Effect of Diagnosis (Refractory Anemia With Excess Blasts, Refractory Anemia With Excess Blasts in Transformation, or Acute Myeloid Leukemia [AML]) on Outcome of AML-Type Chemotherapy

By Elihu Estey, Peter Thall, Miloslav Beran, Hagop Kantarjian, Sherry Pierce, and Michael Keating

In current medical practice, patients with refractory anemia with excess blasts in transformation (RAEB-t), and especially patients with RAEB, receive chemotherapy regimens (AML Rx) administered to patients with acute myeloid leukemia (AML) less often than do patients with AML. These entities are distinguished primarily by marrow blast percentage (5% to 19% RAEB, 20% to 29% RAEB-t, and ≥30% AML). The poor prognosis of many RAEB or RAEB-t patients, if untreated, led us to give them AML Rx using the same plan as for AML. The purpose of this analysis was to see if diagnosis (RAEB, RAEB-t, or AML) affected outcome. We treated 372 patients with AML (acute promyelocytic leukemia [APL] excluded), 106 with RAEB-t, and 52 with RAEB. AML Rx produced a 62% complete remission (CR) rate in RAEB, essentially identical to the rates in RAEB-t and AML, but event-free survival (EFS) from CR and from start of treatment (start of Rx), as well as overall survival, were poorer in RAEB than in AML or RAEB-t, with AML and RAEB-t being identical. However, patients with RAEB or RAEB-t were more likely to have poor prognostic characteristics, in particular complex abnormalities involving chromosomes 5 and/or 7. Multivariate analyses indicated that, when considered together with cytogenetics and other patient characteristics, a diagnosis of RAEB rather than AML or RAEB-t had no effect on EFS from start of Rx, EFS from CR, survival, or achievement of CR. These analyses suggested a trend for patients with RAEB-t to have better EFS from start of Rx than patients with AML or RAEB (*P* = .08; relative risk, 0.80; 95% confidence interval, 0.62 to 1.03), but there were no differences with respect to the other outcomes. Our data suggest that the propriety of administering AML Rx to patients with RAEB or RAEB-t who have poor prognosis without treatment is identical to the propriety of treating AML in this fashion. Deterrents to standard AML Rx in these patients could justifiably include cytogenetics, age, etc, but not a diagnosis of RAEB or RAEB-t per se.

THE WIDELY USED French-American-British (FAB) classification system distinguishes acute myeloid leukemia (AML) from the myelodysplastic syndromes refractory anemia with excess blasts (RAEB) and RAEB in transformation (RAEB-t).[1] Patients whose bone marrows are dysplastic with 5% to 20% blasts and who have less than 6% circulating blasts are said to have RAEB. If the marrow has 20% to 29% blasts, or if the blood has 5% to 29% blasts, or if Auer rods are present, RAEB-t is diagnosed. Patients with ≥30% myeloblasts are said to have AML. These distinctions have important therapeutic implications. Patients with AML generally receive myelosuppressive combination chemotherapy (AML Rx), eg, ara-C + daunorubicin or idarubicin. The same is often true of patients with RAEB-t, although these patients still receive AML Rx less frequently than do AML patients. In contrast, patients with RAEB often are not treated or, if treated, receive blood transfusions, steroids, androgens, or cytokines rather than AML Rx.[2,3] Although there is no evidence that these treatments prolong survival, there is also a belief that AML Rx is ineffective in RAEB and may shorten survival.[4] Cooperative groups and single institutions have formalized this belief, because patients with RAEB, and even RAEB-t, have until very recently been ineligible for the AML studies conducted by these centers.[5-12]

Nonetheless, although many RAEB patients with relatively normal blood counts, only a slight excess of blasts, and a normal karyotype can have an indolent course, RAEB accompanied by significant cytopenias and/or cytogenetic abnormalities, and certainly RAEB-t, have prognoses more reminiscent of untreated AML than of indolent myelodysplastic syndromes.[13-18] This has led us to treat high-risk RAEB (RAEB together with either a hemoglobin level <10 g/dL, a neutrophil count <1,500/μL, a platelet count <100,000/μL, or an abnormal karyotype) and RAEB-t exactly as we do newly diagnosed AML. The purpose of the analysis reported here was to see if, with the regimens used, diagnosis (AML, RAEB-t, or RAEB) affected outcome of AML Rx.

PATIENTS AND METHODS

We treated 579 patients with newly diagnosed AML, RAEB-t, or RAEB between January 1991 and May 1995. Four hundred seven had AML by FAB criteria. We excluded from analysis the 49 of these 407 treated for acute promyelocytic leukemia (APL). We excluded the APL patients because, uniquely, they received all-trans retinoic acid + idarubicin, reflecting the belief that APL is a distinct disease characterized by the PML-RARα rearrangement.[19] One hundred seventy-two of the 579 patients had less than 30% marrow blasts. These 172 included 120 with RAEB-t and 52 with RAEB, as defined by the FAB system. However, 14 of the 120 FAB RAEB-t patients had either 30% or more blasts in the blood or more than 10,000/μL circulating blasts, thus meeting criteria for peripheral AML.[20] As recommended by a National Cancer Institute-sponsored workshop,[21] we classified these 14 as AML. Addition of the 14 to the 358 (ie, 407 − 49) other AML patients gave us 372 patients with AML, 106 with RAEB-t, and 52 with RAEB. In general, patients with RAEB were treated because of thrombopenia (<50,000/μL), red blood cell transfusion requirements, or an abnormal karyotype.

