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ORIGINAL REPORT

Patients With Acute Myeloid Leukemia and *RAS* Mutations Benefit Most From Postremission High-Dose Cytarabine: A Cancer and Leukemia Group B Study

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ABSTRACT

Purpose
RAS mutations occur in 12% to 27% of patients with acute myeloid leukemia (AML) and enhance sensitivity to cytarabine in vitro. We examined whether *RAS* mutations impact response to cytarabine in vivo.

Patients and Methods
One hundred eighty-five patients with AML achieving complete remission on Cancer and Leukemia Group B study 8525 and randomly assigned to one of three doses of cytarabine postremission were screened for *RAS* mutations. We assessed the impact of cytarabine dose on cumulative incidence of relapse (CIR) of patients with (mut*RAS*) and without (wild-type; wt*RAS*) *RAS* mutations.

Results
Thirty-four patients (18%) had *RAS* mutations. With 12.9 years median follow-up, the 10-year CIR was similar for mut*RAS* and wt*RAS* patients (65% *v* 73%; $P = .31$). However, mut*RAS* patients receiving high-dose cytarabine consolidation (HDAC; 3 g/m^2 every 12 hours on days 1, 3, and 5 or 400 mg/m^2/d × 5 days) had the lowest 10-year CIR, 45%, compared with 68% for wt*RAS* patients receiving HDAC and 80% and 100%, respectively, for wt*RAS* and mut*RAS* patients receiving low-dose cytarabine (LDAC; 100 mg/m^2/d × 5 days; overall comparison, $P < .001$). Multivariable analysis revealed an interaction of cytarabine dose and *RAS* status ($P = .06$). After adjusting for this interaction and cytogenetics (core binding factor [CBF] AML *v* non-CBF AML), wt*RAS* patients receiving HDAC had lower relapse risk than wt*RAS* patients receiving LDAC (hazard ratio [HR] = 0.67; $P = .04$); however, mut*RAS* patients receiving HDAC had greater reduction in relapse risk (HR = 0.28; $P = .002$) compared with mut*RAS* patients treated with LDAC.

Conclusion
AML patients carrying mut*RAS* benefit from higher cytarabine doses more than wt*RAS* patients. This seems to be the first example of an activating oncogene mutation favorably modifying response to higher drug doses in AML.

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INTRODUCTION

Activating mutations in the *RAS* proto-oncogenes occur frequently in many types of human cancer,[1] including myelodysplastic syndromes[2] and acute myeloid leukemia (AML).[3-11] In de novo AML, between 12% and 27% of patients harbor *RAS* mutations.[4-11] Moreover, in patients without *RAS* mutations, the RAS-dependent pathways are also frequently affected by relatively frequent mutations in other genes (ie, *FLT3*, *KIT*, and *PDGFR*).[12] These mutations and those in *RAS* activate pro-proliferative and antiapoptotic signals critical for myeloid leukemogenesis and are often referred to as class I mutations.[13] In addition, AML is often characterized by class II mutations that involve transcription factor signaling that impairs hematopoietic differentiation, frequently via gene fusions generated by balanced chromosomal rearrangements, such as *RUNX1(AML1)-RUNX1T1(ETO)* and t(8;21)(q22;q22), *CBFB-MYH11* and inv(16)(p13q22)/t(16;16)(p13;q22), or *PML-RARA* and t(15;17)(q22;q12).[12] Mouse models show that these fusion genes rarely cause overt leukemia on their own unless complemented by class I mutations.[14]

Although mutations in *RAS* are frequent in AML and seem to contribute to leukemogenesis in a subset of patients, their prognostic significance has not been firmly established. Some reports have suggested that patients with AML having *RAS* mutations have worse[7-9] or similar[4,5,10,11,15-17] clinical outcomes than patients carrying wild-type *RAS* genes, whereas others have found that mutations in *RAS* are associated with a more favorable prognosis.[5,6] Although these conflicting results may stem from variation in the pretreatment features of patient populations analyzed in different series, they may also be related to differences in treatment regimens used.

