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ORIGINAL REPORT

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

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ABSTRACT

Purpose

Extramedullary disease (EMD) at diagnosis in patients with acute myeloid leukemia (AML) has been recognized for decades. Reported herein are results from a large study of patients with AML who were treated in consecutive ECOG-ACRIN Cancer Research Group frontline clinical trials in an attempt to define the incidence and clinical implications of EMD.

Methods

Patients with newly diagnosed AML, age 15 years and older, who were treated in 11 clinical trials, were studied to identify EMD, as defined by physical examination, laboratory findings, and imaging results.

Results

Of the 3,522 patients enrolled, 282 were excluded, including patients with acute promyelocytic leukemia, incorrect diagnosis, or no adequate assessment of EMD at baseline. The overall incidence of EMD was 23.7%. The sites involved were: lymph nodes (11.5%), spleen (7.3%), liver (5.3%), skin (4.5%), gingiva (4.4%), and CNS (1.1%). Most patients (65.3%) had only one site of EMD, 20.9% had two sites, 9.5% had three sites, and 3.4% had four sites.

The median overall survival was 1.035 years. In univariable analysis, the presence of any EMD ($P = .005$), skin involvement ($P = .002$), spleen ($P < .001$), and liver ($P < .001$), but not CNS ($P = .34$), nodal involvement ($P = .94$), and gingival hypertrophy ($P = .24$), was associated with a shorter overall survival. In contrast, in multivariable analysis, adjusted for known prognostic factors such as cytogenetic risk and WBC count, neither the presence of EMD nor the number of specific sites of EMD were independently prognostic.

Conclusion

This large study demonstrates that EMD at any site is common but is not an independent prognostic factor. Treatment decisions for patients with EMD should be made on the basis of recognized AML prognostic factors, irrespective of the presence of EMD.

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INTRODUCTION

One of the known manifestations of acute myeloid leukemia (AML) is extramedullary disease (EMD). The overall incidence of EMD reported in the literature is not clearly established, ranging from 2.5%[1] to 30%,[2] and varies among different types of AML; patients with monocytic AML[3] and those with t(8;21)[4,5] have a relatively higher incidence. The prognostic impact of EMD is unfavorable in some reports[2,5] but not in others.[6-8] Reports on the prognosis of specific EMD sites, such as the CNS, are also contradictory.[9,10]

The current analysis evaluated a large cohort of patients with newly diagnosed AML from 11 consecutive clinical trials conducted by the ECOG-ACRIN Cancer Research Group.[11-20] The objectives were to describe the demographic, clinical, and biologic characteristics of patients with newly diagnosed AML with EMD and to evaluate how the presence, extent, and characteristics of EMD may affect response to treatment and outcome.

Table 1. Acute Myeloid Leukemia Protocols Included in the Analysis

Protocol No.	Clinical Trial Phase	Induction	Consolidation	Maintenance	Activation-Termination Dates	Final Accrual (patients included)
E1479[11]	III	One or two courses of: dauno 60 mg/m^2/d, days 1-3; ARA-C 25 mg/m^2 IV push followed by continuous IV 200 mg/m^2/d, days 1-5; and PO 6-TG 100 mg/m^2 × 2/d, days 1-5 (DAT).	Randomly assigned to either: a) two courses of consolidation therapy followed by maintenance, or b) begin maintenance immediately. A consolidation course consisted of dauno 45 mg/m^2, days 1 and 2; ARA-C 100 mg/m^2 IV push; and PO 6-TG 100 mg/m^2 × 2/d, days 1-5.	PO 6-TG 40 mg/m^2 × 2/d, 4 days, followed by SC ARA-C 60 mg/m^2 on the fifth day. Duration: 2 years.	Feb 1980 to Apr 1982	318 (289)
E3480[15]	III	One or two courses of either: a) full DAT (above), or b) attenuated-dose DAT: dauno 50 mg/m^2/d on day 1, SC ARA-C 100 mg/m^2 × 2/d, days 1-5 and PO 6-TG 100 mg/m^2 × 2/d, days 1-5.		PO 6-TG 40 mg/m^2 × 2/d, 4 days, followed by SC ARA-C 60 mg/m^2 on the fifth day. Duration: 2 years.	Jul 1981 to Nov 1982	45 (39)
E3483[12]	III	One or two courses of DAT.	Age < 41 years plus HLA-matched sibling: alloBMT. Others were initially randomly assigned to one of three arms: a) observation, b) maintenance, or c) one course of consolidation. After interim analysis, the observation arm was closed. Consolidation therapy: IV ARA-C, 3 g/m^2 over 1 hour × 2/d, days 1-6, followed by IV amsacrine, 100 mg/m^2/d, days 7-9.	PO 6-TG 40 mg/m^2 × 2/d, for 4 days, followed by SC ARA-C 60 mg/m^2 on the fifth day. Duration: 2 years.	Mar 1984 to Jan 1988	534 (445)
PC486[13]	II	One or two courses of DAT.	Patients in CR: a) age < 41 years and HLA identical sibling: alloBMT, and b) all others: autoBMT.		Apr 1987 to Apr 1990	123 (98)
E3489[14]	III	One or two courses of idarubicin 12 mg/m^2/d, days 1-3; and ARA-C 25 mg/m^2 IV push, followed by continuous IV 100 mg/m^2/d, days 1-7.	Idarubicin 12 mg/m^2/d, days 1 and 2; and ARA-C 25 mg/m^2 IV push, followed by continuous IV 100 mg/m^2/d, days 1-5. a) Patients with an HLA-matched or single-mismatched family member: alloBMT. All others were randomly assigned to b) autoBMT, or c) a single course of IV ARA-C 3 g/m^2 over 3 hours × 2/d, days 1-6.		Feb 1990 to Feb 1995	808 (753)
E1490[16]	III	One or two courses of dauno 60 mg/m^2/d, days 1-3; ARA-C 25 mg/m^2 IV push followed by continuous IV 100 mg/m^2/d, days 1-7; plus GM-CSF *v* placebo from day 11.	A single course of IV ARA-C 1.5 g/m^2 over 1 hour × 2/d, days 1-6, plus GM-CSF *v* placebo from day 11.		Sep 1990 to Nov 1992	124 (115)
E3993[17]	III	GM-CSF *v* placebo as priming, ARA-C continuous IV 100 mg/m^2/d, days 1-7. Patients were randomly assigned to receive either: a) dauno 45 mg/m^2/d, days 1-3; b) mitox 12 mg/m^2/d, days 1-3; or c) idarubicin 12 mg/m^2/d, days 1-3.	Age < 70 years: IV ARA-C 1.5 g/m^2 over 1 hour × 2/d, days 1-6, plus GM-CSF from day 5. Age > 70 years: IV ARA-C 1.5 g/m^2 over 1 hour × 2/d, days 1-3, plus GM-CSF from day 5.		Apr 1993 to Feb 1997	362 (343)
E4995[21]	II	Two cycles of: dauno 45 mg/m^2/d, days 1-3; ARA-C continuous IV 100 mg/m^2/d, days 1-7; and ARA-C 2 g/m^2 over 75-90 min × 2/d, days 8-10.	Age < 51 years plus HLA-matched sibling: alloPBSCT. Others: two courses of ARA-C 3 g/m^2 over 3 hours × 2/d, days 1, 3, 5, and then autoPBSCT.		Aug 1996 to Feb 1997	66 (59)
E3997[18]	II	Dauno 45 mg/m^2/d, days 1-3; ARA-C continuous IV 100 mg/m^2/d, days 1-7; and ARA-C 2 g/m^2 over 60-90 min x 2/d, days 8-10 plus rhIL-11 and GM-CSF from days 11 to 12.	Two courses of: ARA-C 3g/m^2 over 3 hours × 2/d, days 1, 3, 5 plus rhIL-11 and GM-CSF from day 6.		Jun 1998 to Apr 1999	36 (35)