Regardless of diagnosis, we assigned patients to AML Rx according to their presenting leukemia cell karyotype, as previously described.[22] Patients with a normal karyotype, an inv (16), or a t(8;21) were placed in a better prognosis group, as were the 20% of patients who presented with white blood cell (WBC) count greater than 50,000/μL, thus demanding treatment before cytogenetic results were known. Patients with abnormalities of chromosomes 5 and/or 7 (−5, 5q−, −7, 7q−) or +8 fell into a worse prognosis group.

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Submitted December 26, 1996; accepted June 17, 1997.

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0006-4971/97/9008-0020$3.00/0

Patients with other abnormalities were considered as better prognosis if they did not have an antecedent hematologic disorder (AHD) and as worse prognosis if they had an AHD. AHD was defined as a history of a hemoglobin level less than 12 g/dL, a platelet count less than 150,000/μL, a neutrophil count less than 1,500/μL, or a WBC count greater than 20,000/μL for at least 1 month before M.D. Anderson presentation. This, our definition of AHD, had previously been used for AML and was simply extended to RAEB-t and RAEB. Because, despite a median AHD length of 5 months, the majority of patients who presented to us with an AHD had not had a prior bone marrow examination, we do not know, for example, the proportion of patients who had RAEB when they received AML-type chemotherapy who had refractory anemia (RA)[1] when their AHD began, just as we have never known the proportion of the 33% of patients with AML and an AHD who had RAEB (or RA, RAEB-t, or AML) when their AHD began.

Once assigned to the better or worse group, patients received the specific regimen being administered to that group. Ninety percent of the AML, RAEB-t, and RAEB patients were treated within 1 month of M.D. Anderson presentation. The presentation to treatment interval was greater than 2 months in 1%, 3%, and 4% of the AML, RAEB-t, and RAEB patients, respectively. For the better prognosis group, induction treatment was idarubicin + high-dose ara-C (I + A) from January 1991 to January 1992, fludarabine + high-dose ara-C (F + A) from then until July 1992, F + A + G-CSF (FLAG) from July 1992 until June 1993, and I + A + G-CSF (I + A + G) for the next 2 years. Regimens for the worse prognosis group were F + A from January 1991 to March 1992, FLAG from then until July 1993, and FLAG + idarubicin (FLAG + ida) from then until May 1995. I + A consisted of 12 mg/m^2 idarubicin intravenously (IV) on days 1, 2, and 3 and 1.5 g/m^2 ara-C per day on days 1 through 4 by continuous IV infusion. I + A + G was identical except for the addition of 400 mg/m^2 G-CSF IV or subcutaneously (SC) daily on days -1 through $+8$. In F + A, the dose of fludarabine was 30 mg/m^2 IV and that of ara-C was 2 g/m^2 IV daily on days 1 through 5. FLAG included 400 mg/m^2 G-CSF IV or SC daily from day -1 until complete remission (CR). FLAG + ida added idarubicin at 12 mg/m^2 IV on days 2, 3, and 4, administered fludarabine and ara-C on days 1 through 4 only, and administered G-CSF on days -1 through $+8$. Patients with a WBC count greater than 50,000/μL who were assigned to G-CSF–containing regimens began the cytokine on the same day as chemotherapy rather than 1 day before. Patients received treatment in a laminar air flow room (LAFR) whenever such a room was available, with preference being given to patients 50 years of age and older. All patients received oral fluconazole plus oral trimethoprim/sulfamethoxasole to prevent infection. Patients who had persistent disease (>20% blasts in a marrow that was ≥20% cellular in AML or RAEB-t, >5% blasts in a similarly cellular marrow in RAEB) 14 and 21 days after the start of chemotherapy without improvement between these dates received a second course identical to the first. The same criteria, in two consecutive marrow samples, were used for starting a second course in patients whose marrow had decreased blasts or was less than 20% cellular on days 14 or 21 but in whom disease reappeared. We defined CR as a marrow sample with less than 5% blasts and a blood sample with more than 1,000 granulocytes and 100,000 platelets/μL. Patients not in CR after two courses of therapy were removed from study and offered other therapies. Once in CR, patients in the better group received therapy for 12 months. Those in the worse group were treated for 6 months from time of CR. Postremission therapy consisted of lower daily doses and lower doses per course of the regimens used during induction. Patients receiving IAG, FLAG, or FLAG + ida received 400 mg/m^2 G-CSF SC daily during and for 3 days after the completion of each course of chemotherapy. Although the intent was to transplant only at relapse, 9 patients (6 AML, 2 RAEB-t, and 1 RAEB) received an allogeneic bone marrow transplant in first CR. These 9 patients represent 2.6% of all the patients who achieved CR (2.4% of the AML and 2.9% of the RAEB/RAEB-t). We did not censor the 9 patients at time of transplant because we could not, retrospectively, be sure that the physician's decision to transplant and the chances of relapse or death in CR were independent of each other, ie, the patients may have been transplanted because the doctor felt they were likely to do particularly well with or particularly poorly without transplant. If such independence does not exist, censoring should not be performed because this would invalidate inferences based on such an analysis.[23] With all regimens, courses began once the neutrophil count exceeded 1,000 and once the platelet count exceeded 100,000/μL. Recurrence was defined by the presence of ≥5% blasts in the marrow unrelated to recovery of blood counts from the preceding course of chemotherapy.[21] At recurrence, patients received salvage therapies as previously described.[24] Approval was obtained from the Institutional Review Board for these studies. Informed consent was provided according to the Declaration of Helsinki.

