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CNS involvement in AML at diagnosis is rare and does not affect response or survival: data from 11 ECOG-ACRIN trials

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Key Points

- There was no significant difference in CR rate and OS among patients with CNS involvement, other EMD, or no EMD.
- The incidence of CNS involvement of newly diagnosed AML is low, irrespective of whether an LP is mandatory or not.

Central nervous system (CNS) involvement in patients with newly diagnosed acute myeloid leukemia (AML) is rare, and systematic data regarding outcome are scarce. This retrospective study summarized data from 11 consecutive Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) clinical trials for patients with newly diagnosed AML. In all, 3240 patients with AML were analyzed, and 36 (1.11%) were found to have CNS involvement at diagnosis. The incidence of CNS disease among the 5 studies with per protocol mandatory lumbar puncture (LP) was similar to the incidence among studies in which LP was performed at the discretion of the investigator (0.86% vs 1.41%; $P = .18$). There was no significant difference in the rate of complete remission (CR) among patients with CNS involvement and those with other extramedullary disease (EMD) sites or those with no EMD (52.8% vs 59.3%-60%). The median overall survival (OS) for patients who were CNS positive, who had other EMD, or who had no EMD was 11.4, 11.3, and 12.7 months, respectively. There was no difference in OS among patients with CNS involvement, those with other EMD (hazard ratio [HR], 0.96; adjusted $P = .84$), and those with no EMD (HR, 1.19; adjusted $P = .44$). In conclusion, the reported incidence of CNS involvement in patients with newly diagnosed AML is low (1.1%), irrespective of whether an LP is mandatory or not. The presence of CNS disease at diagnosis in and of itself does not seem to portend a poor prognosis for achieving an initial CR or for OS.

Introduction

Extramedullary disease (EMD) is a known manifestation of acute myeloid leukemia (AML) with an overall reported incidence ranging between 2.5%[1] and 30%,[2] depending on, among other things, the precise definition of EMD. Its rate is highest among patients with monocytic AML[3] and in those with t(8;21).[4,5] Its prognostic impact is controversial.[2,5-9]

Data regarding central nervous system (CNS) involvement in patients with newly diagnosed AML are scarce, and the prognostic implication of CNS involvement is controversial.[10-12] There is also no current agreement regarding whether lumbar puncture (LP) should routinely be performed in every patient with

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Table 1. AML protocols included in this study

Protocol No.	Phase	Induction	Consolidation	Maintenance	LP	Guidance for CNS therapy	Final accrual (patients included)	Years
E1479[14]	3	1-2 courses of daunorubicin 60 mg/m^2 per day on days 1-3; cytosine arabinoside continuous IV 200 mg/m^2 per day on days 1-5; 6-thioguanine by mouth 100 mg/m^{2}per day × 2 on days 1-5 (DAT)	Random assignment to consolidation × 2 plus maintenance or direct maintenance. Consolidation course: daunorubicin 45 mg/m^2 on days 1-2; cytosine arabinoside IV push 100 mg/m^2; 6-thioguanine oral 100 mg/m^2 per day × 2 on days 1-5	6-thioguanine by mouth 40 mg/m^2 per day × 2 for 4 days; cytosine arabinoside SC 60 mg/m^2 on day 5; 2 years' duration	Optional; strongly recommended if blast count is high	Methotrexate IT 10-15 mg every other day until clearance; whole brain RT optional.	318 (289)	1980-1982
E3480[18]	3	1-2 courses of full DAT or attenuated-dose DAT; daunorubicin 50 mg/m^2 per day on day 1, cytosine arabinoside SC 100 mg/m^{2}per day × 2 on days 1-5, and 6-thioguanine by mouth 100 mg/m^2 per day × 2 on days 1-5		6-thioguanine by mouth 40 mg/m^2 per day × 2 for 4 days; cytosine arabinoside SC 60 mg/m^2 on day 5; 2 years' duration	Optional; strongly recommended if blast count is high	Induction: methotrexate IT 10-15 mg every third day until clearance. Whole brain RT optional. Consolidation: investigator choice. Recommended: methotrexate IT once per week × 4, then IT once per month	45 (39)	1981-1982
E3483[15]	3	1-2 courses of DAT	Age younger than 41 years + HLA-matched sibling allo-BMT. Others were randomly assigned to observation, maintenance, or consolidation × 1. After interim analysis, the observation arm was closed. Consolidation: cytosine arabinoside IV 3 g/m^2 over 1 hour per day × 2 on days 1-6; amsacrine IV 100 mg/m^2 per day on days 7-9	6-thioguanine by mouth 40 mg/m^2 per day × 2 for 4 days; cytosine arabinoside SC 60 mg/m^2 on day 5; 2 years' duration	Mandatory	Induction: methotrexate IT once every 3 days. Consolidation: high-dose cytarabine or HSCT, if the patient was randomly assigned to maintenance-only cranial RT	534 (445)	1984-1988
PC486[16]	2	1-2 courses of DAT	Age younger than 41 years and HLA-identical sibling allo-BMT; all others auto-BMT		Mandatory	Mitoxantrone IT 10-15 mg every third day until clearance and 2 doses thereafter; (patients with leukemic meningitis will not be eligible for autologous transplant)	123 (98)	1987-1990
E3489[17]	3	1-2 courses of idarubicin 12 mg/m^2 per day on days 1-3 and cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-7	Idarubicin 12 mg/m^2 per day on days 1-2, and cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-5. Patients with an HLA-matched or single-mismatched family member, allo-BMT; all others were randomly assigned to auto-BMT or 1 course of cytosine arabinoside IV 3 g/m^2 over 1 hour per day × 2 on days 1-6		Mandatory	Off study	808 (752)	1990-1995
E1490[19]	3	1-2 courses of daunorubicin 60 mg/m^2 per day on days 1-3; cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-7 plus GM-CSF or placebo from day 11	A single course of cytosine arabinoside IV 1.5 g/m^2 over 1 hour per day × 2 on days 1-6 plus GM-CSF or placebo from day 11		Mandatory	Induction: methotrexate IT 10-15 mg every third day until clearance and 2 doses thereafter; Consolidation: high-dose cytarabine	124 (115)	1990-1992
E3993[20]	3	GM-CSF or placebo as priming, cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-7. Patients were randomly assigned to daunorubicin 45 mg/m^2	Age younger than 70 years, cytosine arabinoside IV 1.5 g/m^2 over 1 hour per day × 2 on days 1-6 plus GM-CSF from day 5. Age older than 70 years, cytosine arabinoside IV 1.5 g/m^2 over		Mandatory	Induction: methotrexate IT once every 3 days. Consolidation: high-dose cytarabine. If the patient was CSF positive after consolidation, methotrexate IT plus cranial RT	362 (343)	1993-1997

