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Survival Is Poorer in Patients With Secondary Core-binding Factor Acute Myelogenous Leukemia Compared With De Novo Core-binding Factor Leukemia

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Abstract

Background—Therapy related secondary acute myelogenous leukemia (AML) was commonly associated with prior exposure to alkylating agents or topoisomerase inhibitor. The long-term outcome of such patients with secondary AML was found to be worse than that of patients with de novo AML. Earlier reports suggested similar outcomes for patients with de novo and secondary AML associated with core-binding factor (CBF) abnormalities.

Methods—A total of 188 patients with CBF AML were analyzed. The frequency of secondary CBF AML was 9%.

Results—Patients with secondary CBF AML were found to have significantly worse overall (OS) and event-free survival (EFS) compared with patients with de novo CBF AML. Secondary CBF AML status appeared to have only marginal significance in multivariate analysis.

Conclusions—Matched analysis (by age, Eastern Cooperative Oncology Group performance status, and additional cytogenetic abnormality) indicated worse OS and EFS in patients with secondary CBF AML.

Keywords

therapy-related; core-binding factor; acute myelogenous leukemia; overall survival; event-free survival; matched analysis

Core-binding factor-associated acute myelogenous leukemias (CBF AMLs) are characterized by balanced chromosomal translocations^{1,2} and sensitivity to high-dose cytarabine-based therapy. Most patients achieve disease remission with cytarabine-based induction therapy, and consolidation with more than 1 cycle of high-dose cytarabine is considered standard.³⁻⁵ Stem cell transplantation in patients in first disease remission has not been reported to improve survival in patients with CBF AML.^{3,6,7} In a small percentage of patients, CBF AML can develop as a “secondary” malignancy from prior exposure to chemotherapeutic agents and/or radiation.^{8,9} Taxanes and DNA topoisomerase inhibitors are implicated in the development of secondary leukemias with balanced translocations.^{9,10} Reports of the long-term outcome of patients with secondary CBF AML are scarce because most reports of CBF AML do not distinguish between patients with de novo and those with secondary disease.

Herein, we report on outcomes of patients with secondary CBF AML and compare long-term outcome data with that of patients with de novo CBF AML.

Materials and Methods

Patients

Between 1991 and 2007, 188 patients with CBF AML were treated at The University of Texas M. D. Anderson Cancer Center. Based on a history of a prior diagnosis of malignancy (except skin or in situ cancers), patients with exposure to chemotherapy and/or radiation were classified as having either de novo or secondary CBF AML. Patient characteristics are summarized in Table 1.

Treatment

All patients underwent induction chemotherapy with intermediate-dose to high-dose cytarabine-based chemotherapy (total dose of 6 to 10 g/m²), and patients achieving a complete remission (CR) received high-dose cytarabine in consolidation (median, 6 cycles; range, 1 cycle-14 cycles).

Informed Consent

All patients were treated on a protocol approved by The University of Texas M. D. Anderson Cancer Center Institutional Review Board after informed consent was obtained.

Statistical Analysis

Patient characteristics at the time of presentation between patients with de novo and secondary CBF AML were compared. Wilcoxon rank sum tests were used to assess the difference in continuous variables, and categoric variables were assessed using chi-square tests or Fisher exact tests.

The Kaplan-Meier product limit method was used to generate survival curves and event-free survival (EFS) curves, for which the overall survival (OS) is defined as the time between admission to The University of Texas M. D. Anderson Cancer Center and last follow-up. EFS was calculated from the date of achieving CR to the date of the earliest disease

recurrence or death or last follow-up. The log-rank test was subsequently used to assess the difference in OS or EFS between the 2 groups. In addition, to study the effect of patient characteristics on survival and EFS, Cox proportional hazards regression models were used to assess the hazard ratios. In univariate Cox regression, the effects of the variables were modeled individually. All variables were then included into an initial multivariate Cox proportional hazards model, and a stepwise model selection procedure was performed with equal entering and staying probabilities of 0.1. At the end of model selection, variables with P values $<.05$ were retained.