Statistical methods. Patient characteristics (covariates) examined for their effects on outcomes were diagnosis (AML, RAEB-t, or RAEB), pretreatment age, hemoglobin level, WBC count, platelet count, percentage of bone marrow blasts and cellularity, performance status, length of AHD, cytogenetics, bilirubin level, albumin level, and creatinine level. We also examined the effects of treatment in an LAFR and the treatment regimen administered.

Differences in patient characteristics between treatment groups were assessed using the Fisher exact test and its generalizations for categorical variables and the Kruskal-Wallis test for quantitative variables. Analyses of event-free survival (EFS) from start of treatment (EFS from start of Rx), of EFS from time of CR, and of survival from start of treatment were performed using Kaplan-Meier plots, log rank tests, and their generalizations.[25-28] For the EFS from start of Rx analysis, the event was (1) being taken off-study because of failure to enter CR, (2) disease recurrence, or (3) death. For the EFS from CR analysis, the event was disease recurrence or death. The Cox proportional hazards regression model[29] and its generalizations[28,30] were used to assess the ability of patient covariates to predict EFS from start of Rx, EFS from CR, and survival. Logistic regression was used to assess the ability of these covariates to predict the probability of CR. To obtain each multivariate Cox or logistic regression model, each covariate was first evaluated individually in a univariate regression model and transformed as appropriate. Variables that were predictive with $P < .05$ were allowed to compete for inclusion in the multivariate model. Variables not significant at P value cutoff .05 were eliminated from the model using a stepwise backward algorithim. As a final step, each individual variable that had been deleted was allowed to re-enter the model if its P value was $<.05$ when assessed together with the variables remaining in the model.

Together with these conventional techniques, we also used several methods that have appeared only recently in the statistical literature. Martingale and partial residual plots[31-33] were used to determine graphically the form of the relationship between each potential prognostic factor and outcome. For example, these methods show that the risk of relapse, death, or failure to enter CR increases sharply as the length of AHD increases from 0 (ie, no AHD) and then plateaus at length of AHD equal to 10 to 20 weeks (Fig 1). We modeled this effect by transforming the variable [length of AHD] to [length of AHD]/[1 + length of AHD]. The Grambsch-Therneau test[34] and corresponding graphical method was used to determine whether the effect of a prognostic factor (eg, age) on EFS or survival was constant as time elapsed from start of treatment (as assumed in the usual Cox model) or, rather, varied as time elapsed (eg, if, as might be suspected clinically, age is primarily a predictor of early

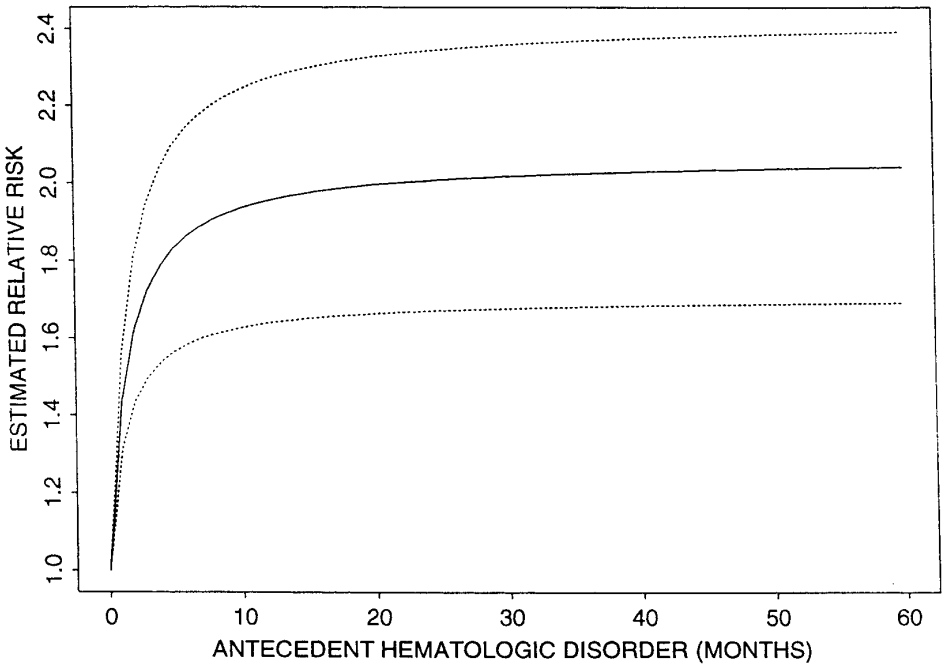

Fig 1. Estimated relative risk of an event versus length of AHD (measured in months). Events are death, failure to achieve CR, or recurrence after CR. Relative risk if no AHD defined as 1.0. Dashed lines show 95% confidence limits.

but not late death). If a time-varying effect is present, this analysis shows the nature and the duration of the effect. Taken together, these methods provide a greatly improved fit of the statistical model to the data, thus allowing, for example, a better estimate of the effect of diagnosis on outcome after adjusting for the effects of other prognostic factors. All computations were performed on a DEC Alpha 2100 5/250 system computer (Digital Electronics Corp, Nashua, NH) in StatXact (Cytel Software Corp, Cambridge, MA) or Splus,[35] using both standard Splus functions and the Splus survival analysis package of Therneau.[30]

RESULTS

Patient characteristics (Tables 1 and 2). The median age for all 530 patients was 59 years, with a tendency for the RAEB patients to be, on average, 3 to 4 years older ($P = .06$). Neither pretreatment hemoglobin level ($P = .39$) nor platelet count ($P = .21$) differed among the AML, RAEB-t, and RAEB groups. The RAEB patients had a median platelet count of 36,000/μL and a median hemoglobin level of 8.1 g. Only 25% had a normal karyotype. Using the new International Scoring System,[18] 80% of the RAEB patients had a score of intermediate-2 or high, associated with median survival times of 0.3 to 1.8 years.