AML is initially treated with induction chemotherapy, frequently consisting of standard-dosage cytarabine and an anthracycline (eg, daunorubicin). Patients entering complete remission are then treated with either chemotherapy or autologous or allogeneic stem-cell transplantation (SCT), depending on individual risk profiles. After publication of the Cancer and Leukemia Group B (CALGB) 8525 treatment trial, multicycle high-dose cytarabine has become preferential postinduction chemotherapy for patients not receiving SCT.[18] Importantly, it seems that certain subsets of patients benefit from this therapy more than others. Indeed, several studies have shown that both t(8;21) and inv(16) sensitize AML blasts to high-dose cytarabine given as consolidation therapy.[19-21] However, it is at present unknown whether other genetic alterations also influence response of patients with AML to treatment with high-dose cytarabine.

Intriguingly, in vitro data have suggested that mutant *RAS* proto-oncogenes may sensitize leukemia and carcinoma cells to cytarabine.[22,23] Therefore, to determine whether *RAS* mutation status also influences response to cytarabine in vivo, we have analyzed retrospectively the outcome of patients with AML with and without *RAS* mutations enrolled onto a single treatment study, CALGB 8525. Our data show that the presence of *RAS* mutations sensitize AML cells to high-dose cytarabine therapy in vivo, suggesting that patients with AML having *RAS* mutations treated with chemotherapy alone should preferentially be administered high-dose cytarabine as postremission treatment.

PATIENTS AND METHODS

Patients

We studied 185 adult patients with a primary diagnosis of AML (excluding acute promyelocytic leukemia) who were enrolled onto the CALGB treatment trial 8525.[18] CALGB 8525 was a study comparing the duration of complete remission and overall survival in patients treated postremission with high, intermediate, or standard doses of cytarabine.[18] Only those patients for whom the *RAS* mutation status was determined, who had a successful cytogenetic and/or molecular genetic analysis of a pretreatment sample that allowed determination of whether patients had or did not have core binding factor (CBF) AML (ie, whether they were positive or negative for t(8;21)/*RUNX1-RUNX1T1* and inv(16)/t(16;16)/*CBFB-MYH11*),[24] achieved a complete remission, and were randomly assigned to one of three consolidation treatment arms on CALGB 8525 were eligible for inclusion in this study. There was no significant difference in outcome between the 185 patients included in the current analysis and those who were not included because of lack of available tissue ($P > .68$). Written, institutional review board–approved, protocol-specific informed consent was obtained when each patient entered the study.

Treatment

On CALGB 8525, patients 60 years of age or younger received induction chemotherapy of daunorubicin 45 mg/m^2/d intravenously for 3 days and cytarabine 200 mg/m^2/d as a continuous infusion for 7 days, whereas patients older than 60 years received daunorubicin 30 mg/m^2/d intravenously for 3 days and cytarabine 200 mg/m^2/d as a continuos infusion for 7 days. Those who attained a complete remission after one or two courses of induction therapy were randomly assigned to one of three postinduction arms that differed with regard to dose-intensity of cytarabine. These arms included four cycles of (1) 100 mg/m^2 of cytarabine as a continuous infusion $\times$ 5 days, (2) 400 mg/m^2 of cytarabine as a continuous infusion $\times$ 5 days, or (3) 3 g/m^2 of cytarabine over 3 hours every 12 hours on days 1, 3, and 5. In each case, this was followed by maintenance treatment consisting of four monthly treatments with cytarabine (100 mg/m^2 every 12 hours) for 5 days by subcutaneous injection and daunorubicin 45 mg/m^2 on the first treatment day.[18] Among the 185 patients included in the current analysis, there was no significant difference in cumulative incidence of relapse (CIR) between the 400-mg and 3-g cytarabine arms, whereas patients on the 100-mg arm had significantly higher CIR as compared with that of the patients on the 400-mg arm or those on the 3-g arm. Therefore, patients receiving postremission therapy on the 400-mg and 3-g cytarabine arms were combined into one high-dose cytarabine group (HDAC) for subsequent comparison of their CIR with that of patients who were in the 100-mg cytarabine arm, referred to as the low-dose cytarabine (LDAC) group. No patient received SCT in first complete remission.