allo, allogeneic; auto, autologous; BMT, bone marrow transplantation; DAT, daunorubicin, low-dose cytosine arabinoside, and 6-thioguanine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; IT, intrathecal; IV, intravenous; PBSCT, peripheral blood stem cell transplantation; rhIL-11, recombinant human interleukin-11; RT, radiotherapy; SC, subcutaneous.

Table 1. (continued)

Protocol No.	Phase	Induction	Consolidation	Maintenance	LP	Guidance for CNS therapy	Final accrual (patients included)	Years
		per day on days 1-3 or mitoxantrone 12 mg/m^2 per day on days 1-3 or idarubicin 12 mg/m^2 per day on days 1-3	1 hour per day × 2 on days 1-3 plus GM-CSF from day 5					
E4995[29]	2	2 cycles of daunorubicin 45 mg/m^2 per day on days 1-3, cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-7, and cytosine arabinoside 2 g/m^2 over 75-90 minutes per day × 2 on days 8-10	Age younger than 51 years plus HLA-matched sibling, allo-PBSCT. Others, 2 courses of cytosine arabinoside 3 g/m^2 over 3 hours per day × 2 on days 1, 3, and 5 and then auto-PBSCT		Only for CNS symptoms	Not mentioned (maybe because every patient received high-dose cytarabine)	66 (59)	1996-1997
E3997[21]	2	Daunorubicin 45 mg/m^2 per day on days 1-3, cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-7, and cytosine arabinoside 2 g/m^2 over 60-90 minutes per day × 2 on days 8-10 plus rhIL-11 and GM-CSF from days 11 to 12	2 courses of cytosine arabinoside 3 g/m^2 over 3 hours per day × 2 on days 1, 3, and 5 plus rhIL-11 and GM-CSF from day 6		Only for CNS symptoms	Because patients received high-dose cytarabine in the induction, additional treatment is not necessary. It is possible to give methotrexate IT once every 3 days	36 (35)	1998-1999
E3999[22]	3	1-2 courses of daunorubicin 45 mg/m^2 per day on days 1-3, cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-7, and zosuquidar or placebo	Cytosine arabinoside 1.5 g/m^2 over 1 hour on days 1-6. Age younger than 70 years, per day × 2; age older than 70 years, per day × 1 (a course identical to the induction regimen that included either zosuquidar or placebo)		Only for clinical suspicion	Not mentioned	449 (421)	2002-2005
E1900[23]	3	Daunorubicin 45 or 90 mg/m^2 per day on days 1-3, cytosine arabinoside continuous IV 100 mg/m^2 per day on days 1-7	Unfavorable or intermediate risk cytogenetic profile or WBC >100 × 10^3/μL at diagnosis plus HLA-matched sibling, allo-HSCT. All others: 2 courses of cytosine arabinoside 3 g/m^2 over 3 hours per day × 2 on days 1, 3, and 5. Randomly assigned patients received gemtuzumab ozogamicin 6 mg/m^2 or no gemtuzumab ozogamicin, and auto-HSCT		Only in patients with FAB M4/M5 with CNS signs and symptoms	Methotrexate IT 12 mg twice per week until clearance and then once per month for 6 months; alternative: cytosine arabinoside IT 30 mg	657 (644)	2002-2008

allo, allogeneic; auto, autologous; BMT, bone marrow transplantation; DAT, daunorubicin, low-dose cytosine arabinoside, and 6-thioguanine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; IT, intrathecal; IV, intravenous; PBSCT, peripheral blood stem cell transplantation; rhIL-11, recombinant human interleukin-11; RT, radiotherapy; SC, subcutaneous.

