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Factors associated with risk of central nervous system relapse in patients with non-core binding factor acute myeloid leukemia

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Abstract

Central nervous system (CNS) relapse is uncommon in patients with acute myeloid leukemia (AML) with the use of high-dose cytarabine containing chemotherapy regimens. The clinical and molecular features associated with a higher risk of CNS relapse are not well defined. We assessed the incidence and outcome of CNS relapses among 1245 patients with relapsed/refractory AML referred to our institution between 2000 and 2014. CNS leukemia relapse was observed in 51 patients (4.1%). Using a multivariate regression model and after adjusting for age, *FLT3*-ITD mutation (OR = 2.33; $P = .02$) and elevated LDH (>1000 IU/L, OR = 1.99; $P = .04$) were independent predictive factors for CNS relapse. Patients under 64 years of age with 0, 1, or 2 baseline adverse features had a probability of 3.8%, 7.0%–8.0%, and 13.9% for developing CNS disease, respectively. Our study identifies patients with AML at higher risk for CNS relapse in whom prophylactic CNS therapy may be warranted.

1 | INTRODUCTION

The high risk of central nervous system (CNS) relapse in acute lymphoblastic leukemia (ALL) became apparent with improvement in systemic therapy and overall survival.[1,2] This

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

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necessitated the development of effective prophylactic CNS-directed therapy, which led to a substantial reduction in the overall incidence of CNS disease. The majority of children and half of adults with ALL who receive appropriate systemic and CNS therapies are cured. CNS relapse occurs in acute myeloid leukemia (AML) at low rates of 2%–8%,[3–7] except in inversion 16 AML where the incidence was 30% with standard-dose cytarabine regimens but was nearly eliminated with high-dose cytarabine regimens.

CNS prophylaxis does not appear to result in a significant benefit in adults in newly diagnosed AML.[8] This is likely attributable to the low incidence of CNS involvement in adult AML. Studies have attempted to identify risk factors for developing CNS involvement, hoping to identify and target only high-risk patients for prophylactic intrathecal therapy. Traditionally identified risk factors included younger age, high initial white blood cell (WBC) count, leukemic cells in the cerebrospinal fluid (CSF) at diagnosis, elevated lactate dehydrogenase (LDH), presence of organ infiltration (eg hepatomegaly), M4 and M5 morphologies, expression of CD56, and particular cytogenetic aberrations including inversion 16, chromosome 11 abnormalities, t (8:21) and trisomy 8.[4,6,7,9]

In this study, our objective was to identify the clinical, biologic, and molecular features predictive of CNS relapse in patients with AML.

2 | MATERIALS AND METHODS

We retrospectively reviewed data of patients with relapsed/refractory AML (excluding acute promyelocytic and core binding factor leukemia) seen at The University of Texas MD Anderson Cancer Center between January 1, 2000 and January 1, 2014. Patients with core binding factor AML were excluded because these patients uniformly receive high-dose cytarabine-based regimens at our institution, which has been associated with decreased risk of CNS relapse. The institutional review board of The University of Texas MD Anderson approved the study. The baseline patient characteristics, laboratory values, response to therapy and outcome for the whole group were recorded. Parameters analyzed included: age, sex, WBC count, hemoglobin, platelet count, peripheral blood blasts, bone marrow blasts, LDH, French American British (FAB) classification, cytogenetics, antecedent hematological disorder (AHD) and *FLT3* mutational status.

We identified patients who presented with CNS relapse, either isolated or with concomitant systemic relapse. CNS leukemia was diagnosed by the presence of leukemic blasts in a cytocentrifuge preparation of CSF according to criteria set by the European Organization for Research and Treatment of Cancer (EORTC) Study 58881.[2] Patients with blasts in the CSF together with high numbers of red blood cells (> 5) were not considered to have CNS disease if the blasts were elevated in the peripheral blood (ie, $\geq 5 \times 10^9$/L). Fifty-one patients with a diagnosis of AML and CNS relapse were identified. All patients with evidence of CNS disease underwent a bone marrow examination. Cytogenetic results were reported according to the International System for Human Cytogenetic Nomenclature.[10] Cytogenetic abnormalities were grouped according to published WHO criteria into complex, intermediate and low risk.[11]

FLT3 internal tandem duplication (ITD) and codon 835/838 tyrosine kinase domain (TKD) mutations were determined from genomic DNA obtained from bone marrow aspirates using a sort-cycle polymerase chain reaction-based method with subsequent restriction-digest using EcoRV for the TKD reaction and size fractionation by capillary electrophoresis.