DNA Extraction and RAS Mutations Detection

The genetic analyses were performed as part of CALGB companion protocols 8361 and 8765, which procured blood and bone marrow samples prospectively on patients entered on CALGB treatment studies. All molecular analyses were conducted in a blinded fashion on DNA extracted from cryopreserved cells taken at the time of diagnosis. Screening for *RAS* mutations was performed initially using single-strand conformation polymorphism analysis and a slot blot technique,[6,25] and subsequently a denaturing high-performance liquid chromatography method[11,26] and polymerase chain reaction enrichment assay based on PNA-mediated clamping.[27] The inclusion of the positive and negative controls in all runs suggested similar performance by the two approaches. All suspected mutations identified by the screening techniques were confirmed by sequence analysis either directly or after subcloning.

Statistical Analysis

The purpose of the study was to determine whether mutations in the *RAS* proto-oncogenes influenced response to different doses of postremission cytarabine in vivo. The primary end point was CIR, with time calculated from date of complete remission until relapse. Patients alive without relapse were censored, whereas those who died without relapse were counted as a competing cause of failure. The secondary end point was survival, which was measured from the date of diagnosis until death or date last known alive, censoring for patients alive at last follow-up. Estimated probabilities for survival were calculated using the Kaplan-Meier method, and the log-rank test evaluated differences between survival distributions.

Fisher's exact and Wilcoxon rank sum tests compared, respectively, categoric and continuous variables. Estimates of CIR were calculated, and Gray's k-sample test[28] was used to evaluate differences in relapse rates for the following variables: *RAS* mutation, age, sex, race, hemoglobin, platelets, WBC count, percentage of blood blasts, percentage of bone marrow blasts, cytogenetic group (CBF AML *v* non-CBF AML), spleen involvement, liver involvement, and consolidation treatment (LDAC *v* HDAC). Gray's method was constructed to build a multivariable CIR model using a limited backwards selection procedure.[29] Variables significant at $\alpha = .20$ from the univariable analyses were considered for multivariable analyses. Estimates for hazard ratios (HR) and corresponding 95% CIs were obtained for each significant prognostic factor. Adjusted CIR curves were generated using average covariate values from the multivariable CIR model.

An interaction term evaluating the differential effect of HDAC by *RAS* mutational status was included in the final multivariable CIR model and in the resultant adjusted CIR plots, supporting the primary hypothesis of the study. All analyses were performed by the CALGB Statistical Center.

Table 1. Pretreatment Characteristics, Treatment, and Clinical Outcome of Patients With and Without *RAS* Gene Mutations Among 185 Patients With Acute Myeloid Leukemia Studied

Characteristic	Mutated *RAS* (n = 34)		Wild-Type *RAS* (n = 151)		*P*
	No. of Patients	%	No. of Patients	%	
Age, years					.48
Median	42		43		
Range	17-78		18-77		
> 60	5	15	34	23	.36
Male sex		50		52	.85
Race					**.02***
White	25	74	135	89	
African American	7	21	9	6	
Other	2	6	7	5	
Hemoglobin, g/dL					.86
Median	9.4		9.3		
Range	5.3-12.5		4.5-14.2		
Platelet count, $\times 10^9$/L					.59
Median	53		51		
Range	12-401		11-433		
WBC count, $\times 10^9$/L					.63
Median	36.1		29.7		
Range	4-229		0.5-500.0		
Percentage of PB blasts					.40
Median	72		70		
Range	4-87		0-99		
Percentage of BM blasts					**.03**
Median	68		75		
Range	15-93		14-97		
FAB					
M0	0	0	1	< 1	
M1	1	3	37	25	
M2	14	41	51	34	
M4	8	24	31	21	
M5	5	15	20	13	
M6	1	3	2	1	
Cytogenetic group					.47
CBF	8	24	27	18	
non-CBF	26	76	124	82	
Extramedullary involvement					
CNS	0	0	2	1	1.00
Hepatomegaly	3	9	10	7	.71
Splenomegaly	5	15	11	7	.18
Lymphadenopathy	7	21	22	15	.44
Skin Infiltrates	4	12	15	10	.76
Gingival hypertrophy	5	15	24	16	1.00
Consolidation treatment					1.00
LDAC	12	35	56	37	
HDAC	22	65	95	63	
Relapse	22	65	110	73	.40
Death in first CR	3	9	9	6	.46
CIR†					.31
Median, years	1.5		1.1		
% Relapsed, 10 years	65		73		
95% CI	48 to 82		66 to 88		