(continued on following page)

Table 1. Acute Myeloid Leukemia Protocols Included in the Analysis (continued)

Protocol No.	Clinical Trial Phase	Induction	Consolidation	Maintenance	Activation-Termination Dates	Final Accrual (patients included)
E3999[19]	III	One or two courses of dauno 45 mg/m^2/d, days 1-3; ARA-C continuous IV 100 mg/m^2/d, days 1-7; and zosuquidar *v* placebo.	1) ARA-C 1.5 g/m^2 over 1 hour, days 1-6: age < 70 years, × 2/d; age > 70 years, × 1/d. 2) A course identical to the induction regimen, including either zosuquidar or placebo.		Jul 2002 to Sep 2005	449 (421)
E1900[20]	III	Dauno 45 *v* 90 mg/m^2/d, days 1-3; ARA-C continuous IV 100 mg/m^2/d, days 1-7.	Unfavorable/intermediate risk cytogenetic profile or a WBC count > 100,000/μL at diagnosis plus HLA-matched sibling: alloHSCT. All others: 1) two courses of ARA-C 3 g/m^2 over 3 hours × 2/d, days 1, 3, and 5; 2) random assignment: GO 6 mg/m^2 *v* no GO; and 3) autoHSCT.		Dec 2002 to Nov 2008	657 (644)

Abbreviations: allo, allogeneic; ARA-C, cytarabine; auto, autologous; BMT, bone marrow transplantation; CR, complete remission; d, day; DAT, daunorubicin plus ARA-C plus 6-TG; dauno, daunorubicin; GM-CSF, granulocyte-macrophage colony-stimulating factor; GO, gemtuzumab ozogamicin; HSCT, hematopoietic stem-cell transplantation; IV, intravenous; mitox, mitoxantrone; PBSCT, peripheral blood stem-cell transplantation; PO, orally; rhIL-11, recombinant human interleukin 11; SC, subcutaneous; 6-TG, thioguanine.

METHODS

Patient Population

Between 1980 and 2008, 3,522 patients age 15 years and older with untreated AML were enrolled in 11 consecutive, phase II and III, ECOG-ACRIN–led clinical trials.[11-20] The treatment protocols, their activation dates, and accrual numbers are summarized in Table 1.

Patients were excluded from the current analysis if they had a diagnosis other than AML, had no documented EMD ascertainment at baseline, withdrew from the study before treatment had begun, or had no survival follow up. Patients with acute promyelocytic leukemia were included in the older AML studies but are excluded from the analysis as a result of the unique behavior and treatment of this disease. Each protocol was approved by an institutional review board. 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 Cytogenetics Committee, according to the definitions established by the Southwest Oncology Group and ECOG-ACRIN.[22] The favorable risk category included patients with inv(16)/t(16;16)/del(16q) or t(8;21), with or without other chromosomal abnormalities. The intermediate risk category included patients characterized by +8; −Y; +6; del(9q); del(12p), or normal karyotype. The unfavorable risk category was defined by the presence of one or more of −5/del(5q); −7/del(7q); inv(3q)/t(3;3); deletion 20q or 21q; translocation involving 11q23, t(6;9); t(9;22); deletion 17p; or complex karyotype, defined as three or more chromosomal abnormalities. Minimal cytogenetic information was available for patients enrolled in the following earlier protocols: E1479, E1490, E3480, E3483, or PC486.