The major differences between the AML, RAEB-t, and RAEB groups involved cytogenetics and AHD status. Whereas 9% of the AML patients had the prognostically favorable inv(16) or t(8;21) abnormalities, these were less frequent in the RAEB-t patients (4%) and nonexistent in those with RAEB. As described below, analysis of the 530 patients presented here indicated that complex abnormalities involving chromosomes 5 and/or 7 were associated with the worst outcomes. These abnormalities were more frequent in RAEB-t (17%) and particularly in RAEB (35%) than in AML (11%) ($P < .001$). An AHD was present (ie, an abnormal blood count had existed for $\geq$1 month before M.D. Anderson presentation) in 54% of the RAEB patients and 50% of the RAEB-t patients, but in only 33% of the AML patients ($P < .001$). Table 2 compares the lengths of the AHDs in the AML, RAEB-t, and RAEB groups. The longest AHDs occurred in the AML and RAEB-t groups. However, among patients with AHDs, there were no differences in AHD length between the three groups ($P = .77$ RAEB *v* AML, $P = .66$ RAEB-t *v* AML, $P = .60$ RAEB *v* RAEB-t). Thus, the AML, RAEB-t, and RAEB groups differed in the proportion of patients who had an AHD but not in the duration of these AHDs. Using the system devised to assign patients to treatment (described in the Patients and Methods), 63% of the RAEB, 50% of the RAEB-t, and 40% of the AML patients were considered poor prognosis. Reflecting the preponderance of poor prognosis patients in the RAEB and RAEB-t groups and the assignment of poor prognosis patients exclusively to F + A, FLAG, or FLAG + ida, the RAEB and RAEB-t patients more often received these regimens (Table 1).

Univariate analyses. The CR rate was 62% (32/52) in patients with RAEB, 66% (70/106) in patients with RAEB-t, and 66% (247/372) in patients with AML ($P = .79$). Cytogenetic abnormalities could not be detected at CR in 14 of the 16 RAEB patients (88%), 11 of the 14 RAEB-t patients (77%), and 59 of the 73 AML patients (81%) who presented with abnormalities and in whom analysis was repeated at CR ($P = .85$). Once in CR the probability of EFS was similar in AML and RAEB-t but lower in RAEB (Fig 2). The same was true if EFS was measured from start of treatment (Fig 3). Likewise, survival from start of treatment appeared shorter in RAEB than in AML or RAEB-t, with AML and RAEB-t having similar survival probabilities ($P = .017$ comparing RAEB to RAEB + AML, with the curves very similar to those in Fig 3).

Table 1. Patient Characteristics

Variable	AML (N = 372)	RAEB-t (N = 106)	RAEB (N = 52)	*P* Value†
Age	58 (16-87)	59 (18-88)	63 (30-82)	.055
Hg	8.4 (2.8-14.4)	8.1 (3.3-14.7)	8.2 (6.5-12.5)	.393
WBC	15.9 (.4-367.2)	5.7 (.2-89.7)	4.6 (.7-92.7)	<.001
PLT	44.0 (2-835)	43.5 (1-471)	36.0 (4-191)	.208
PS > 2	57 (15.3%)	17 (16.0%)	2 (3.9%)	.051
AHD	124 (33.3%)	53 (50.0%)	28 (53.9%)	<.001
inv (16) or t(8;21)	35 (9.4%)	4 (3.8%)	0 (0%)	<.001
Complex abnormality of chromosomes 5 and/or 7	41 (11.0%)	18 (17.0%)	18 (34.6%)	
Other abnormal cytogenetics or IM	187 (50.3%)	45 (42.5%)	21 (40.4%)	
Normal karyotype	109 (29.3%)	39 (36.8%)	13 (25.0%)	
LAFR	198 (53.2%)	71 (67.0%)	39 (75%)	.0013
I + A	61 (16.4%)	17 (16.0%)	0 (0%)	<.001
I + A + G	109 (29.3%)	24 (22.6%)	10 (19.2%)	
F + A	53 (14.3%)	21 (19.8%)	4 (7.7%)	
FLAG	89 (23.9%)	23 (21.7%)	21 (40.4%)	
FLAG + Ida	60 (16.1%)	21 (19.8%)	17 (32.7%)	

All measurements are pretreatment. Values are medians with ranges for quantitative variables and counts with percentages for categorical variables.

Abbreviations: Hg, hemoglobin; WBC, white blood count; PLT, platelet count; PS, Zubrod performance status; AHD, antecedent hematologic disorder (see text); inv (16), pericentric inversion of chromosome 16; t(8;21), 8, 21 translocation; IM, insufficient metaphases for cytogenetic analysis; LAFR, laminar air flow room; I + A, I + A + G, F + A, FLAG, and FLAG + Ida are treatments described in text.

† Kruskal-Wallis test for quantitative variables, generalized Fisher exact test for categorical variables.