newly diagnosed AML, similar to that performed in patients with acute lymphoblastic leukemia or in pediatric patients with AML[13] instead of being reserved for certain clinical scenarios of adult patients with AML at higher risk for CNS involvement or when neurologic signs or symptoms are present. In this retrospective study, a very large database of 11 consecutive clinical trials of patients with newly diagnosed AML was reviewed. The focus was on 3 issues: first, whether the incidence of CNS involvement at diagnosis was higher among the 5 studies in which an LP was mandatory for all patients (n = 1753) than in studies in which patients received an LP only if neurologic symptoms were present and/or at the discretion of the physician (n = 1487). The second issue was to describe the characteristics of patients with CNS involvement compared with patients without any EMD or with EMD other than in the CNS. The third issue was to report the prognosis of patients with CNS involvement compared with that of patients with other or no EMD.

Methods

Patient population

Between 1980 and 2008, 3522 patients age 15 years or older with untreated AML were enrolled on 11 consecutive, phase 2 or phase 3 clinical trials led by Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN).[14-23] The treatment protocols, their activation dates, and accrual numbers are summarized in Table 1. Of the 3522 enrolled

Table 2. Number and incidence of patients with CNS involvement in each trial

Protocol No.	Mandatory LP	Years	No.	Patients with CNS involvement	
				No.	%
E1479	No	1980-1982	289	12	4.15
E3480	No	1981-1982	39	1	2.56
E3483	Yes	1984-1988	445	7	1.57
PC486	Yes	1987-1990	98	0	
E3489	Yes	1990-1995	752	4	0.53
E1490	Yes	1990-1992	115	0	
E3993	Yes	1993-1997	343	4	1.17
E4995	No	1996-1997	59	1	1.69
E3997	No	1998-1999	35	1	2.86
E3999	No	2002-2005	421	0	
E1900	No	2002-2008	644	6	0.93

patients, 282 were excluded because of diagnosis of acute promyelocytic leukemia (n = 168) or leukemia other than AML (n = 29), no EMD evaluation at baseline (n = 41), ineligibility for retrospective central review (n = 24) or no survival data (n = 20). Each protocol was approved by the institutional review boards, and all patients signed a written informed consent.

Cytogenetic risk classification

Cytogenetic risk was classified as favorable, intermediate, unfavorable, or undetermined after central review by the ECOG-ACRIN Leukemia Cytogenetics Subcommittee, according to the definitions established by the Southwest Oncology Group (SWOG) and ECOG-ACRIN.[24] Only minimal cytogenetic information was available for patients enrolled on earlier protocols E1479, E1490, E3480, E3483, or PC486.

EMD assessment

In all 11 trials, bone marrow (BM) leukemic involvement was an eligibility criterion, meaning that patients with an isolated extramedullary myeloid sarcoma, including isolated CNS leukemia, without BM involvement were not included. The presence of EMD at baseline was defined clinically by physical examination and radiology without necessarily requiring a biopsy.[9]

Diagnosis and treatment of CNS involvement

An LP was mandatory in 5 trials (E3483, PC486, E3489, E1490, E3993) and recommended for patients with high blast count in 2 trials (E1479, E3480) or if CNS signs or symptoms were present in 4 trials (E4995, E3997, E3999, E1900). The presence of any unequivocal blasts in the cerebrospinal fluid (CSF) was considered as CNS involvement. For all studies, the intended postremission systemic chemotherapy was not altered by the initial presence of CNS disease or any EMD. In several trials, high-dose cytarabine (HiDAC), which can penetrate into the CSF, was part of the regular protocol but not as a supplement for CNS-positive patients.

The treatment of CNS involvement was not uniform among the different trials. In 7 trials (E1479, E3480, E3483, PC486, E1490, E3993, E1900), intrathecal methotrexate (IT MTX) was mandatory, and in another trial (E3997) that used HiDAC as part of induction as well as consolidation therapy, it was optional. In 2 studies (E1479, E3480), cranial radiotherapy was optional; in E3483, it was recommended for patients who were randomly assigned to receive only maintenance therapy; and in E3993, it was recommended for patients with persistent leukemic cells in the CSF after consolidation therapy. In 3 studies (E1490, E3993, E3999), HiDAC was given to all of the patients as part of consolidation, and in 2 studies (E4995, E3997), it was given as part of induction therapy. In 2 studies (E4995, E1900), HiDAC was given as consolidation only to patients who did not undergo transplantation, and in E3483, it was given as consolidation in only 1 arm of randomly assigned patients. In E3489, patients with CNS leukemia went off study. In this latter trial, because the CSF was examined only after full blast clearance, patients went off study only after induction, at which point they were observed for survival.