Flow Cytometry

The diagnosis of AML was confirmed by multiparameter flow cytometry for patients in protocols E3489, E1490, E3993, E3997, E4995, PC486, E3999, and E1900. Three adhesion molecules (CD11a, CD11b, and CD56) were evaluated for their association with EMD.

EMD Assessment and Treatment

In all 11 trials, bone marrow (BM) leukemic involvement was an eligibility criterion; thus patients with an isolated extramedullary myeloid sarcoma without BM involvement are not included. The presence of EMD was recorded at baseline. EMD in these studies was defined clinically by physical examination and radiology without necessarily requiring a biopsy. A lumbar puncture (LP) was mandatory (five trials), recommended for patients with high blast count (two trials) or if CNS signs or symptoms were present (three trials).

The treatment of CNS involvement was on the basis of intrathecal methotrexate in seven trials, high-dose cytarabine in two trials where this was part of the induction protocol, or physician's choice.

Individual EMD sites were first evaluated as a whole group, then separately by site and finally, by classifying them as three organ-based subgroups: hematopoietic (lymph nodes [LNs], spleen, or liver), non-hematopoietic (skin or gingiva with or without EMD in hematopoietic sites), and rare areas of involvement (CNS, bone, lung, or myeloid sarcoma with or without EMD in previous sites).

Hematopoietic Stem-Cell Transplantation

Among the 11 studies, hematopoietic stem-cell transplantation (HSCT) was part of the treatment regimen in five (E3483, E3489, PC486, E4995, and E1900), and patients were classified according to the type of transplantation received. In most cases, HSCT was done as part of protocol treatment. However, if a patient's record had a definitive comment indicating that the patient received HSCT off-protocol, this information was applied. All other patients were classified as no transplantation.

Statistical Analysis

Descriptive statistics were used to characterize patients and their disease. A *t* test was used to explore potential differences in continuously parameterized disease and patient characteristics between patients with and without EMD. χ^2 tests or Fisher's exact tests were used to test for differences in categorical features. A two-sided *P* value of .05 was considered statistically significant for these tests.

Univariable analyses of potential prognostic factors were done. The method of Kaplan and Meier was used to estimate median overall survival (OS) within each prognostic category. Differences were assessed using a one-sided log-rank test. Cox proportional hazards models were used to examine the effect of one-unit increases in continuous variables on OS.

Multivariable models were built using backward selection. First, factors (or groups of factors) significant at the .10 level in univariable analyses were included in the model. Factors were dropped one at a time by comparing

nested models using the Schwarz-Bayesian criterion and −2 log-likelihood. The final model is the one that minimized these criteria. To minimize the effect of missing data, indicator variables for missing values were included.

RESULTS

Incidence and Sites

Of the 3,522 enrolled 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), retrospective central review ineligibility (n = 24), or no survival data (n = 20). The overall incidence of EMD was 23.7% (769 of 3,240 patients). The involved sites were LNs, 11.5% (374 patients); spleen, 7.3% (238); liver, 5.3% (173); skin, 4.5% (146); gingiva, 4.4% (143); CNS, 1.1% (36); peripheral nervous system and myeloid sarcoma, 0.2% (8) each; and other sites, 1.1% (35). Most patients with EMD (n = 502, 65.3%) had only one site of EMD, 161 (20.9%) had two sites, 73

Table 2. Patient Characteristics: Categorical Factors

Factor	Patients Without Extramedullary Disease (n = 2,472)		Patients With Extramedullary Disease (n = 769)		Total (n = 3,240)	
	No.	%	No.	%	No.	%
Sex, $P = .005$						
Male	1,284	52.0	445	57.9	1,729	53.4
Female	1,185	48.0	324	42.1	1,509	46.6
Unknown	2		—		2	
Race/ethnicity, $P = .27$						
White	2,193	89.5	679	89.3	2,872	89.4
Hispanic	69	2.8	17	2.2	86	2.7
Black	143	5.8	50	6.6	193	6.0
Asian	20	0.8	2	0.3	22	0.7
Other	26	1.1	12	1.6	38	1.2
Unknown	20		9		29	
ECOG performance status, $P < .001$						
0	914	37.3	198	25.9	1,112	34.6
1	1,194	48.7	387	50.5	1,581	49.2
2	265	10.8	128	16.7	393	12.2
3	67	2.7	40	5.2	107	3.3
4	11	0.5	13	1.7	24	0.8
Unknown	20		3		23	
FAB class, $P < .001$						
M0	56	2.3	7	0.9	63	2.0
M1	489	19.9	116	15.1	605	18.8
M2	688	28.0	127	16.6	815	25.3
M4	639	26.0	299	39.0	938	29.1
M5	166	6.8	122	15.9	288	8.9
M6	100	4.1	12	1.6	112	3.5
M7	12	0.5	—	—	12	0.4
RAEB-T	12	0.5	3	0.4	15	0.5
AML, NOS	129	5.2	45	5.9	174	5.4
Other	169	6.9	35	4.6	204	6.3
Unknown	11		3		14	
Cytogenetics, $P = .61$						
Favorable	174	12.9	26	10.7	200	12.5
Intermediate	492	36.3	84	34.4	576	36.1
Unfavorable	316	23.3	59	24.2	375	23.5
Undetermined	372	27.5	75	30.7	447	28.0
Unknown	1,117		525		1,642	
Response to induction, $P = .77$						
CR	1,472	60.0	451	59.0	1,923	59.7
PR	3	0.1	1	0.1	4	0.1
SD	687	28.0	227	29.7	914	28.4
PD	131	5.3	34	4.4	165	5.1
Unevaluable	161	6.6	52	6.8	213	6.6
Unknown	17		4		21	
Underwent transplantation, $P = .07$						
No	1,614	82.1	538	85.3	2,152	82.8
Yes	353	18.0	93	14.7	446	17.2
Unknown	504		138		642	

Abbreviations: AML, acute myelogenous leukemia; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; FAB, French-American-British; NOS, not otherwise specified; NR, not reached or not estimable; OS, overall survival; PD, progressive disease; PR, partial response; RAEB-T, refractory anemia with excessive blasts in transformation; SD, stable disease.