Other factors besides diagnosis were predictive of outcome. These are given for CR, EFS from CR, and EFS from start of Rx in Tables 3, 4, and 5, respectively. The factors predictive of survival were essentially the same as those predictive of EFS from start of Rx. For the categorical variables in the tables (cytogenetics, performance status, LAFR, treatment regimen, and diagnosis), the univariate *P* values refer to comparisons of a given subgroup with all other relevant subgroups, eg, [inv16 or t(8;21)] *v* [complex −5, −7] + [other abnormal] + [normal karyotype]. As in previous analyses, the principal predictors of outcome were cytogenetics [normal karyotype, and in particular inv16 or t(8;21); favorable], an AHD (unfavorable), increasing age (unfavorable), poor performance status (unfavorable), and treatment in an LAFR (favorable). A few elaborations from these prior analyses will be noted. The 4-group cytogenetic classification seen in the tables differs from that used to assign patients to treatment and reflects the finding that the 77 patients with complex abnormalities (≥2 clones) involving −5, 5q−, −7, or 7q− had worse outcomes (eg, $P = .002$ for EFS from start Rx) than the 59 patients with simple abnormalities involving −5, 5q−, −7, or 7q−, with the latter patients more closely resembling those with abnormalities other than inv16 or t(8;21). Whereas in past analyses the cutpoint for AHD was assumed to be ≥1 month as reflected in the treatment assignment scheme, here we used martingale and partial residual plots to more closely examine the relationship between AHD and outcome. Considering all 530 patients, the risk of shorter EFS from either start of Rx or from CR increased sharply as length of AHD increased from 0 (ie, no AHD) up to a plateau at an AHD length of 10 to 20 months, beyond which longer AHDs conferred the same risk. Figure 1 shows this for EFS from start of Rx. Similarly, the probability of achieving CR decreased with increasing length of AHD, although there was no plateau for this effect. In particular, there was no cutpoint for AHD in terms of its effect on any outcome, and we took this into account in the multivariate analyses, as described below. Considering the individual diagnoses, increasing length of AHD was found to be predictive of CR, EFS from CR, and EFS from start of Rx in AML, RAEB-t, but not RAEB (eg, *P* values of <.001, .02, and .58, respectively, for the 3 groups with regard to EFS from start of Rx). Finally, several variables (indicated in Tables 4 and 5) were best described by noting that their effects on EFS varied with time. For example, treatment in an LAFR was favorable for EFS from start of Rx for only the first 8 weeks after treatment began, indicating only an effect on early death. In contrast, the effect of complex abnormalities of chromosomes 5 and/or 7 on EFS from start of Rx increased continuously with time from treatment, probably reflecting more of an effect on resistance to therapy than on early death.

Treatment regimen was also predictive of outcome. In

Table 2. Antecedent Hematologic Disorders in AML, RAEB-t, and RAEB Groups

	AML (N = 372)	RAEB-t (N = 106)	RAEB (N = 52)
Patients with AHD	124 (33.3%)	53 (50.0%)	28 (53.9%)
Length of AHD (mo)*			
Median	5.0	4.0	5.5
Mean	18.0	11.3	6.8
Range	1-402	1-100	1-32

* Among patients with AHDs.

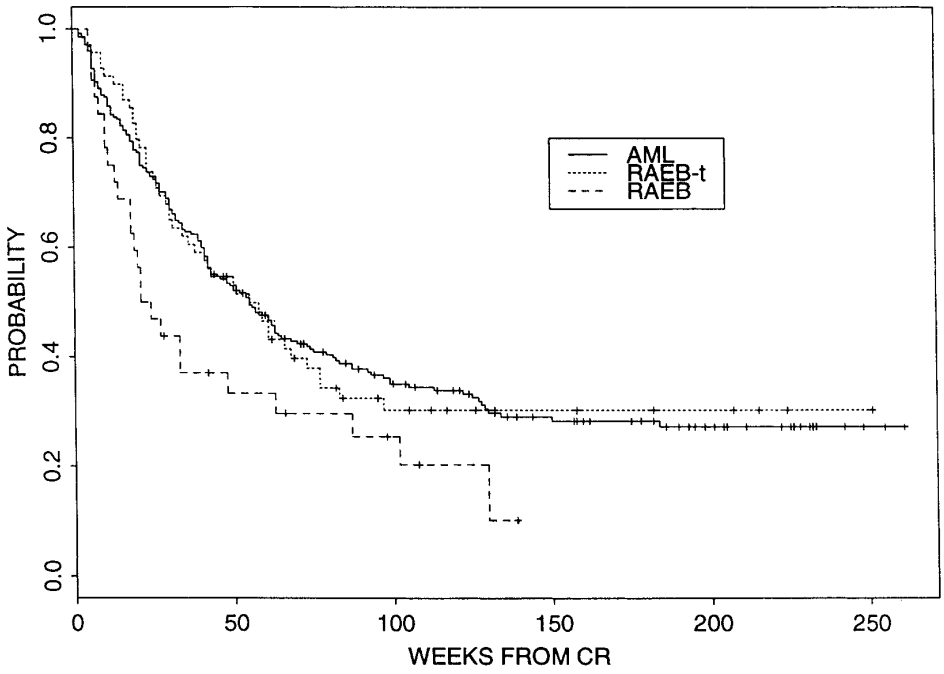

Fig 2. Probability of EFS dated from time of CR in AML, RAEB-t, and RAEB groups. Log rank *P* value = .017 for comparison of RAEB versus RAEB-t + AML. There have been 167 events in the AML group (n = 247), 45 in the RAEB-t group (n = 70), and 25 in the RAEB group (n = 32). Median follow-up for patients alive in CR = 2.2 years.

general, IA and IA + G were associated with the best outcomes, FLAG with an intermediate outcome, and F + A and FLAG + ida with the worst outcomes (Tables 3, 4, and 5), although whether this reflected the preponderance of patients with unfavorable cytogenetics or an AHD receiving these regimens awaited results of the multivariate analyses described below. There was no evidence that a particular regimen produced results in a particular diagnosis (AML, RAEB-t, and RAEB) that differed from those produced by that regimen in all patients.