Statistical analysis

Descriptive statistics were used for patient demographics and disease characteristics. Wilcoxon 2-sample tests (for continuous variables) and Fisher's exact tests (for categorical variables) were used to explore potential differences between groups. The Kaplan-Meier method was used to estimate median overall survival (OS). Univariable and multivariable Cox proportional hazard models were used to evaluate the effect of CNS involvement on OS, with variables significant at the 0.10 level in univariable analyses adjusted as covariates in the multivariable models. Because of the exploratory nature of this study, no statistical adjustments were made for multiple comparisons. A 2-sided P value of .05 was considered statistically significant.

Results

Incidence of CNS involvement

Of the 3240 patients included in this analysis, 36 patients had CNS involvement (CNS-positive) at the time of diagnosis. The overall incidence was 1.11%, but it varied among the different studies (from 0% to 4.2%; Table 2). The incidence of CNS disease among all patients in the 5 studies that mandated an LP was similar to the incidence among all patients in trials in which LP was performed solely on the basis of neurologic symptoms and/or at the discretion of the attending physician (0.86% vs 1.41%; $P = .18$).

Characteristics of patients with CNS involvement

Half of the CNS-positive patients were males, the median age was 44.5 years (range, 17-79 years), 38.9% had an ECOG performance status (ECOG PS) of 2 or higher, and 55.6% had FAB (French-American-British classification of AML for acute myelomonocytic leukemia) -M4 disease. Among the 39 patients, cytogenetic analysis was available in only 9 (which included 5 patients with normal karyotype and 1 patient each with t(8;21)(q22;q22) with −Y, t(6;9)(p23;q34), del (16)(q22), or +2mar with −Y).

The characteristics of CNS-positive patients were compared with those of patients with EMD other than CNS (n = 733) and with those without EMD (n = 2471) (Table 3). The rate of ECOG PS 2 to 4 was highest among CNS-positive patients (38.9%), intermediate among patients with other EMD sites (22.9%), and lowest among patients without EMD (14%). Similar grading, respectively, was found regarding other characteristics such as the rate of FAB-M4 classification (55.6%, 38.2%, and 26%, respectively) and the

Table 3. Characteristics of patients with AML who have CNS involvement, with EMD outside the CNS, and with no EMD involvement

	CNS involvement (n = 36)		EMD but no CNS involvement (n = 733)			No EMD (n = 2471)		
Characteristic	**No.**	**%**	**No.**	**%**	***P***	**No.**	**%**	***P***
Age, y					. 33/.71			1.00/.07
<60	24	66.7	550	75.0		1638	66.3	
≥60	12	33.3	183	25.0		831	33.7	
Median (range)	44.5 (17-79)		45 (14-93)			52 (15-86)		
Sex					.39			.87
Male	18	50.0	427	58.3		1284	52.0	
Female	18	50.0	306	41.7		1185	48.0	
Unknown	0	–	0	–		2	–	
Race/ethnicity*					.24			.29
White	30	85.7	649	89.5		2193	89.5	
Hispanic	2	5.7	15	2.1		69	2.8	
African American	2	5.7	48	6.6		143	5.8	
Asian	0	0.0	2	0.3		20	0.8	
Other	1	2.9	11	1.5		26	1.1	
Unknown	1	–	8	–		20	–	
ECOG PS†					.04			.0002
0	5	13.9	193	26.4		914	37.3	
1	17	47.2	370	50.7		1194	48.7	
2-4	14	38.9	167	22.9		343	14.0	
Unknown	0	–	3	–		20	–	
FAB classification‡					.053			.0002
M0	0	0.0	7	1.0		56	2.3	
M1	4	11.1	112	15.3		489	19.9	
M2	2	5.6	125	17.1		688	28.0	
M4	20	55.6	279	38.2		639	26.0	
M5	5	13.9	117	16.0		166	6.7	
M6	0	0.0	12	1.6		100	4.1	
M7	0	0.0	0.0	0.0		12	0.5	
Other	5	13.9	78	10.6		310	12.6	
Unknown	0	–	3	–		11	–	
Cytogenetics					.12			.12
Favorable	1	8.3	25	10.8		174	12.9	
Intermediate	5	41.7	79	34.1		492	36.3	
Unfavorable	0	0.0	59	25.4		316	23.3	
Undetermined	6	50.07	69	29.7		372	27.5	
Unknown	24	–	501	–		1117	–	
No. of EMD sites					.005			
0	–	–	–	–		2471	100	
1	13	36.1	445	60.7		0	0.0	
2-6	23	63.9	288	39.3		0	0.0	
Response to induction§					.49			.49
CR	19	52.8	432	59.3		1472	60.0	

Patients with M3 (APL) were excluded from this study. All data are presented as No. (%) unless otherwise specified. *P* values were determined by using Fisher's exact test (excluding cases with unknown values, unless otherwise specified) and/or Wilcoxon 2-sample test; when 2 *P* values are reported, the first is for the Fisher's exact test and the second is for the Wilcoxon test.