(9.5%) had three sites, 26 (3.4%) had four sites, and seven (0.9%) had five or six sites.

EMD Assessment

There were several versions of case report forms in use over the time interval, and the diagnosis method was characterized in four different ways. In general, multiple methods of diagnosis were not captured. Among 308 extramedullary sites identified for studies E1479 and E3480, 89.6% were identified by physical examination, 2.6% by biopsy, and 7.8% by other, which included x-ray, scan, or chemical means. For no other studies was there a distinction between physical examination and imaging as a basis for diagnosis. There were 92 distinct sites noted on study E3999, 94.6% by being clinically involved and 5.4% by being pathologically involved. For study E1900, no details about the method of diagnosis were captured. For all other studies, among 735 distinct sites, 92.9% were diagnosed clinically and 7.1% pathologically. Thus, the vast majority (> 90%) were diagnosed by physical examination rather than by biopsy, but the role of scans is unclear (Appendix Table A1, online only).

Characteristics of Patients With EMD

Patients with EMD, compared with those without EMD, were younger (median age, 45.7 *v* 52.9 years; $P < .001$) and males (57.9% *v* 52%; $P = .006$). They had a poorer performance status (PS; 76.4% with Eastern Cooperative Oncology Group PS 0-1 *v* 86%; $P < .001$) and higher WBC count (median, 41.6/μL *v* 10.2/μL; $P < .001$). The median percentage of blasts in the BM and in the peripheral blood was higher in the EMD group. Other characteristics did not differ significantly by EMD status (Tables 2 and 3).

FAB Category and EMD

The proportion of patients classified as French-American-British (FAB) M4 and M5 was higher among those with EMD (39% and 15.9%, respectively) compared with others (26% and 6.8%, respectively). In every EMD subgroup, the most common FAB category was M4 (approximately 40% of the patients in every subgroup, compared with 26% of the non-EMD patients). Among 815 patients with FAB M2, 15.6% had EMD and among the 98 patients with recorded t(8;21), only 10.2% had EMD.

Responses

The complete remission (CR) rate for all patients was 59.7% and was similar for patients with or without EMD (59% and 60%, respectively). The CR rate was similar for patients with individual EMD sites except for those with splenic and gingival involvement, who had a nonsignificant lower CR rate compared with the whole cohort ($P = .06$ and .08, respectively).

Survival

The median OS was 1.035 years. There were 2,625 deaths among the 3,240 patients included in the analysis. In univariable analysis (Table 4), EMD was associated with a shorter OS ($P = .005$; Fig 1A). Among individual EMD sites, the analysis revealed that skin ($P = .002$), spleen ($P < .001$; Fig 1B), and liver ($P < .001$), but not CNS ($P = .34$; Fig 1C), nodal involvement ($P = .94$), and gingival hypertrophy ($P = .24$), were associated with shorter OS.

A greater number of EMD-involved sites, both as a categorical variable ($1 \nu \geq 2$) and as a continuous variable, was negatively associated with OS ($P = .002$ and $P < .001$, respectively). Each additional site of EMD conferred a 9.5% increase in the risk of death. Among EMD subgroups (hematopoietic, nonhematopoietic, and rare), the rare areas of involvement had an OS advantage compared with the other two subgroups (median OS of 12.4 *v* 11.2 and 10.9 months, respectively; $P = .01$).

Parameters associated with longer OS were good PS, female sex, M2 FAB category, favorable cytogenetic risk group, undergoing HSCT, achieving CR postinduction, younger age, later year of registration, lower WBC count at diagnosis, higher platelet count, and low percentage of blasts in the BM.

A multivariable model (Table 5) was constructed to examine the effect of EMD on OS after adjusting for known prognostic factors. Earlier year of registration, older age, high WBC count, low platelet count, worse PS (compared with Eastern Cooperative Oncology Group PS 0), high cytogenetic risk status, and not achieving a CR were associated with shorter OS. Neither the presence of EMD, the number of extramedullary sites, nor any EMD-specific site, including the CNS, contributed prognostic significance to the multivariable models.

Table 3. Patient Characteristics at Baseline: Continuous Factors

Factor	No Extramedullary Disease					Extramedullary Disease				Total			
	P	No.	Mean	Median	SD	No.	Mean	Median	SD	No.	Mean	Median	SD
Age (years)	< .001	2,469	51.4	52.9	15.9	769	46.4	45.7	16.6	3,238	50.2	51.1	16.2
Hemoglobin (g/dL)	.001	2,448	9.2	9.1	2.1	754	9.5	9.4	2.3	3,202	9.2	9.2	2.1
Platelets	.90*	2,449	80.4	54.0	92.1	764	79.0	53.5	95.0	3,213	80.0	54.0	92.8
WBC	< .001*	2,459	25.2	8.6	39.4	765	52.4	31.7	65.1	3,224	31.6	12.0	48.2
Blasts, marrow (%)	< .001	2,287	61.2	63.0	24.9	699	69.6	76.0	24.4	2,986	63.1	68.0	25.0
Blasts, PB (%)	< .001	2,357	34.6	26.0	31.1	739	44.6	44.0	32.9	3,096	37.0	30.0	31.8
CD11a	.04	992	63.2	79.0	35.7	108	70.5	86.5	32.1	1,100	63.9	80.0	35.4
CD11b	< .001	1,175	24.8	9.0	32.0	133	38.2	29.0	36.0	1,308	26.1	10.0	32.6
CD56	.46	980	13.3	0.0	28.0	108	15.5	0.5	29.8	1,088	13.5	0.0	28.2

Abbreviations: PB, peripheral blood; SD, standard deviation.
** t* test done on log-transformed values.