For comparison, patients who had AML with CNS relapse were compared with patients with relapsed/refractory AML who had received induction chemotherapy at our institution and had detailed information about baseline characteristics. Baseline characteristics were compared with the Chi-Square/Fischer exact test and Mann-Whitney *U* test for categorical and continuous variables, respectively. A logistic regression model was used for the multivariate analysis, and variables were included in a backward method. Statistical analysis was performed using SPSS software (version 19.0; SPSS Inc., Chicago, Ill). Subsequently, competing risks regression model was used for the multivariate analysis for predicting CNS relapse.

3 | RESULTS

3.1 | Patient characteristics

We reviewed the medical records of 1245 patients with relapsed/refractory AML who were followed and treated at our institution. CNS leukemia was detected during follow-up in 51 patients (4.1%). Baseline characteristics of these 51 patients and the overall population are presented in Table 1.

3.2 | CNS disease

CNS involvement was detected after a median of 7.6 months from initial diagnosis (range, 1 to 68 months). The median time to CNS disease was 16 months in patients who have achieved first complete remission (range, 3 to 185 months) and 3.3 months (range, 2 to 140 months) in patients who were primary refractory. Four patients had isolated CNS relapse followed by systemic relapse after a median of 2 weeks (range, 3 days to 7 weeks). Thirty-nine had neurologic symptoms at the time of CNS relapse, including headache ($N = 11$), involvement of cranial nerves ($N = 17$), visual impairment ($N = 17$), seizures ($N = 8$), confusion ($N = 17$), and peripheral neuropathy ($N = 13$) (one patient had more than one symptom). Details on diagnostic features at the time of CNS relapse are shown in Supporting Information Table S1.

MRI imaging was performed in 32 patients; 19 of them (59%) had abnormal findings by MRI suggestive of CNS disease. The median cell count in the CSF was 29 (range, 0 to 22,880) and median blast percentage was 47% (range, 1% to 100%). Four patients had zero cells with blasts detected on cytocentrifuge preparation only. None of the 4 patients had circulating blasts and all had abnormal findings on brain MRI suggestive of CNS relapse.

3.3 | CNS therapy

Treatment for CNS disease consisted of intrathecal chemotherapy (methotrexate alternating with cytarabine) in all patients, whole brain radiation therapy in 14, and spinal radiation in 8. Patients with abnormal findings on MRI were more likely to receive cranial and/or spinal

irradiation than those without imaging abnormalities (9 out of 19 [47%] versus 1 out of 13 [8%], respectively; $P = .02$). Therapy was successful in clearing all signs of CNS disease in 29 (57%) patients. Nineteen of the 29 patients (65%) subsequently had additional CNS relapses after a median of 3 months (range, 1 to 24 months). Stem cell transplantation (SCT) was performed in 15 patients (29%), 6 with active disease and 9 in complete remission. The median overall survival after CNS relapse was 16 weeks (range, 10 to 22 weeks). The 2-year survival rate after CNS relapse was 13%. There was no difference in overall survival (from time of diagnosis) among patients with or without CNS disease (median 56 versus 53 weeks; $P = .9$)

3.4 | Multivariate analysis for CNS disease

All baseline variables were used in the univariate analysis. Younger patients (less than 64 years old), and those with *FLT3*-ITD mutation, high LDH (> 1000 IU/L), elevated WBC count ($> 10 \times 10^9$/L), without history of antecedent hematologic disorder, or with extramedullary disease at diagnosis had a higher incidence of CNS relapse (Table 2). In the multivariate regression model for CNS relapse, only age (<64 years; odds ratio = 0.49, $P = .04$), mutated *FLT3*-ITD (odds ratio = 2.16; $P = .03$), and higher LDH (odds ratio = 1.87; $P = .06$) were independently associated with higher risk for CNS relapse (Table 3).