PD, progressive disease; PR, partial response; SD, stable disease.

*Comparison between races with respect to White vs all others (including unknown).

†Comparison between ECOG PS groups with respect to status of 0-1 vs 2-4.

‡Comparison between FAB classes with respect to M4 vs all others (excluding unknown).

§Comparison between Responses to induction groups with respect to CR vs all others (including unknown).

Table 3. (continued)

Characteristic	CNS involvement (n = 36) No.	%	EMD but no CNS involvement (n = 733) No.	%	P	No EMD (n = 2471) No.	%	P
PR	1	2.8	0	0.0		3	0.1	
SD	14	38.9	213	29.2		687	28	
PD	0	0.0	34	4.7		131	5.3	
Unevaluable	2	5.5	50	6.9		161	6.6	
Unknown	0	–	4	–		17	–	
Hemoglobin, g/dL					.11/.07			.03/.009
<10	19	52.8	474	66.0		1720	70.3	
≥10	17	47.2	244	34.0		728	29.7	
Median (range)	9.7 (3.3-15.4)		9.4 (0.5-31.0)			9.1 (0.2-39.5)		
Platelet count × $10^3/\mu L$					.87/.97			1.00/.94
<60	17	47.2	332	45.6		1134	46.3	
≥60	19	52.8	396	54.4		1315	53.7	
Median (range)	64.5 (3-262)		53 (0.7-1660)			54 (1-999)		
WBC count × $10^3/\mu L$					.37/.77			.0001/.0004
<50	20	55.6	467	64.1		2048	83.3	
≥50	16	44.4	262	35.9		411	16.7	
Median (range)	36.2 (0.8-270)		31.7 (0.2-497)			8.6 (0.3-600)		
Bone marrow blast (%)					.45			.27
Median (range)	71 (3-99)		77 (0-100)			63 (0-100)		
Peripheral blood blast (%)					.43			.23
Median (range)	37 (0-93)		44 (0-99)			26 (0-99)		

Patients with M3 (APL) were excluded from this study. All data are presented as No. (%) unless otherwise specified. *P* values were determined by using Fisher's exact test (excluding cases with unknown values, unless otherwise specified) and/or Wilcoxon 2-sample test; when 2 *P* values are reported, the first is for the Fisher's exact test and the second is for the Wilcoxon test.

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‡Comparison between FAB classes with respect to M4 vs all others (excluding unknown).

§Comparison between Responses to induction groups with respect to CR vs all others (including unknown).

median initial white blood cell (WBC) count (36.2, 31.7, and 8.6 × $10^3/\mu L$, respectively).

Compared with patients without EMD, CNS-positive patients were younger (median age. 44.5 vs 52 years; $P = .07$) and had a higher median WBC count ($P = .0004$). The rate of CNS involvement was significantly higher among patients with WBC ≥50 × $10^3/\mu L$ compared with those with WBC <50 × $10^3/\mu L$ (2.32% vs 0.79%; $P = .002$). A similar pattern was seen when comparing CNS involvement in patients with WBC counts above or below 100 × $10^3/\mu L$ (2.99% vs 0.97%; $P = .01$).

Response and survival by CNS involvement

The rate of complete remission (CR) among CNS-positive patients was similar to that in the other groups (52.8% vs 59.3%-60%; $P = .49$). The median OS was 11.4 months (95% confidence interval [CI], 7.2-17.7 months) among CNS-positive patients, 11.3 months

Table 4. Median OS and HR of death for various cohorts

Cohort	Median OS (mo)	95% CI	Univariable No. of events/total no. of patients	CNS vs target HR	95% CI	Wald P	Multivariable* No. of events/total No.	CNS vs target HR	95% CI	Wald P
CNS involvement	11.4	7.2-17.7	32/36	–		–	30/34			–
EMD but no CNS involvement	11.3	10.4-12.8	621/733	1.07	0.75-1.53	.70	564/660	0.96	0.66-1.41	.84
No EMD	12.7	12.1-13.7	1972/2471	1.22	0.86-1.74	.26	1793/2258	1.19	0.77-1.84	.44

All tests used Cox proportional hazards model.

*Multivariable models were adjusted for age, sex, ECOG PS (0 vs 1 vs 2-4), marrow blasts, log-transformed WBC and platelet values, registration year, the number of EMD sites (0 [if applicable] vs 1 vs 2-6), cytogenetics (favorable vs intermediate vs unfavorable vs undetermined vs unknown), CR to induction treatment (no vs yes), and the EMD involvement (no vs yes, if applicable).