Table 4. Univariate Analyses: Overall Survival

Categorical Variable	No.	No. of Deaths	Median OS (months)	95% CI (months)	Log-Rank *P*
EMD					
No	2,471	1,972	12.7	12.1 to 13.7	.005
Yes	769	653	11.3	10.4 to 12.8	
EMD category*					
Hematopoietic	398	329	10.9	9.8 to 12.9	.01
Nonhematopoietic	208	183	11.2	9.4 to 12.9	
Rare	164	141	12.4	10.3 to 14.8	
No. of EMD sites					
0	2,471	1,972	12.7	12.1 to 13.7	.002
1	502	420	12.2	10.6 to 13.5	
2-5	267	233	10.2	9.2 to 12.0	
CNS involvement					
No	3,204	2,593	12.4	11.9 to 13.1	.34
Yes	36	32	10.5	7.2 to 17.7	
Liver involvement					
No	3,067	2,470	12.6	12.0 to 13.3	< .001
Yes	173	155	9.7	8.1 to 11.9	
Splenic involvement					
No	3,002	2,418	12.7	12.1 to 13.4	< .001
Yes	238	207	9.5	7.8 to 11.2	
Nodal involvement					
No	2,866	2,317	12.5	11.9 to 13.2	.94
Yes	374	308	11.3	10.2 to 13.5	
Skin involvement					
No	3,094	2,496	12.6	12.0 to 13.4	.002
Yes	146	129	10.1	8.1 to 12.3	
Gingival involvement					
No	3,097	2,500	12.4	11.9 to 13.1	.24
Yes	143	125	12.0	10.5 to 16.4	
Lung involvement					
No	3,217	2,605	12.4	11.9 to 13.1	.34
Yes	23	20	9.2	4.4 to 16.0	
Bone involvement					
No	3,232	2,619	12.4	11.8 to 13.1	.92
Yes	8	6	12.8	0.3 to NR	
Myeloid sarcoma					
No	3,232	2,618	12.4	11.8 to 13.1	.93
Yes	8	7	14.1	8.4 to 26.2	
Other EMD					
No	3,205	2,595	12.4	11.9 to 13.1	.29
Yes	35	30	10.5	7.2 to 14.7	
Performance status					
0	1,112	841	16.3	14.6 to 18.3	< .001
1	1,581	1,297	12.0	11.0 to 12.8	
2-4	524	466	8.1	7.1 to 9.3	
Sex					
Male	1,729	1,441	11.7	10.8 to 12.4	< .001
Female	1,509	1,182	13.4	12.5 to 14.5	
Race/ethnicity					
White	2,872	2,335	12.4	11.7 to 13.1	.17
Hispanic	86	64	12.9	8.9 to 20.6	
Black	193	161	11.4	10.2 to 14.2	
Asian	22	14	28.2	12.2 to NR	
Other	38	29	13.8	8.7 to 29.8	
FAB class (log-rank test for each class *v* all others)					
M0	63	59	10.7	8.6 to 15.3	.03
M1	605	480	12.3	11.1 to 14.0	.44
M2	815	631	14.5	12.9 to 15.8	< .001
M4	938	760	12.8	11.6 to 14.1	.50
M5	288	241	10.7	9.8 to 12.5	.06
M6	112	98	9.2	7.7 to 10.2	.009
M7	12	8	14.2	2.9 to NR	.42
Other	393	335	11.4	9.9 to 13.2	.01

(continued on following page)

Table 4. Univariate Analyses: Overall Survival (continued)

Categorical Variable	No.	No. of Deaths	Median OS (months)	95% CI (months)	Log-Rank *P*
Cytogenetic risk category					
Favorable	200	101	94.2	42.2 to 167.6	< .001
Intermediate	576	430	16.9	14.3 to 20.8	
Unfavorable	375	357	6.8	6.1 to 8.0	
Undetermined	447	376	11.0	9.9 to 12.9	
Received transplantation					
No	2,152	1,906	9.4	8.8 to 10.0	< .001
Yes	446	259	40.6	33.2 to 65.0	
Response to induction					
CR	1,923	1,393	22.3	20.7 to 24.0	< .001
PR	4	4	4.1	3.3 to NR	
SD	914	845	6.0	5.3 to 6.5	
PD	165	164	3.1	2.3 to 4.6	
Unevaluable	213	200	2.2	1.3 to 5.2	

NOTE. The No. of extramedullary sites was a continuous variable. Total No., 3,240; No. of deaths, 2,625; hazard ratio, 1.095; 95% CI, 1.043 to 1.148; Wald $P < .001$.
Abbreviations: CR, complete remission; EMD, extramedullary disease; FAB, French-American-British; NR, not reached or not estimable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.
*EMD category: none = no site of EMD disease; hematopoietic = EMD in nodes, liver, spleen only; nonhematopoietic = EMD in skin or gingiva with or without EMD in hematopoietic sites; rare = CNS, bone, lung, or myeloid sarcoma with or without EMD in previous sites.