All computations were performed using SAS 9.1 statistical software (SAS Institute Inc, Cary, NC) using the Windows XP 2002 operating system. All reported P values were for 2-sided tests, and a P value $<.05$ was considered statistically significant.

Patients with secondary CBF AML were matched by age (± 5 years), Eastern Cooperative Oncology Group (ECOG) performance status, and the presence of additional chromosomal abnormalities to patients with de novo CBF AML. Kaplan-Meier estimates were used to generate survival curves, and the log-rank test was performed to evaluate the difference between groups.

Results

A total of 188 AML patients with CBF AML were included in this analysis. Among them, 17 (9%) patients had secondary CBF AML. Patient characteristics are summarized in Table 1. Twelve patients with secondary CBF AML had prior exposure to both an alkylating agent and topoisomerase inhibitor. Six patients had prior lymphoma and 5 had a prior diagnosis of breast cancer. The median time from treatment of prior malignancy to the development of AML was 2 years (range, 1 year–17 years). None of the patients with secondary CBF AML had a documented phase of myelodysplastic syndrome (MDS). Patients with secondary CBF AML were significantly older than those with de novo disease ($P = .02$) and had lower white blood cell (WBC) counts at the time of presentation ($P = .02$). Among all patients with CBF AML, 94 (50%) patients had chromosomal abnormalities in addition to CBF abnormality but there was no difference noted among the de novo (87 of 171) and secondary (7 of 17) disease groups with regard to the frequency of additional chromosomal abnormalities ($P = .63$). Two (2 of 17) patients in the secondary CBF AML group had chromosome 7q deletion, and 2 others had sex chromosome loss. Three (3 of 171) patients in the de novo group had 7q deletion.

Treatment Outcomes

One hundred seventy-three (92%) patients achieved a CR or CR with incomplete platelet recovery (CRp). There were 6 (3%) induction-related deaths, 3 patients were resistant to induction therapy, and 2 patients refused therapy. Five of the 15 (33%) patients with secondary CBF AML who achieved a CR had developed disease recurrence compared with 57 of 158 (36%) patients with de novo CBF AML. Of these 5 patients, 3 received cytarabine-based salvage therapy, 1 was treated with a histone deacetylase inhibitor, and another received thalidomide for secondary MDS with chromosome 5 and 7 abnormality without the previously present inversion 16 abnormality.

Survival Analysis

The median OS among all patients was 269 weeks (95% confidence interval [95% CI], 170 weeks->800 weeks). The median duration of CR for the entire group was >600 weeks (95% CI, 94 weeks to >734 weeks). The OS ($P = .004$) (Fig. 1) and EFS ($P = .04$) of patients with secondary CBF AML were found to be significantly worse than that of patients with de novo CBF AML.

Univariate and Multivariate Analysis

On univariate analysis, age, secondary CBF AML, bilirubin, and hemoglobin were found to significantly impact OS. After adjusting for age, bilirubin, and hemoglobin; secondary CBF AML status was found to have a marginally significant effect ($P = .11$) on OS. Similarly, on univariate analysis, age, secondary CBF AML, higher bilirubin, lower hemoglobin, and higher WBC counts were found to be significantly associated with a worse EFS. However, after adjusting for age, WBC count, and bilirubin; secondary AML status was not found to be significantly associated with a worse EFS ($P = .26$).

Matched Analysis

Patients with secondary CBF AML were matched 1:1 with patients with de novo disease based on age, ECOG performance status, and the presence of additional chromosomal abnormalities (Table 2). Patients with secondary CBF AML had a worse OS ($P = .001$) (Fig. 2) and EFS ($P = .003$) compared with matched patients with de novo disease.