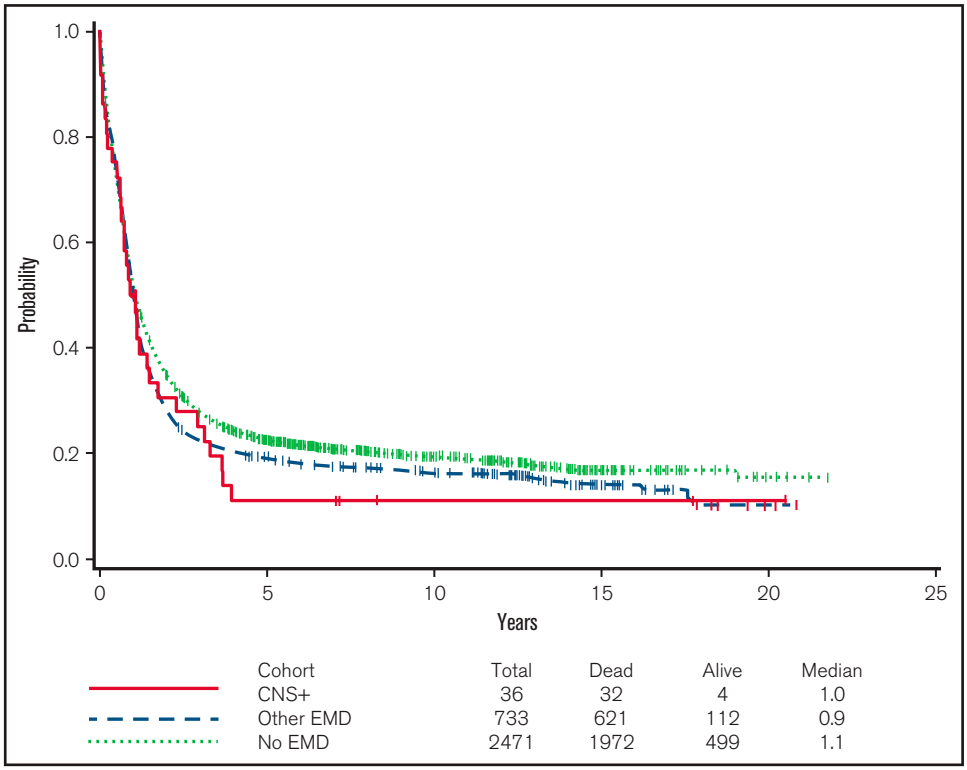

Figure 1. OS of the 3 patient groups: CNS-positive, other EMD, no EMD.

(95% CI, 10.4-12.8 months) among patients with other EMD, and 12.7 months (95% CI, 12.1-13.7 months) among those without EMD (Figure 1). By univariable analysis, the differences among these groups were not significant. The hazard ratios (HRs) for OS of CNS-positive patients compared with the other EMD patients was 1.07 (95% CI, 0.75-1.53; $P = .70$) and 1.22 (95% CI, 0.86-1.74) compared with patients without EMD ($P = .26$). In multivariable analysis, adjusting for covariates (listed in Table 4), there were also no significant differences in OS between patients with CNS involvement and those with other EMD (HR, 0.96; 95% CI, 0.66-1.41; adjusted $P = .84$) or no EMD (HR, 1.19; 95% CI, 0.77-1.84; adjusted $P = .44$).

Among the 36 patients who were CNS-positive, there was no significant difference in the CR rate between patients with other EMD (n = 23) and those with CNS only (n = 13) (60.9% vs 38.5%; $P = .30$). Similarly, no significant difference in OS was observed between the CNS-positive patients with other EMD and the CNS only groups (HR for other EMD vs CNS only, 1.95; 95% CI, 0.89-4.30; $P = .10$). The same conclusion remains using multivariable analysis ($P = .26$).

Discussion

CNS involvement in adults with newly diagnosed AML is a rare phenomenon with limited published data.[10-12] The need for and clinical impact of a routine LP have remained unclear.[10,12] Among pediatric patients, CNS assessment is part of the routine evaluation but the prognostic impact of CNS involvement remains controversial.[2,6,13,25] This study examined a very large database of 11 ECOG-ACRIN consecutive clinical trials that had a total of 3240 patients with newly diagnosed AML to gain more information about this phenomenon, focusing on the relationship between CNS involvement and other sites of EMD, its incidence with or without a routine LP, and its overall prognostic impact. The incidence of CNS involvement at diagnosis was 1.1%, similar to the 0.9% that was published relatively recently by the MD Anderson Cancer Center (MDACC) group[10] or the 2.2% published by an Italian group.[26] The rate of FAB-M4 disease, incidence of ECOG PS 2 to 4, and median level of initial WBC count were highest in CNS-positive patients, intermediate in patients with EMD other than CNS, and lowest in patients without EMD. Although the differences in PS may be related to the debilitating effects of CNS involvement, the higher rate of FAB-M4 and higher WBC counts places CNS involvement and other EMD sites on a continuum with the same risk factors but with CNS on the high end of the spectrum. Almost two-thirds of CNS-positive patients also had other sites of EMD, which supports the assumption that the ability of the disease to involve extramedullary sites is an intrinsic character of the specific leukemic phenotype, possibly related to expression of surface adhesion molecules.[2,27]