EMD Throughout the Years of Registration

The year of registration was found to be a significant statistical variable in most of the different multivariable models that were performed ($P = .043$ to $< .001$). Among patients registered before 2002, the presence of EMD did not affect OS. Patients enrolled before 1990 had median survival of approximately 12.5 months and it was 12.8 months among those enrolled between 1990 and 1999, regardless of EMD status. Among patients enrolled after 2002, survival continued to improve over time among patients without EMD (median survival, 14.1 months; $P < .001$), but not among patients with EMD (median survival, 8.3 months; $P = .353$). The negative impact of EMD on outcome was seen predominantly among older patients with EMD enrolled in E3999, but not with younger patients enrolled in E1900 during the same time period.

EMD and Cytogenetics

Cytogenetic data were available in 49% of the study cohort. Of these, 200 patients had known favorable cytogenetics, and EMD was present in only 26 patients (13%). No significant difference in OS was found between the groups, but the numbers are too small for a definitive assessment (Fig 1D). The incidence of EMD among those patients with other than favorable cytogenetics was 15.1%, similar to that in patients with favorable cytogenetics. Although both the presence of EMD and other than favorable cytogenetic risk were significant predictors of poor survival (by pairwise survival estimates and hazard ratios) compared with no-EMD and favorable cytogenetic risk, respectively, the interaction of these factors was not significant ($P = .61$).

EMD and Adhesion Molecules

There was a higher incidence of CD11b-positive AML among patients with EMD (29%) than patients without EMD (9%; $P < .001$). The percentage of CD11a and CD56-positive blasts was comparable between the two groups.

EMD and HSCT

Data about transplantation, in studies where this was not part of the protocol, are limited. The percentage of patients who underwent a transplantation was slightly lower among the EMD group compared with the others (14.7% *v* 18%, respectively; $P = .07$). The median OS of the 446 patients who underwent HSCT was 40.6 months, compared with 9.4 months of the 2,152 patients who did not ($P < .001$). Nevertheless, undergoing transplantation was not found to be a significant variable in a multivariable analysis.

DISCUSSION

On the basis of data from 11 consecutive ECOG-ACRIN clinical trials, the presence of EMD at diagnosis does not have independent prognostic value. This observation is clinically meaningful, given that the incidence of EMD in adults with newly diagnosed AML was approximately 24%. The rate of EMD reported in the literature has a broad range related to definitions and method of evaluation. Some define EMD as organ involvement, not including liver, spleen, and LNs.[6] Using the terms myeloid sarcoma or chloroma, some imply a discrete mass of myeloblasts, not including cases of organ infiltration.[1]

We and others[2] used clinical assessment of EMD without requiring a biopsy, whereas others established the diagnosis of EMD only if pathologically confirmed.[1,23] LNs, spleen, and gingiva are likely to be considered as EMD sites by physical examination, but usually would not be biopsied and therefore not be considered as pathologically proven EMD. With more sensitive diagnostic tools, such as positron emission tomography (PET), the rate of presumed EMD at diagnosis is likely to be even higher.[24] For example, in 26 patients with newly diagnosed AML, Cribe et al[25] demonstrated that ^{18}F-labeled fluorodeoxyglucose PET testing doubled the rate of EMD, from 31% by clinical examination to 65%. It is possible that many patients with AML have clusters of leukemic cells in different organs, in addition to the blood and marrow, and the only question is the resolution of the test used for