Abbreviations: PB, peripheral blood; BM, bone marrow; FAB, French-American-British classification; CBF, core binding factor; LDAC, low-dose cytarabine (cytarabine 100 mg/m^2 as a continuous infusion $\times$ 5 days); HDAC, high-dose cytarabine (cytarabine 3 g/m^2 by intravenous bolus over 3 hours every 12 hours on days 1, 3, and 5, or cytarabine 400 mg/m^2/d as a continuous infusion $\times$ 5 days); CR, complete remission; CIR, cumulative incidence of relapse.

*Comparison of white patients with nonwhite patients.

†The median follow-up for patients alive (n = 55) is 12.9 years, ranging from 4.3 to 18.8 years.

RESULTS

Clinical Characteristics and Treatment

Mutations in *RAS* were detected in leukemia cells from 34 patients (18%), with the remaining 151 patients (82%) having wild-type *RAS* alleles. In Table 1, we compare pretreatment features of patients with and without *RAS* mutations. Patients with *RAS* mutations were more often nonwhite ($P = .02$) and had lower percentages of bone marrow blasts ($P = .03$). Other pretreatment characteristics were similarly distributed between the two groups (Table 1). In addition, there was no difference in the percentage of patients treated with LDAC or HDAC between the *RAS* mutated and *RAS* wild-type groups (Table 1).

Clinical Outcome

There was no significant difference in CIR when patients who had *RAS* mutations were compared with those who had wild-type *RAS* (Table 1 and Appendix Fig A1, online only). With a median follow-up of 12.9 years (range, 4.3 to 18.8 years), the estimated 10-year CIR for patients with *RAS* mutations was 65% (95% CI, 48% to 82%) compared with 73% (95% CI, 66% to 88%) for those with wild-type *RAS* ($P = .31$; Table 1).

When both the *RAS* status and consolidation therapy were taken into account (Fig 1A), *RAS*-mutated patients treated with HDAC had a lower rate of relapse than *RAS*-mutated patients treated with LDAC ($P < .001$; 10-year CIR, 45% *v* 100%). Patients with wild-type *RAS* also benefited from HDAC, but to a lesser extent ($P = .038$; 10-year CIR, 68% *v* 80%). Among patients treated with HDAC, those with *RAS* mutations experienced relapse less frequently than patients with wild-type *RAS* ($P = .05$; 10-year CIR, 45% *v* 68%; Fig 1A). In contrast, among patients treated with LDAC, there was no significant difference in CIR between patients with and without *RAS* mutations ($P = .20$; 10-year CIR, all patients experienced relapse within 7 years *v* 80%). Similar results were also observed in a subset analysis of patients who had a normal karyotype. In this subset, patients with *RAS* mutations in the HDAC group experienced relapse at a lower rate than those with *RAS* mutations in the LDAC group ($P = .02$), whereas the effect of consolidation dose on outcome did not reach significance among patients with wild-type *RAS* ($P = .13$).