An intriguing issue regarding CNS involvement in AML is whether routine performance of an LP in every patient with AML, regardless of symptoms, will increase the rate of detection. The ECOG-ACRIN policy regarding routinely performing LP changed during the years from mandatory to possible (Tables 1 and 2), which enabled this issue to be evaluated. Our data suggest that a routine LP does not increase the detectable rate of CNS involvement. In contrast, a study from MDACC compared 1307 patients who did not undergo a routine LP during the course of AML treatment to 42 patients who underwent a routine LP at diagnosis and found an increase in the incidence of CNS involvement from 3.3% to 19%.[10] However,

it should be noted that neither this study nor the MDACC study used flow cytometry (FC) as part of the CSF assessment. In fact, an Italian study group reported that CNS involvement increased from 11 patients when conventional cytology was used to 33 patients when FC was used.[12] It is unknown whether using more sensitive tools such as FC to detect blasts in the CSF would have an impact on outcome. This becomes even more challenging with the use of HiDAC as part of the consolidation therapy in AML, which penetrates the CSF and may eradicate the few residual blasts.[28]

Importantly, patients who are CNS positive do not have a worse OS compared with other patients who have EMD or those without EMD. Data from studies by the Italian study group[12] and a Taiwanese study group[11] support these findings, whereas the MDACC analysis[10] reported a negative prognostic impact of CNS disease. It should be noted that in this study, other than the initial therapy at diagnosis (for example, adding IT MTX according to each protocol), the protocols did not permit for any significant deviations, such as administering more intensive therapy to patients with CNS involvement. Thus, the similar prognosis probably cannot be attributed to additional or more intensive therapy.

There are some obvious limitations to our study. It was a retrospective analysis that examined clinical trials that spanned 3 decades. Thus, intra-study comparisons of trials need to be cautiously interpreted. In addition, data about CNS imaging studies and BM cytogenetics are clearly limited, and FC was not part of the CSF assessment. Although few patients had CNS involvement in each of the 11 studies, the consistent pattern in this very large cohort of 3500 patients lends credence to the overall analysis and conclusions.

Hitherto, CNS involvement at diagnosis was perceived as a prognostically adverse factor. Some major clinical trials groups have excluded CNS-positive patients from standard clinical trials, such as in E3489, and even in the most contemporary ECOG-ACRIN AML clinical trial, E2906. Our data strongly suggest that, in general, patients with newly diagnosed AML who have CNS involvement should not be precluded from participating in clinical trials.

In conclusion, this retrospective analysis reported a low incidence of CNS involvement in patients with newly diagnosed AML and does not encourage routinely performing an LP. Assuming that prompt CNS-directed therapy is given, our data do not support a prognostic characterization or a recommendation for using a different systemic chemotherapy.

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Authorship

Contribution: C.G. designed the research , analyzed the data, and wrote the paper; J.-W.L. and D.D. analyzed the data; H.F.F., S.M.L., H.M.L., L.D.C., P.H.W., M.S.T., and M.R.L. performed the research; and J.M.R. and E.M.P. analyzed the data and wrote the paper.

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References

1. Muss HB, Moloney WC. Chloroma and other myeloblastic tumors. *Blood.* 1973;42(5):721-728.
2. Chang H, Brandwein J, Yi QL, Chun K, Patterson B, Brien B. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. *Leuk Res.* 2004;28(10):1007-1011.
3. Tallman MS, Kim HT, Paietta E, et al; Eastern Cooperative Oncology Group. Acute monocytic leukemia (French-American-British classification M5) does not have a worse prognosis than other subtypes of acute myeloid leukemia: a report from the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2004;22(7):1276-1286.
4. Tallman MS, Hakimian D, Shaw JM, Lissner GS, Russell EJ, Variakojis D. Granulocytic sarcoma is associated with the 8;21 translocation in acute myeloid leukemia. *J Clin Oncol.* 1993;11(4):690-697.
5. Byrd JC, Weiss RB, Arthur DC, et al. Extramedullary leukemia adversely affects hematologic complete remission rate and overall survival in patients with t(8;21)(q22;q22): results from Cancer and Leukemia Group B 8461. *J Clin Oncol.* 1997;15(2):466-475.
6. Kobayashi R, Tawa A, Hanada R, Horibe K, Tsuchida M, Tsukimoto I; Japanese childhood AML cooperative study group. Extramedullary infiltration at diagnosis and prognosis in children with acute myelogenous leukemia. *Pediatr Blood Cancer.* 2007;48(4):393-398.
7. Oestgaard LSG, Sengeloev H, Holm MS, et al. Extramedullary leukemia and myeloid sarcoma in AML: Results from a population-based registry study of 2261 patients [abstract]. *Blood.* 2011;118(21). Abstract 2003.
8. Tsimberidou AM, Kantarjian HM, Wen S, et al. Myeloid sarcoma is associated with superior event-free survival and overall survival compared with acute myeloid leukemia. *Cancer.* 2008;113(6):1370-1378.