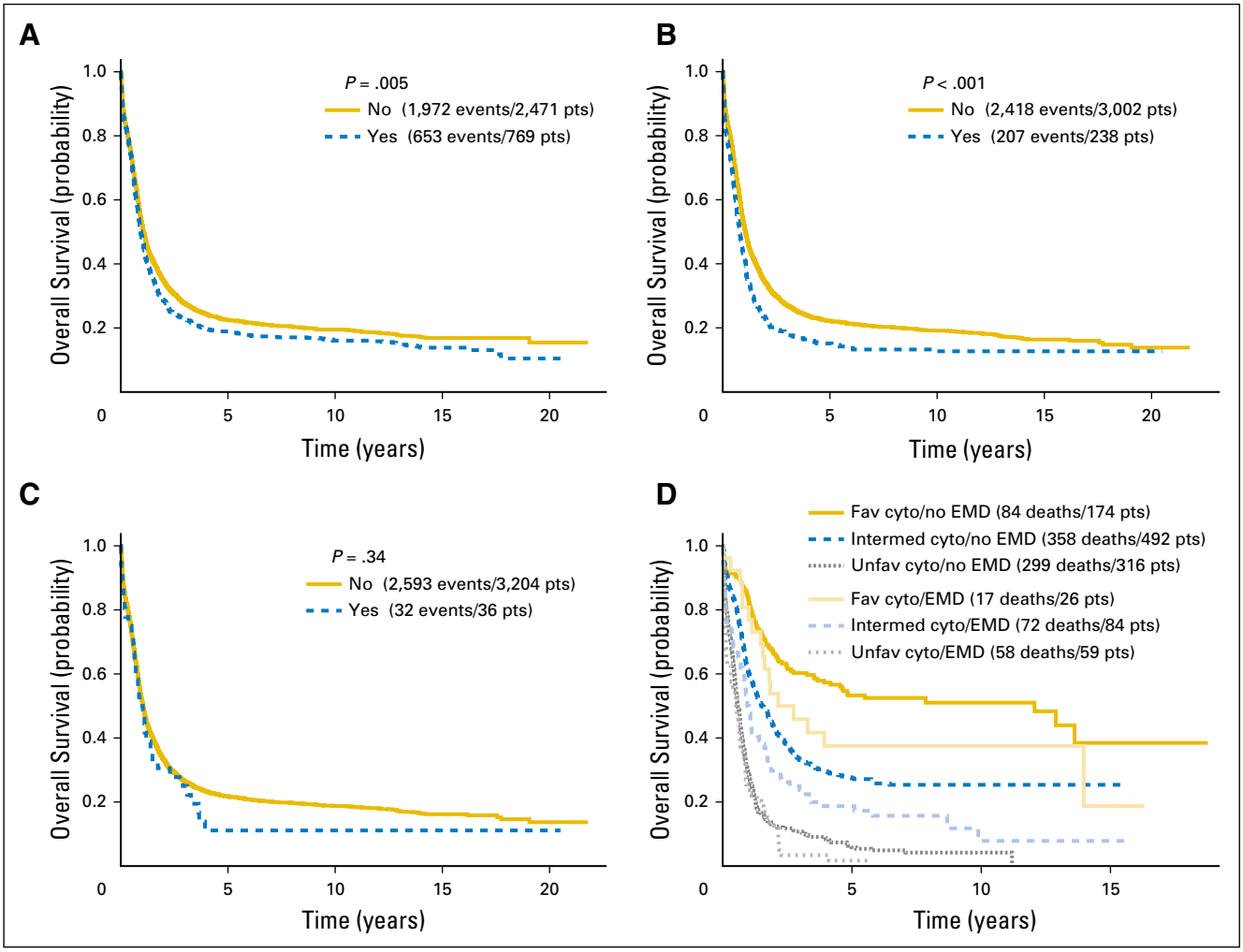

Fig 1. Differences in overall survival by (A) presence of extramedullary disease, (B) presence of splenic involvement, (C) presence of CNS involvement, and (D) combination of cytogenetic risk and presence of extramedullary involvement. *P* values are from the log-rank test. Cyto, cytogenetic; EMD, extramedullary disease; fav, favorable; intermed, intermediate; pts, patients; unfav, unfavorable.

assessment. However, it is neither ethical nor practical to biopsy every suspected EMD site, and it would be prohibitively costly to perform PET-computed tomography for every patient with AML. Therefore, despite its limitations, clinical evaluation remains the main assessment method for EMD in routine practice.

To the best of our knowledge, this is the largest study of EMD with information on the distribution of EMD among different sites. LNs and spleen were the most common sites reported, with incidences of 11.5% and 7.3%, respectively, followed by liver (5.3%), skin (4.5%), and gingiva (4.4%), whereas CNS involvement was observed in only 1.1%. The low incidence of CNS involvement is the only variable that is consistent in early studies[24,26] as well as contemporary studies.[27] Rozovski et al[9] recently reported a 3.3% incidence of CNS involvement among 1,412 patients with newly diagnosed AML who did not undergo a routine LP compared with 19% of 42 patients who underwent a routine LP. We did not observe such a difference; therefore, the rarity of the reported CNS involvement supports not performing a routine LP in patients with AML unless neurologically indicated.

The number of involved sites is usually not reported in the literature. In our study, 35% of patients with EMD had more than one involved site; 9.5% had three sites and some patients even had five and six involved sites. The relatively high rate of multiple-site EMD involvement suggests that the development of EMD is an intrinsic feature of the leukemic cells and depends on factors such as the expression of cell surface adhesion molecules.[2,28] In our cohort, the median percentage of CD11b-positive blasts was significantly higher among the patients with EMD but, in contrast to the report by Chang et al,[2] CD56 was not.

In the multivariable model, earlier year of registration, older age, high WBC count, low platelet count, poor PS, high cytogenetic risk status, and not achieving a CR were associated with a shorter OS. However, EMD as a group, as well as every individual EMD site, had no independent effect on prognosis. It is possible that individual sites of EMD are in fact associated with poorer prognosis; however, these patients also have other unfavorable prognostic factors, such as high WBC count and unfavorable cytogenetics, whereas EMD has no independent prognostic effect. Indeed, patients with EMD, in this series and in others,[2,29,30] had higher WBC

Table 5. Multivariable Model

Factor	Parameter Estimate	Standard Error	*P*	Hazard Ratio	95% HR Confidence Limits
Presence of extramedullary disease	−0.038	0.090	.671	0.963	0.807 to 1.148
No. of extramedullary sites	0.277	0.187	.138	1.320	0.915 to 1.903
Year registered to study	−0.022	0.003	.000	0.978	0.973 to 0.983
Age	0.023	0.001	.000	1.024	1.021 to 1.026
Log WBC	0.068	0.015	.000	1.070	1.040 to 1.102
Log platelets	−0.059	0.023	.010	0.943	0.902 to 0.986
Hemoglobin	−0.022	0.010	.024	0.978	0.960 to 0.997
PS 1*	0.128	0.045	.005	1.136	1.039 to 1.242
PS 2-4*	0.193	0.062	.002	1.213	1.075 to 1.368
Male	0.067	0.040	.094	1.070	0.988 to 1.158
Extramedullary site: gingiva	−0.118	0.211	.576	0.888	0.587 to 1.345
Extramedullary site: nodes	−0.237	0.199	.235	0.789	0.534 to 1.166
Extramedullary site: spleen	−0.157	0.201	.436	0.855	0.576 to 1.268
Extramedullary site: liver	−0.204	0.203	.314	0.815	0.548 to 1.213
CNS involvement	−0.331	0.286	.247	0.718	0.410 to 1.257
Extramedullary site: skin	−0.098	0.213	.648	0.907	0.597 to 1.378
Extramedullary site: lung	−0.087	0.303	.774	0.917	0.507 to 1.659
Extramedullary site: bone	−0.277	0.448	.537	0.758	0.315 to 1.826
Myeloid sarcoma	−0.433	0.426	.309	0.648	0.281 to 1.494
FAB intermediate risk*	0.024	0.049	.619	1.025	0.931 to 1.128
FAB high risk*	0.185	0.089	.038	1.203	1.010 to 1.433
FAB other*	0.087	0.069	.207	1.091	0.953 to 1.248
Achieved CR to induction	−1.132	0.042	.000	0.322	0.297 to 0.350