Since younger patients may live longer and are therefore at higher cumulative risk for CNS relapse, we subsequently performed a multivariate competing risks regression for CNS relapse on age, cytogenetics, FAB, *FLT3*-ITD, antecedent hematologic disorder, extramedullary disease at diagnosis and LDH. Age was the only independent predictive factor for CNS relapse [Sub-distribution hazard ratio (SHR) = 0.38 (95% CI: 0.17–0.89); $P = .02$]. We repeated the multivariate logistic regression model for CNS relapse on *FLT3*-ITD mutation and LDH only; *FLT3*-ITD mutation (odds ratio = 2.33; $P = .02$) and higher LDH (odds ratio = 1.99; $P = .04$) were the independent predictors for CNS relapse (Supporting Information Table S2).

3.5 | Predictive model for CNS relapse

A predictive scoring system was developed using age, *FLT3*-ITD mutation status and LDH among all patients. Since the relative risk for CNS relapse was similar for age, *FLT3*-ITD mutation status and a high LDH, we assigned an arbitrary value of 1 to each of them. Table 4 summarizes the results for patients under 64 years of age. Patients with no additional adverse feature (n = 214; wild type *FLT3*-ITD and low LDH) had a probability of 3.8% for developing CNS disease; patients with one adverse feature ($n = 155$) had a probability of 7.0%–8.0%; patients with two adverse features ($n = 55$; both *FLT3*-ITD mutation and high LDH) had the highest probability of developing CNS disease (13.9%).

4 | DISCUSSION

The present study confirms that the occurrence of CNS relapse is rare in adults with AML,[6,7,9,12,13] with an incidence of 4.1% among 1245 patients with relapsed/refractory disease treated at our institution. This incidence is in line with previous studies which reported CNS relapse rates of 2% to 4%.[6,12–14] There was high incidence of CNS disease among patients

with *FLT3*-ITD mutations (29%) and higher LDH (51%), justifying a potential incorporation of CNS prophylaxis in such patients.

The association between specific cytogenetic abnormalities and CNS disease in patients with AML has been previously described. A study from our institution showed that patients with CNS disease had a higher frequency of inversion 16, chromosome 11 abnormalities, trisomy 8, and complex cytogenetics compared with patients who had AML without CNS disease.[14] In a study by the Children's Cancer group, patients with chromosome 11 abnormalities (specifically 11q23) were more prone to develop CNS disease.[6] Higher levels of LDH were shown to be associated with CNS disease, particularly among patients with acute promeylocytic leukemia.

Certain cytokines have been shown to be shared by both the hematopoietic and nervous system. They may serve different functions in different locations. In the context of extramedullary disease in patients with AML, one such identified molecule is CD56.[9,15] CD56 is identical to the previously recognized neural-cell adhesion molecule (NCAM) and modulates homotypic neuronal growth.[16] CD56 expression has been associated with skin and CNS infiltration in patients with lymphoma.[17,18] There is association between CD56 expression and extramedullary dissemination of AML.[9,19] Another such molecule is neuronal growth factor (NGF) which acts as a colony stimulating factor in the hematopoietic system and a promoter of sensory neuronal survival in the nervous system.[20,21] FLT3 mRNA has been identified in nervous tissue.[22,23] Because FLT3 is a potent co-stimulator of hematopoietic stem cell survival and proliferation, Brazel et al sought to determine whether it had similar effects on the neural stem cells. Surprisingly, they found that FLT3 inhibits the proliferation of neural stem cells, but promotes the survival of subsets of mature neurons.[24] They also noted that FLT3 synergized with nerve growth factor (NGF) to increase survival of subsets of differentiated neurons. These observations suggest that FLT3 mutation in leukemic cells may determine specific sites of involvement in leukemic disease. A similar mechanism may explain CNS involvement in cases of AML associated with *FLT3* mutation.