A trend for survival similar to that of CIR was also observed for the entire cohort of patients included in this analysis (Fig 1B). Among patients with mutated *RAS*, those in the HDAC group tended to have a better survival than patients in the LDAC group, whereas among patients with wild-type *RAS*, there was no substantial benefit from receiving HDAC. For multivariable analysis for CIR, *RAS* mutation (mutated *v* wild-type), consolidation therapy (HDAC *v* LDAC), percentage of bone marrow blasts, WBC count, cytogenetic group (CBF AML *v* non-CBF AML), and the interaction of *RAS* mutation and consolidation therapy fulfilled the inclusion criteria. The final multivariable model included *RAS* mutation status, cytogenetic group, consolidation therapy, and the interaction of *RAS* mutation and consolidation therapy. The difference in the consolidation dose of cytarabine had greater impact on patients with *RAS* mutations than on those with wild-type *RAS* (Table 2 and Fig 2A). In the same model, CBF status also predicted a lower CIR (Table 2 and Fig 2A). Once adjusting for CBF status ($P < .001$), among patients with mutated *RAS*, those in the HDAC group had a markedly lower relapse rate compared with those in the LDAC group (HR = 0.28; $P = .002$; Table 2 and Fig 3A). The impact of HDAC consolidation on CIR in patients with wild-type *RAS* was substantially less (HR = 0.67; $P = .044$; Table 2 and Fig 3B). Notably, the only group in which more than 50% of patients remained in remission was that with mutated *RAS* treated with HDAC.