Multivariate analyses. Multivariate analyses were performed to determine whether the seemingly poorer EFS (Figs 2 and 3 and Tables 4 and 5) and survival seen in patients with RAEB were a result of this diagnosis or, rather, reflected the association of RAEB with such unfavorable prognostic indicators as complex abnormalities involving chromosomes

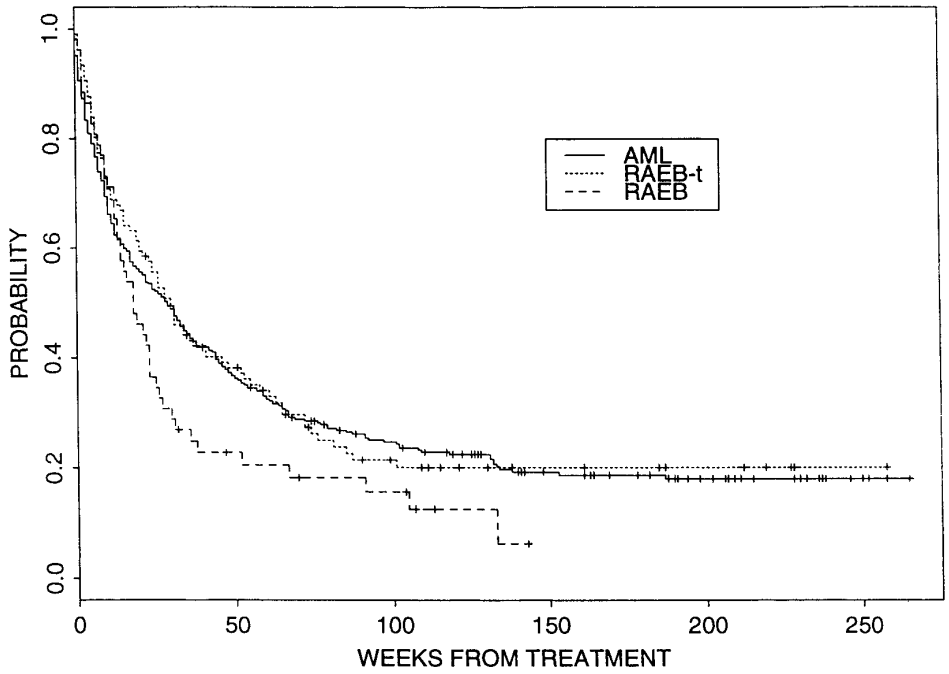

Fig 3. Probability of EFS dated from start of treatment in AML, RAEB-t, and RAEB groups. Log rank *P* value = .047 for comparison of RAEB versus RAEB-t + AML. There have been 289 events in the AML group (n = 372), 81 in the RAEB-t group (n = 106), and 45 in the RAEB group (n = 52). Median follow-up for patients alive in CR = 2.3 years.

Table 3. CR Analyses

Variable	CR Rate	Univariate *P* Value*	Multivariate *P* Value
inv16 or t(8;21)	37/39 (95%)	<.001	.008
Complex −5, −7	35/77 (45%)	<.001	.008
Other abnormal or IM	160/253 (63%)	.23	NS
Normal karyotype	117/161 (73%)	.027	—
PS ≤ 2	321/454 (71%)	<.001	<.001
PS > 2	28/96 (37%)		—
LAFR	273/308 (72%)	<.001	<.001
No LAFR	126/222 (57%)		—
IA	64/78 (82%)	<.001	—
IA + G	107/143 (75%)	.007	NS
F + A	43/78 (55%)	.033	NS
FLAG	86/133 (65%)	.739	NS
FLAG + Ida	49/98 (50%)	<.001	.034
RAEB	32/52 (62%)	.49	NS
RAEB-t	70/106 (66%)	.96	NS
AML	247/372 (66%)	.68	—
Age	Decreases with increasing age	<.001	.028
AHD	Decreases with increasing length of AHD	<.001	<.001

Abbreviation: NS, not significant.

* χ^2 test.