Our study has identified two independent baseline characteristics as predictive for CNS relapse including *FLT3*-ITD mutation and higher level of LDH. Since the relative risk of each factor was similar, we were able to provide a simple scoring system that identifies, at diagnosis, a subgroup of patients with higher risk for CNS relapse, particularly among younger patients. In these patients with one or two adverse features, a prophylactic approach with intrathecal chemotherapy during induction/consolidation may be warranted.

In summary, relapses in the CNS in patients with AML are more common with younger age, elevated LDH and mutation of *FLT3*-ITD. This study identifies a statistically significant association between elevated LDH and *FLT3*-ITD mutation and CNS involvement. A validation of our findings is needed and warrants a prophylactic approach in patients with higher risk for CNS relapse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline patient characteristics

	***N* (%)**		
Characteristics	**Overall (*N* = 1245)**	**CNS− (*N* = 1194)**	**CNS1 (*N* = 51)**
Age > 64 years	665 (53)	645 (54)	20 (39)
Prior HiDAC	985 (79)	945 (79)	40 (78)
Refractory/Relapse	582 (47)/663 (53)	561(47)/633 (53)	21 (41)/30 (59)
Poor cytogenetics	394 (32)	384 (32)	10 (20)
FAB M4/M5	276 (22)	259 (22)	17 (33)
FLT3-ITD mutation	160 (13)	145 (12)	15 (29)
FLT3-D835 mutation	41 (3)	40 (3)	1 (2)
NPM1 mutation	95 (8)	92 (8)	3 (6)
RAS mutation	89 (7)	83 (7)	6 (12)
AHD	494 (40)	482 (40)	12 (24)
WBC > 10×10^9/L	432 (35)	406 (34)	26 (51)
LDH > 1000 IU/L	448 (36)	417 (35)	31 (61)
Platelets > 49×10^9/L	606 (49)	582 (49)	24 (47)
Hgb > 8.7 g/dL	565 (51)	543 (47)	22 (44)
BM blasts > 50%	518 (42)	492 (41)	26 (51)
PB Blasts > 50%	279 (22)	263 (22)	16 (31)
Albumine > 3.5 g/dL	535 (45)	514 (45)	21 (42)
Bilirubin > 0.5 mg/dL	554 (44)	527 (44)	27 (53)
Creatinine > 0.9 mg/dL	528 (42)	507 (42)	21 (41)
Extramedullary disease at diagnosis	23 (2)	19 (2)	4 (8)

AHD, antecedent of hematologic disorder; BM, bone marrow; HiDAC, high-dose cytarabine; Hgb, hemoglobin; LDH, lactate dehydrogenase; PB, peripheral blood; WBC, white blood cell.

TABLE 2

Univariate logistic regression for CNS relapse

Parameter	Level	*P*-value
Age < 64 years	Yes vs. No	.04
FLT3-ITD mutation	Yes vs. No	.001
LDH > 1000 IU/L	Yes vs. No	<.001
WBC > 10×10^9/L	Yes vs. No	.02
No AHD	Yes vs. No	.02
Extramedullary disease at diagnosis	Yes vs. No	.004

AHD, antecedent of hematologic disorder; LDH, lactate dehydrogenase; WBC, white blood cell.

TABLE 3

Multivariate logistic regression for CNS relapse ($N = 915$)

Parameter	Level	OR	95% CI	P-value
Age ≥ 64 years	Yes vs. No	0.49	(0.25–0.96)	0.04
FLT3-ITD	Yes vs. No	2.16	(1.08–4.33)	0.03
LDH > 1000 IU/L	Yes vs. No	1.87	(0.97–3.60)	0.06

CI, confidence interval; LDH, lactate dehydrogenase; OR, odds ratio.

TABLE 4

The summary of predictive scoring system for patients under 64 years of age

# adverse event (in addition to age)	0	1		2
Probability (%)	**3.8%**	**7.0%**	**8.0%**	**13.9%**
N	214	122	33	55
FLT3-ITD status	Wild type	Wild type	Mutated	Mutated
LDH > 1000 IU/L	No	Yes	No	Yes

The predictive scoring system was developed based on all patients (≥64 and <64 years of age).