9. Ganzel C, Manola J, Douer D, et al. Extramedullary disease in adult acute myeloid leukemia is common but lacks independent significance: Analysis of patients in ECOG-ACRIN Cancer Research Group Trials, 1980-2008. *J Clin Oncol.* 2016;34(29):3544-3553.

10. Rozovski U, Ohanian M, Ravandi F, et al. Incidence of and risk factors for involvement of the central nervous system in acute myeloid leukemia. *Leuk Lymphoma.* 2015;56(5):1392-1397.

11. Cheng C-L, Li C-C, Hou H-A, et al. Risk factors and clinical outcomes of acute myeloid leukaemia with central nervous system involvement in adults. *BMC Cancer.* 2015;15(1):344.

12. Del Principe MI, Buccisano F, Soddu S, et al. Involvement of central nervous system in adult patients with acute myeloid leukemia: Incidence and impact on outcome. *Semin Hematol.* 2018;55(4):209-214.

13. Felix A, Leblanc T, Petit A, et al. Acute myeloid leukemia with central nervous system involvement in children: Experience from the French Protocol Analysis ELAM02. *J Pediatr Hematol Oncol.* 2018;40(1):43-47.

14. Cassileth PA, Begg CB, Bennett JM, et al. A randomized study of the efficacy of consolidation therapy in adult acute nonlymphocytic leukemia. *Blood.* 1984;63(4):843-847.

15. Cassileth PA, Lynch E, Hines JD, et al. Varying intensity of postremission therapy in acute myeloid leukemia. *Blood.* 1992;79(8):1924-1930.

16. Cassileth PA, Andersen J, Lazarus HM, et al. Autologous bone marrow transplant in acute myeloid leukemia in first remission. *J Clin Oncol.* 1993; 11(2):314-319.

17. Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med.* 1998;339(23):1649-1656.

18. Kahn SB, Begg CB, Mazza JJ, Bennett JM, Bonner H, Glick JH. Full dose versus attenuated dose daunorubicin, cytosine arabinoside, and 6-thioguanine in the treatment of acute nonlymphocytic leukemia in the elderly. *J Clin Oncol.* 1984;2(8):865-870.

19. Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). *Blood.* 1995;86(2):457-462.

20. Rowe JM, Neuberg D, Friedenberg W, et al; Eastern Cooperative Oncology. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. *Blood.* 2004;103(2):479-485.

21. Cripe LD, Rader K, Tallman MS, et al. Phase II trial of subcutaneous recombinant human interleukin 11 with subcutaneous recombinant human granulocyte-macrophage colony stimulating factor in patients with acute myeloid leukemia (AML) receiving high-dose cytarabine during induction: ECOG 3997. *Leuk Res.* 2006;30(7):823-827.

22. Cripe LD, Uno H, Paietta EM, et al. Zosuquidar, a novel modulator of P-glycoprotein, does not improve the outcome of older patients with newly diagnosed acute myeloid leukemia: a randomized, placebo-controlled trial of the Eastern Cooperative Oncology Group 3999. *Blood.* 2010; 116(20):4077-4085.

23. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med.* 2009;361(13):1249-1259.

24. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood.* 2000;96(13):4075-4083.

25. Johnston DL, Alonzo TA, Gerbing RB, Lange BJ, Woods WG. The presence of central nervous system disease at diagnosis in pediatric acute myeloid leukemia does not affect survival: a Children's Oncology Group study. *Pediatr Blood Cancer.* 2010;55(3):414-420.

26. Castagnola C, Nozza A, Corso A, Bernasconi C. The value of combination therapy in adult acute myeloid leukemia with central nervous system involvement. *Haematologica.* 1997;82(5):577-580.

27. Byrd JC, Edenfield WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. *J Clin Oncol.* 1995;13(7):1800-1816.

28. Slevin ML, Piall EM, Aherne GW, Harvey VJ, Johnston A, Lister TA. Effect of dose and schedule on pharmacokinetics of high-dose cytosine arabinoside in plasma and cerebrospinal fluid. *J Clin Oncol.* 1983;1(9):546-551.

29. Cassileth PA, Lee SJ, Litzow MR, et al; Eastern Cooperative Oncology Group. Intensified induction chemotherapy in adult acute myeloid leukemia followed by high-dose chemotherapy and autologous peripheral blood stem cell transplantation: an Eastern Cooperative Oncology Group trial (E4995). *Leuk Lymphoma.* 2005;46(1):55-61.