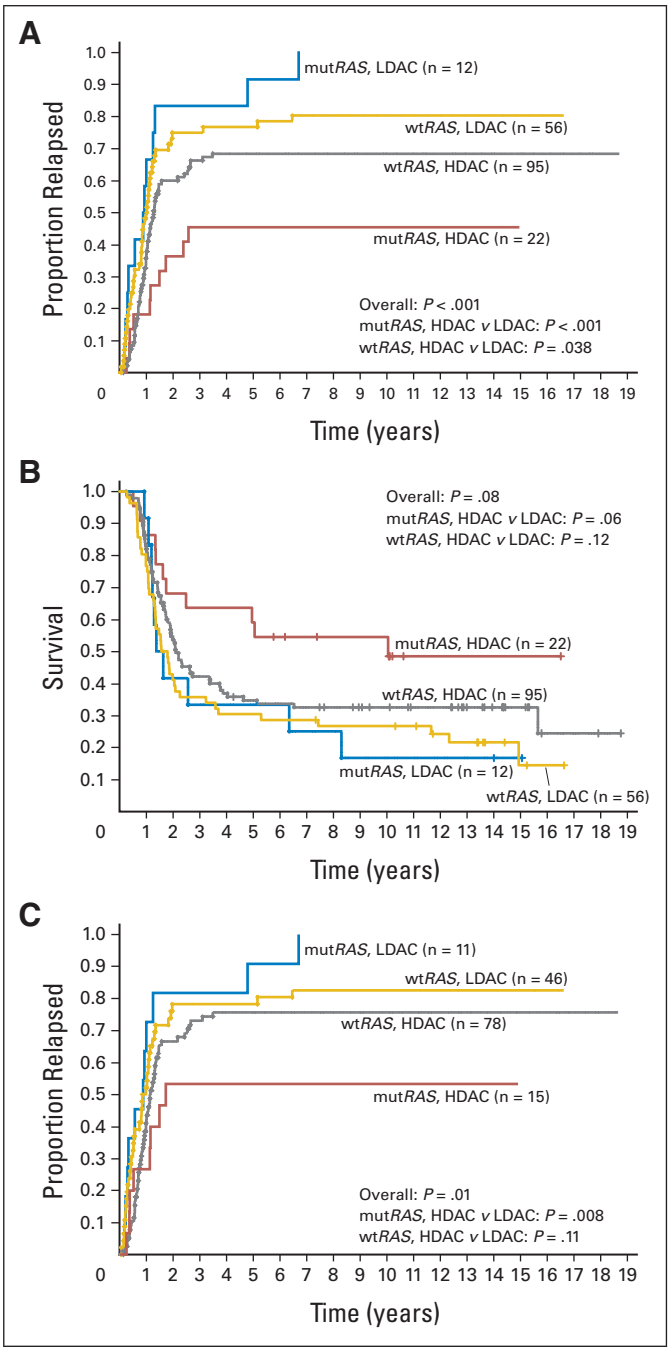

Fig 1. Outcome of 185 patients with acute myeloid leukemia (AML) according to *RAS* mutation status (mut*RAS*, mutated *RAS*; wt*RAS*, wild-type *RAS*) and random assignment to consolidation treatment with high-dose cytarabine (HDAC) or low-dose cytarabine (LDAC). (A) Cumulative incidence of relapse of all patients included in this study. (B) Survival of all patients included in this study. (C) Cumulative incidence of relapse of patients with non–core binding factor AML (ie, those who did not harbor t(8;21)/*RUNX1-RUNX1T1* or inv(16)/t(16;16)/*CBFB-MYH11*).

Table 2. Final Multivariable Model for Cumulative Incidence of Relapse

Variable	Hazard Ratio	95% CI	*P*
Interaction of *RAS* status and consolidation			.06
Mutated *RAS*			
HDAC *v* LDAC	0.28	0.12 to 0.63	.002
Wild-type *RAS*			
HDAC *v* LDAC	0.67	0.44 to 0.99	.044
Cytogenetic group			
CBF AML *v* non-CBF AML	0.42	0.26 to 0.68	< .001

NOTE. Variables considered for model inclusion were *RAS* mutation status (wild-type *v* mutated), WBC, % bone marrow blasts, cytogenetic group, consolidation therapy group (HDAC *v* LDAC), and the *RAS* mutation-consolidation therapy interaction term.

Abbreviations: HDAC, high-dose cytarabine; LDAC, low-dose cytarabine; CBF, core binding factor; AML, acute myeloid leukemia.

Because CBF status was predictive of a lower CIR in addition to postremission cytarabine dose (Table 2 and Fig 2A), we also performed an analysis restricted to patients with non-CBF AML (ie, those who did not harbor t(8;21)/*RUNX1-RUNX1T1* or inv(16)/t(16;16)/*CBFB-MYH11*). Consistent with the results of our overall analysis, the patients with non-CBF AML with mutated *RAS* treated with HDAC had the lowest CIR (Fig 1C). In multivariable analysis (Table 3 and Fig 2B), these patients had a significantly lower relapse rate than the patients with non-CBF AML with mutated *RAS* who were randomly assigned to LDAC (HR = 0.29; *P* = .008). The favorable impact of HDAC on CIR was no longer statistically significant in patients with non-CBF AML with wild-type *RAS* (HR = 0.71; *P* = .13).

DISCUSSION

Earlier studies of the prognostic significance of mutations in *RAS* in AML have yielded contradictory results. Some studies reported that patients with *RAS* mutations had improved overall survival,[5,6] whereas others found that these patients had worse complete remission rates,[8] overall survival,[7-9] and disease-free survival[7] than those with wild-type *RAS*. In contrast, several studies found no significant differences in outcome, including complete remission rates,[4,7,10,11,15,16] overall survival,[4,10,11,15-17] disease-free survival,[8,10,11,16,17] event-free survival,[6,17] or relapse-free survival,[15] between patients with and without *RAS* mutations. Notably, in most of these studies, the type of postremission treatment was not taken into account in the analysis of clinical outcome.[4-7,9-11,15-17]

In the current analysis of adult patients with primary AML, all of whom were enrolled on the same treatment protocol, achieved complete remission, and have prolonged follow-up, there was no significant difference in outcome between patients with and without *RAS* mutations, which was similar to the findings of most previous studies.[6,8,10,11,15-17] However, when we considered both the *RAS* status and consolidation therapy, our analysis revealed for the first time that the impact of *RAS* mutations on the risk of relapse in adult AML depends on the type of postremission chemotherapy. Although therapy with HDAC resulted in a lower CIR both in patients with and without *RAS* mutations, its