Discussion

Although CBF AML is considered to have favorable prognosis, results from larger groups indicate that the EFS at 5 years is in the range of 40% to 50%.^{3,6} This highlights the presence of ample room for improvement. The incidence of secondary CBF AML is relatively low compared with that of secondary AML with unfavorable cytogenetics.^{8,11,12} An earlier report indicated that the outcome of patients with secondary CBF AML is similar to their de novo counterparts.¹³ Conversely, the results of the current analysis highlight a worse outcome in this subgroup of patients with “good-risk” cytogenetics. Given that patients with secondary CBF AML tend to be older than those with de novo disease, the finding that they have secondary leukemia still negatively impacts their OS and EFS, as evidenced by our matched analysis.

Secondary AML associated with balanced translocations usually occur after prior exposure to topoisomerase II inhibitors. With improved survival noted among patients treated with such agents, the incidence of secondary leukemias including secondary CBF AMLs is expected to increase. Whether early referral for stem cell transplantation at the time of first CR for patients with secondary CBF AML will improve outcome is not known.

Recent reports have linked the presence of unusual CBFB-MYH11 transcripts in therapy-related CBF AML with inv16 abnormality.¹⁴ Additional cryptic mutations in patients with therapy-related CBF AML may be responsible for the worse overall outcome, and a systematic approach to document such additional genetic events may help in unraveling its

pathogenesis. Because of the presence of unique transcripts, CBF AML is amenable to molecular monitoring of disease.¹⁵⁻¹⁷ Multiple log reductions in fusion transcripts after induction and consolidation therapies are associated with better EFS.¹⁶ Interventions designed to be implemented at times of molecular progression of disease or lack of optimal molecular response may improve outcome in patients with CBF AML, including secondary CBF AML. However, to our knowledge, the definitions of molecular progression or suboptimal response have not been established in patients with CBF AML. Moreover, unlike for patients with overt clinical disease recurrence, the risk-versus-benefit profile of early intervention will need to be established.

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Figure 1.
Overall survival of all patients (grouped by de novo or secondary disease) is shown.

Figure 2. Overall survival by matched analysis (matched according to age, Eastern Cooperative Oncology Group performance status, and additional cytogenetic abnormality) is shown.

Table 1
Patient Characteristics

Type of Abnormality	De Novo (N=171)	Secondary (N=17)	P
Parameters			
Gender			
Male	96	8	.47
Female	75	9	–
ECOG performance status			
0	24	4	.29
>0	147	13	–
Cytogenetics			
Inv 16	102 (60%)	13 (76%)	
T (8;21)	69 (40%)	4 (24%)	
Additional cytogenetic abnormality	87 (51%)	7 (54%)	
	Median (Range)	Median (Range)	
Age, y	44 (16-88)	62 (31-75)	.02
WBC, $\times 10^6/\text{mL}$	16.4 (0.6-387)	5.3 (0.8-103.8)	.02
Hemoglobin, g/dL	8.2 (2.5-14.3)	7.6 (4.8-10.8)	.18
Platelets, $\times 10^9/\text{mL}$	38 (5-350)	36 (9-139)	.81
Bilirubin, mg/dL	0.6 (0.1-5)	0.1 (0.1-15.3)	.90
Creatinine, mg/dL	0.9 (0.5-2.9)	0.9 (0.5-1.8)	.85

ECOG indicates Eastern Cooperative Oncology Group; WBC, white blood cell.

Table 2
Characteristics of Matched Cohorts

Characteristics	De Novo	Secondary
	Median (Range)	Median (Range)
Age, y	61 (31-73)	62 (31-75)
Hemoglobin, g/dL	8.7 (3.4-11.9)	7.6 (4.8-10.8)
Platelets, $\times 10^9/\text{mL}$	33 (5-237)	36 (9-139)
WBC, $\times 10^6/\text{mL}$	12 (1.4-67.5)	5.3 (0.8-103.8)
	No. (%)	No. (%)
Cytogenetics		
Inv 16	9 (53)	13 (76)
T (8;21)	8 (47)	4 (24)
ECOG performance status		
0-1	15	15
2-3	2	2

WBC indicates white blood cell; ECOG, Eastern Cooperative Oncology Group.