Abbreviations: CR, complete remission; FAB, French-American-British; PS, performance status.
*Reference categories are PS 0, favorable risk cytogenetics.

counts at diagnosis. The similar outcome of patients with CNS involvement to others may also be explained in a different way. CNS is the only EMD site that mandates a specific therapeutic approach, intrathecal methotrexate and/or high-dose cytarabine, which may overcome the potential negative effect of CNS involvement.

The median age of the patients was 51.1 years. Patients with EMD, compared with those without EMD, were younger (median age, 45.7 *v* 52.9 years; $P < .001$). There was a statistically significant decline in the incidence of extramedullary disease with increasing age, and a statistically significant decline in survival with increasing age among patients both with and without EMD. Nevertheless, the interaction of age-by-EMD status was not statistically significant, so the effect of age on survival was similar in both groups (Appendix Table A2, online only).

We classified the patients with EMD into three subgroups: hematopoietic organs (lymph nodes, spleen, or liver), nonhematopoietic organs (skin or gingiva with or without EMD in hematopoietic sites), and rare areas of involvement (CNS, bone, lung, or myeloid sarcoma with or without EMD in previous sites). The rationale for this division was that every subgroup might develop in a different context. The first subgroup is probably influenced by the time from first symptoms to diagnosis and treatment of AML. The second depends on specific subtypes of AML, mainly those with a monocytic component.[3] The third subgroup is composed of rare sites and the context of development is unknown. Interestingly, the third group had better survival compared with the two others.

By stratifying patients with available cytogenetic data (approximately 50% of the cohort) into favorable and other than favorable cytogenetics, we thought that the effect of EMD on prognosis might appear significant, particularly in the patients with favorable cytogenetics. Indeed, the median OS among the favorable cytogenetic group was 32.9 versus 94.2 months, with and without EMD, respectively (Fig 1D). However, the number of patients was small and the difference was not significant ($P = .145$). Nevertheless, the question of the effect of EMD among patients with favorable cytogenetics needs to be studied in larger cohorts.

In conclusion, this large study demonstrates that EMD is more common than previously reported and frequently occurs in multiple sites, although CNS involvement is rare. Perhaps surprisingly, EMD at presentation does not have independent prognostic significance. Importantly, the presence of EMD should not affect the choice of postremission therapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

Table A1. Extramedullary Disease Assessment

Site	E1479, E3480 (n = 328)				E3999 (n = 422)			E1900 (n = 644)		Others (n = 1,847)		
	No.	PE	BX	Other	No.	C	P	No.	Inv	No.	C	P
CNS	324	7	0	3	—	—	—	644	6	—	—	—
Peripheral nervous system	327	6	0	2	—	—	—	644	0	—	—	—
Leukemic meningitis	—	—	—	—	397	0	0	—	—	1,399	5	11
Liver	326	41	0	11	416	9	0	—	—	1,748	112	0
Spleen	326	56	0	4	412	23	0	644	3	1,745	151	0
Nodes	325	68	4	0	—	—	—	—	—	—	—	—
Mediastinal nodes/mass	—	—	—	—	398	5	0	644	2	1,740	14	0
Peripheral nodes	—	—	—	—	415	15	1	—	—	1,796	247	10
Gingival hypertrophy*	322	55			411	17	0	642	32	—	—	—
Cranial nerve palsy	—	—	—	—	411	0	0	—	—	—		
Skin	325	28	2	0	416	11	2	643	7	1,810	75	21
Other	285	15	2	4	367	7	2	622	15	1,199	79	10

NOTE. Dashes indicate terms not appearing on forms.
Abbreviations: BX, biopsy; C, clinically positive or involved; Inv, involved; No., number of responses to the question on the form; Other, x-ray, scan, or chemical; P, pathologically positive or involved; PE, physical examination.
*For E1479 and E3480, gingival hypertrophy appeared as a symptom and not as a site of extramedullary disease; shown is the number of patients with symptoms present. For other studies in particular, comments were reviewed to elicit details about extramedullary disease coded as other; these were recoded in the appropriate category where possible.

Table A2. Extramedullary Disease by Age

Variable	Age Category (years)			
	< 37	37-50	51-63	> 63
Patients	804	816	809	809
Patients with EMD	267	195	160	147
Percent	33.2	23.9	19.8	18.2
Median survival, no EMD (months)	22.6	16.7	11.9	7.7
IQR (months)	9.9 to NR	7.5 to 157.0	5.0 to 32.3	1.9 to 19.1
Median survival, EMD (months)	16.2	13.2	10.5	4.9
IQR (months)	7.9 to 159.8	7.7 to 38.5	2.8 to 21.1	1.0 to 10.8

Abbreviations: EMD, extramedullary disease; IQR, interquartile range; NR, not reached.