5 and/or 7 (Table 1). Tables 3, 4, and 5 indicate the factors that multivariate analyses found associated with, respectively, CR, EFS from CR, and EFS from start of Rx, with the analysis of survival (not shown) again essentially identical to that for EFS from start of Rx. For each categorical variable in the tables (cytogenetics, performance status, LAFR, treatment regimen, and diagnosis), it is necessary to designate a reference group to fit the statistical model.[36] In the tables, the reference group for each variable is denoted by a dash in the final column, eg, normal karyotype is the reference group for cytogenetics. The multivariate *P* value in each row corresponds to comparison of the subgroup in that row to this reference group. For example, the comparison of [inv16 or t(8;21)] to [normal karyotype] has a *P* value of .008 for CR (Table 3). The choice of the reference group does not affect the conclusions.[36] Reflecting the shape of the AHD effect shown by graphical methods (Fig 1), we used the term [length of AHD]/[1 + length of AHD] in the multivariate analyses rather than using a simple yes or no indicator for AHD. As seen in Tables 3, 4, and 5, these analyses indicated that the predictors of outcome, each independent of the other predictors, were complex −5/−7 (highly unfavorable for all three outcomes), other cytogenetic abnormalities (unfavorable for EFS from CR, and EFS from start of Rx), inv16 or t(8;21) (favorable for CR and EFS from start of Rx), increasing length of AHD (unfavorable for all 3 outcomes with a plateau at an AHD length of 10 to 20 months for the EFS outcomes), increasing age and Zubrod performance status (PS) >2 (unfavorable for all 3 outcomes with the effects on EFS decreasing as time elapsed from start of treatment), treatment in an LAFR (favorable for CR and EFS from start of Rx with the effect on the latter present for only the first 8 weeks), and treatment with FLAG + ida or F + A (unfavorable for CR and EFS from start of Rx, respectively). The tables also indicate that, after accounting for these predictors, there was no evidence that diagnosis (AML, RAEB-t, or RAEB) was relevant for CR, EFS from CR, or EFS from start Rx. The same was true for survival. There was a tendency for EFS from start of Rx to be longer in RAEB-t than in AML or RAEB (multivariate *P* value of .08; relative risk, 0.80; 95% confidence interval [CI] for this risk, 0.62 to 1.03), but for the other outcomes the multivariate *P* values for RAEB or RAEB-t were all >.10. Finally, we conducted a separate multivariate analysis in which we replaced the cytogenetics and AHD variables shown in Tables 3, 4, and 5 with a single variable denoting the treatment assignment group (better or worse) given to the patient at start of treatment (as described in the Patients and Methods). This analysis indicated that the treatment assignment variable was strongly predictive of outcome and that, given this variable, the patient's diagnosis was of no predictive value whatsoever ($P = .29$). This is completely consistent with the results in Tables 3, 4, and 5.

DISCUSSION

In current medical practice, RAEB-t, and in particular RAEB, are treated with AML Rx less frequently than is AML. However, with current management, the prognosis of RAEB-t, and even RAEB if accompanied by characteristics such as abnormal cytogenetics or cytopenias, more closely resembles that of untreated AML than that of an indolent MDS.[13-18] This led us to treat RAEB or RAEB-t using the same plan used to treat AML, including use of investigational regimens (F + A, FLAG, and FLAG + Ida) for patients with characteristics (cytogenetics and AHD) associated

Table 4. Analyses of EFS From Date of CR

Variable	Median EFS* (95% CI)	Univariate *P* Value†	Multivariate *P* Value
inv16 or t(8;21)	None [62, −]	.086	NS
Complex −5, −7	20 [14, 24]	<.001	<.001
Other abnormal or IM	41 [34, 51]	<.001	<.001
Normal karyotype	83 [70, 129]	<.001	—
PS ≤ 2	55 [43, 63]	.006	.005
PS > 2	24.5 [16, 75]		—
IA	70 [48, 127]	.13	—
IA + G	79 [63, 99]	.008	NS
F + A	27 [19, 61]	.022	NS
FLAG	42 [30, 63]	.27	NS
FLAG + Ida	36 [27, 43]	.001	NS
RAEB	22.5 [18-87]	.017	NS
RAEB-t	55 [36-77]	.78	NS
AML	55 [43-68]	.26	—
Age	Decreases with increasing age, effect disappears by 40 wk post-CR	<.001	.033
AHD	Decreases with length of AHD up to plateau at AHD of 10-20 mo	<.001	.017

Abbreviation: NS, not significant.

* EFS measured in weeks.

† Log-rank test.

Table 5. Analyses of EFS From Start of Treatment

Variable	Median EFS* (95% CI)	Univariate *P* Value†	Multivariate *P* Value	Comment
inv16 or t(8;21)	None [65, −]	.003	.029	Unfavorable effect complex −5, −7 increases with time
Complex −5, −7	10 [8, 15]	<.001	<.001	
Other abnormal or IM	24 [17, 32]	<.001	.002	
Normal karyotype	46 [30, 76]	<.001	—	
PS ≤ 2	31 [27, 37]	<.001	<.001	Unfavorable effect PS > 2 levels off by 12 weeks
PS > 2	4 [2, 10]		—	
LAFR	31 [27, 41]	<.001	.003	LAFR favorable only for initial 8 weeks
No LAFR	17 [11, 24]		—	
IA	52 [37, 81]	.003	—	Unfavorable effect F + A disappears by 32 weeks
IA + G	57 [33, 76]	<.001	NS	
F + A	12 [10, 28]	.015	.05	
FLAG	23 [15, 31]	.24	NS	
FLAG + Ida	14.5 [12, 21]	<.001	NS	
RAEB	18 [13, 26]	.047	NS	
RAEB-t	30 [21, 46]	.59	NS (.081)	
AML	29 [22, 35]	.48	—	
Age	Decreases with increasing age	<.001	.001	Unfavorable effect increasing age disappears by 40 wk from start of treatment
AHD	Decreases with length of AHD up to plateau at AHD of 10-20 mo	<.001	<.001	

Abbreviation: NS, not significant.

* EFS measured in weeks.

† Log-rank test.

with poor response to usual AML Rx. Likely as a result of physicians' tendencies to refer such patients, the RAEB patients we treated certainly appeared to have in general had a poor prognosis, as defined for example by the new International System.[18] The purpose of the analysis reported here was to determine if diagnosis (AML, RAEB-t, or RAEB) affected outcome of AML Rx. The principal findings are (1) AML Rx produced a CR rate of about 60% in RAEB, although the remissions were usually brief, with EFS from CR, EFS from start Rx, and survival seemingly shorter in RAEB than in RAEB-t or AML (Figs 1 and 2); (2) this seeming association between a diagnosis of RAEB, rather than AML or RAEB-t, and lower probabilities of EFS or survival was entirely due to the association between RAEB and poor prognostic features particularly complex abnormalities of chromosomes 5 and/or 7 (Tables 4 and 5); and (3) although a diagnosis of RAEB-t rather than AML or RAEB tended to have a favorable effect on probability of EFS from start Rx, the *P* values were marginal and there were no effects on EFS from CR or achievement of CR.

