aberrations in a complex karyotype achieved CR, and all 33 died within 2.5 years. These data emphasize the need for novel treatment strategies for the karyotypically complex leukemias bearing chromosome 5 and 7 aberrations.

Direct comparisons of cytogenetic data among published reports are compromised by the inconsistent definitions of selected aberrations, in particular, del(9q) or 11q23 aberrations, complex karyotypes, or the inclusion or exclusion of particular chromosome aberrations such as t(15;17) in the prognostic subgroupings. In addition, groups vary somewhat in their definitions of response criteria. Despite these differences, the cytogenetic data presented in this study were analyzed using 2 different classification schemes, which differed in the classification of 17% of the patients. Our rationale to perform this analysis was to describe the differences and similarities used by different cooperative groups to guide future investigations. The MRC coding appeared to separate the patients into 3 groups with a wider range of CR rates than did SWOG criteria. In particular, by moving a number of patients from the unfavorable to the intermediate risk group and moving the rare aberrations from unknown to intermediate, the MRC coding appears to more effectively identify patients with low CR rate (44%, compared with 55% for those in the SWOG unfavorable risk category). This shift resulted in a lower CR rate in the more heterogeneous intermediate risk group, and it limited the number of unfavorable risk patients randomized to postremission treatment. Conversely, the SWOG scheme was superior in predicting survival from CR. Interestingly, both schemes were deficient at predicting OS, suggesting the need for a more robust classification scheme to tighten treatment correlates in genetically defined AML subsets.

In this adult AML study, 11q23 aberrations were coded as unfavorable based on their wide reported CR range of 25% to 83% and their overall poor survival.[1] Similarly, the German AML cooperative group coded 11q23 aberrations as unfavorable.[6] In contrast, the MRC AML 10 trial coded 11q23 aberrations as intermediate risk.[10] In pediatric AML, the Pediatric Oncology Group has described an unfavorable outcome for 11q23 leukemias, with an overall 4-year event-free survival rate of 23.8%,[2] whereas others have reported a more favorable outcome.[24] This inconsistency in outcome may result from the multiplicity of 11q23 aberrations resulting in different fusion partners, variable molecular rearrangements (balanced rearrangements vs deletions vs truncated chimeric transcripts), or the presence of additional cytogenetic or genetic alterations imparting a prognostic impact, all potentially influencing disease course.

Leukemias characterized by del(9q) may follow a similar pattern. Schoch et al[15] reported that the additional aberration of del(9q) in t(8;21) leukemia imparts an unfavorable outcome, with a significantly shorter median OS, compared with patients with t(8;21) with or without loss of a sex chromosome (12.5 months vs median survival not reached, $P = .0010$). Because only 17 patients had del(9q) in the present study, definitive conclusions cannot be drawn; however, the data suggest an intermediate/unfavorable risk rather than favorable, with a CR rate of 71% (12 of 17 patients; 95% CI, 44%-90%). Twelve of the 17 patients died, with a median survival of 20 months and 5-year survival of 27% (95% CI, 5%-49%). A recent analysis of del(9q) using pooled data from 3 MRC AML trials suggests that OS at 5 years among patients with del(9q) varies with its genotypic makeup. Specifically, they report survival of 80%, 36%, and 31% in patients with del(9q) with t(8;21), del(9q) alone, or del(9q) with other abnormalities, respectively.[25] Such data suggest that certain cytogenetic aberrations provide general prognostic risk assessment, but complete genotypic characterization will be needed for targeted therapeutic approaches and the possibility of individualized therapy strategies.

What is clearly needed is a generally accepted cytogenetic classification system and leukemia cytogenetic database to provide prognostic scoring and real-time data updates, principally for the less frequent and secondary cytogenetic aberrations.

Our study suggests that pretreatment cytogenetics is a significant prognostic factor in determining response to induction therapy for AML. More importantly, the relative impact of different postremission therapies may vary according to cytogenetic risk group. Many of the weaknesses associated with current cytogenetic risk assessment are also evident from our study. First, current categorizations vary among different investigators. Second, enormous variability in response remains with current categories. Third, as we break down categories into smaller groups, much larger clinical trials will be required to describe potential differential effects of treatments. We suggest that an extensive, perhaps international, leukemia cytogenetic database with patient demographics, treatment, and clinical outcome data be developed to establish well-defined cytogenetic subgroups using uniform criteria. Further analyses of these cytogenetic subsets, perhaps using array technology, should increase our understanding of leukemogenesis and define common biologic categories. Just as we can probably lump t(8;21) and inv(16) into a common CBF group, other common groupings may emerge. The adaptation of technologic advances in cytogenetics and integration of molecular biological techniques will most likely enable genetic-based assessments to contribute to understanding the biology of AML and its response to treatment.

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Appendix

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Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group study

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