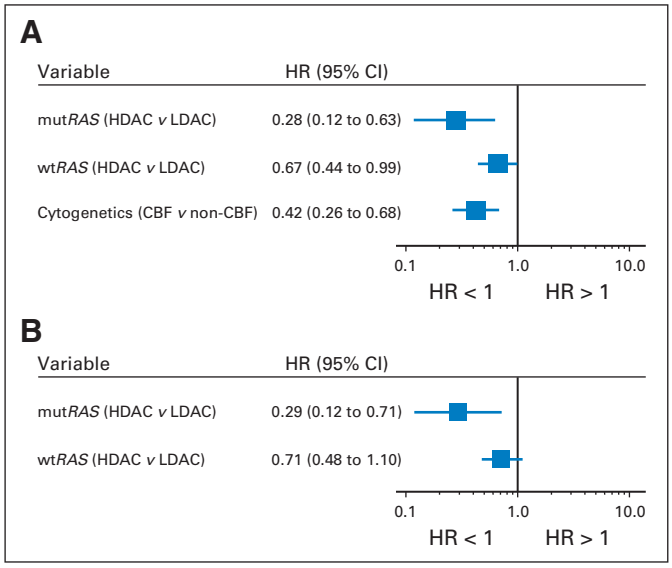

Fig 2. Forest plots summarizing the multivariable models for cumulative incidence of relapse of (A) all 185 patients with acute myeloid leukemia (AML) and (B) 150 patients with non–core binding factor AML. The hazard ratios (HRs) with 95% CIs for each variable in the model are shown. HRs less than 1 indicate lower risk for relapse for the first category listed. mut*RAS*, mutated *RAS*; wt*RAS*, wild-type *RAS*; HDAC, high-dose cytarabine; LDAC, low-dose cytarabine.

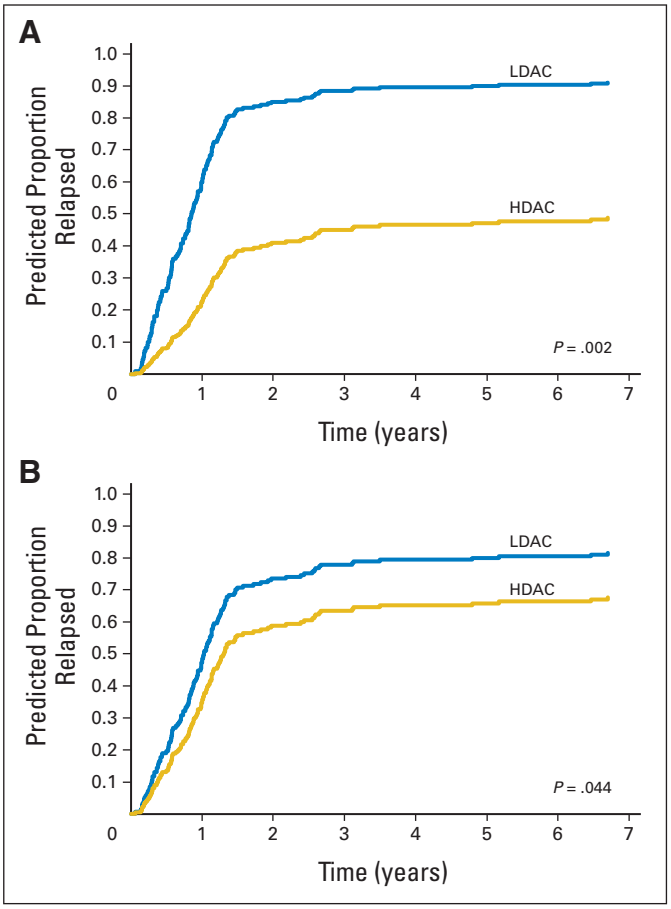

Fig 3. Predicted cumulative incidence of relapse of patients with acute myeloid leukemia receiving high-dose cytarabine (HDAC) and low-dose cytarabine (LDAC) postremission therapy according to *RAS* mutation status (mutated or wild-type) adjusting for core binding factor status. (A) Patients with *RAS* mutation. Model was based on 22 patients on the HDAC arm and 12 patients on the LDAC arm. (B) Patients with wild-type *RAS*. Model was based on 95 patients on the HDAC arm and 56 patients on the LDAC arm.