Although not documented to be common practice, AML-type chemotherapy has been used in RAEB, and especially in RAEB-t, for 15 to 20 years.[37-42] CR rates average 50% to 60%, with median remissions of 7 to 11 months, with most of the responses occurring in RAEB-t. The variability in different series, eg, CR rates ranging from 20%[38] to 65%,[40] is more than can be explained by random fluctuation due to small sample sizes. In fact, this variability is largely due to differences in characteristics such as age, cytogenetics, etc, all of which are also prognostic in AML. For example, Fenaux et al[41] noted that their RAEB and mostly RAEB-t patients whose remissions exceeded 2 years were young with normal karyotypes. Similar results would of course be expected in AML. The association between RAEB-t and favorable karyotypes [inv16, t(8;21)] has been reported.[43] The 4% of our patients with RAEB-t who had inv(16) or t(8;21) may reflect a true overlap between AML and RAEB-t. Alternatively, these patients may simply have presented relatively early, or their blast percentage may have been underestimated, leading to a diagnosis of RAEB-t, rather than AML, in any case indicating the difficulties inherent in distinguishing AML and RAEB-t.

Although the literature suggests that similar prognostic features appear operative in AML, RAEB-t, and perhaps RAEB, the question of whether a diagnosis of AML rather than RAEB-t or especially RAEB is itself prognostic has received comparatively little attention. Rather, many AML studies have at least historically simply excluded patients with RAEB or RAEB-t.[5-12] Although not presenting a multivariate analysis and using definitions of RAEB, RAEB-t, and chronic myelomonocytic leukemia (CMML) at some variance with today's FAB definitions, Mertelsmann et al[37] noted that Auer rods were a better predictor of outcome (present = favorable) than diagnosis of MDS versus AML types M0, M1, or M5a. Reviewing experience on six CALGB protocols operative between 1984 and 1992 and intended exclusively for patients with AML, Bernstein et al[44] reported that central pathology review led to a reclassification of diagnosis in 33 of 907 cases of presumed AML. Twenty-five met FAB criteria for RAEB-t, 7 for RAEB, and 1 for RA. CR rate and duration and survival were similar in the AML and MDS groups. Our report differs from that of Bernstein et al[44] in its prospective nature, ie, our intent was to treat poor prognosis RAEB and RAEB-t–like AML. Bernstein et al[44] included, whereas we excluded, for reasons noted in the Patients and Methods, patients with APL from analy-

sis. APL patients constituted 8% of the patients in the series of Bernstein et al.[44] The regimens given patients in the two series differed, and obviously the number of cases of MDS relative to the number with AML is higher in our series. However, perhaps the major difference was that, whereas the CALGB eligibility criteria excluded patients with an AHD, ours did not (AHD was identically defined by us and the CALGB). Indeed, 51% of our RAEB-t and RAEB patients and 33% of our AML patients had an AHD, although, among patients with an AHD, AHD lengths were similar in AML, RAEB-t, and RAEB (Table 2). This report may be one of the first to formally examine the relationship between outcome and AHD. Our results indicate that AHD behaves as a continuous variable, with outcome becoming worse as AHD length increases from 0, with a plateau effect at 10 to 20 months AHD for the EFS from CR and the EFS from start Rx outcomes. Thus, AHD does not behave in an all-or-none fashion with an arbitrary cutpoint, as is frequently assumed in protocol eligibility criteria or, in our case, treatment assignment systems. At any rate, the patients described here and the patients treated by Bernstein et al[44] appear quite different. It is thus of interest that the conclusions of both reports are fundamentally the same.

We would be remiss if we did not point out that our treatment results in RAEB or RAEB-t were not good (eg, Figs 2 and 3). In fact, our multivariate analyses suggest that F + A and FLAG + Ida (but not FLAG) were worse than the non–fludarabine-containing regimens (Tables 3, 4, and 5). Using our results, one could argue that use of AML Rx in RAEB or RAEB-t is not indicated. Indeed, survival was the same ($P = .418$) in the 52 RAEB patients receiving AML Rx and in the 60 patients with RAEB seen here between 1985 and 1991, all of whom received AML Rx only if they developed AML (14 of the 60 patients). However, our data indicate that, if one argues against use of AML Rx in RAEB or RAEB-t, the same argument should then be made for AML, given that, in the absence of treatment, the natural history of RAEB-t and the RAEB patients we treated is more reminiscent of AML than of an indolent myelodysplastic syndrome. Obviously there are more indolent types of RAEB as recognized by many prognostic factor systems, including the new International System,[14-18] and we would argue against giving these patients AML Rx. However, in RAEB-t and aggressive RAEB, we believe that deterrents to AML Rx could include cytogenetics, AHD status, age, etc, as indicated in Tables 3, 4, and 5, but not a diagnosis of RAEB or RAEB-t per se. Furthermore, these deterrents could be considered to apply only if the patient were to receive standard rather than investigational AML Rx. We hope that our experience indicating that AML Rx can produce CRs in RAEB encourages the use of new regimens in carefully selected patients with this condition, as well as in patients with RAEB-t.

ACKNOWLEDGMENT

The authors thank Soon Woo for expert secretarial assistance.

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