Table 3. Final Multivariable Model for Cumulative Incidence of Relapse for Non-CBF AML Cases

Variable	Hazard Ratio	95% CI	*P*
Interaction of *RAS* status and consolidation			.08
Mutated *RAS*			
HDAC *v* LDAC	0.29	0.12 to 0.71	.008
Wild-type *RAS*			
HDAC *v* LDAC	0.71	0.48 to 1.1	.13

NOTE. Variables considered for model inclusion were *RAS* mutation status (wild-type *v* mutated), WBC, spleen involvement, consolidation therapy group (HDAC *v* LDAC), and the *RAS* mutation-consolidation therapy interaction term.
Abbreviations: CBF, core binding factor; AML, acute myeloid leukemia; HDAC, high-dose cytarabine; LDAC, low-dose cytarabine.

benefit was much more pronounced in patients with mutated *RAS*. With HDAC, patients with mutated *RAS* had a substantial reduction in relapse risk relative to those with wild-type *RAS*. Only 45% of patients with mutated *RAS* experienced relapse. In contrast, all patients with mutated *RAS* in the LDAC group experienced relapse, all but two patients within 16 months after achievement of a complete remission. It is important to underscore that although this was an intent-to-treat analysis, the actual amount of cytarabine administered to patients in each of the consolidation arms was not different between the mutated *RAS* and wild-type *RAS* groups (not shown).

Our results are consistent with in vitro data showing that mutations in *RAS* render tumor cell lines derived from AML and non–small-cell lung and colon carcinomas more sensitive to certain cytotoxic drugs, such as cytarabine or topoisomerase II inhibitors.[22,30] Koo et al[23] have demonstrated that cells harboring an activated *RAS* oncogene fail to arrest in the S phase of the cell cycle in response to cytarabine treatment and that this results in their apoptotic death. In contrast, tumor cells with wild-type *RAS* genes undergo marked S-phase growth arrest on exposure to cytarabine that is reversible once the drug is removed. The authors concluded that the presence of a *RAS* mutation may change cellular response to cytarabine from cytostatic to cytotoxic, most likely because of altered cellular checkpoint functions in response to cytarabine.[23] Recent studies provide experimental evidence that mutated *RAS* not only induces proliferation, apoptosis, senescence, or differentiation (depending on the cellular context in which it is expressed),[31] but it may also induce a DNA damage checkpoint response.[32-34] These results provide biologic plausibility to our clinical observations.

Concordant with our data, Illmer et al[11] have recently shown that among younger (<60 years) patients with AML receiving high-dose cytarabine as induction therapy, activated RAS proteins predicted for a significantly higher response rate and longer overall survival. Additionally, two groups have reported promising response rates with regimens containing high-dose cytarabine in patients with advanced pancreatic carcinoma, a tumor where up to 90% of the patients show *RAS* mutations.[35,36]

In summary, the current study demonstrates that patients with primary AML harboring *RAS* mutations treated with HDAC as postremission therapy are significantly less likely to experience relapse than patients treated with LDAC. Furthermore, among patients receiving HDAC, those with *RAS* mutations also had a lower risk of relapse than patients with the wild-type *RAS*. These results suggest that mutations in the *RAS* gene constitute a novel molecular marker potentially useful in the clinic to identify patients who would optimally benefit from consolidation with HDAC. To date, risk-adapted stratification to HDAC postremission therapy in CALGB protocols has been performed on the basis of cytogenetic and molecular genetic detection of t(8;21)/*RUNX1-RUNX1T1* and or inv(16)/*CBFB-MYH11*. If our findings are confirmed, testing for *RAS* mutations could become useful, in addition to CBF-AML detection, for risk-adapted stratification to HDAC postremission treatment in adults with de novo AML treated with chemotherapy alone. Because *RAS* mutations seem to be the first example of activating oncogene mutations that sensitize AML blasts to higher doses of cell-cycle phase-specific chemotherapeutic agent, further studies are needed to elucidate the molecular mechanisms of this phenomenon.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

