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Extramedullary Infiltration at Diagnosis and Prognosis in Children With Acute Myelogenous Leukemia

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Background. Extramedullary infiltration (EMI) is an occasional clinical symptom in childhood acute myelogenous leukemia (AML), but there is considerable controversy regarding the prognostic significance of EMI in AML. ***Procedure.*** We evaluated the frequency and prognostic significance of EMI at diagnosis of AML in children. ***Results.*** Of 240 cases of de novo AML excluding children with Down syndrome and acute promyelocytic leukemia, 56 (23.3%) showed EMI at diagnosis. Patients with EMI had a higher initial WBC count and a higher proportion of M4/M5 morphological variants. The complete remission rate following induction chemotherapy was lower in patients with EMI. However, the overall survival and event-free survival did not differ between patients with and without EMI. A detailed analysis showed that patients with EMI with a WBC count at diagnosis of over 100×10^9/L or infiltration into the central nervous system are likely to have a poor prognosis. ***Conclusions.*** CNS leukemia and EMI together with a WBC count of $>100 \times 10^9$/L at diagnosis of AML are high risk factors for relapse, and alternative treatment approaches for patients with these characteristics should be explored. Pediatr Blood Cancer 2007;48:393–398.

Key words: AML; childhood; extramedullary infiltration

INTRODUCTION

Acute myelogenous leukemia (AML) refers to a heterogeneous group of diseases, and AML patients may have distinct morphologic, cytochemical, immunophenotypic, and clinical characteristics. Extramedullary infiltration (EMI), which includes tumor nodules (myeloid or granulocytic sarcoma), skin infiltration (leukemia cutis), meningeal infiltration, gingival infiltration, or hepatosplenomegaly [1], has been reported to be more common in myelomonoblastic and monoblastic subtypes of AML (FAB M4 and M5) than in other morphological subgroups [2–8]. The prognostic importance of EMI is controversial, but the outcome of children with AML who initially present with EMI is generally thought to be poor [9–13], although several studies have suggested otherwise [2,14,15]. Using tailored treatment protocol for AML patients, which we refer to as AML99, we evaluated the incidence and prognostic significance of EMI in patients with AML.

PATIENTS AND METHODS

Between January 2000 and December 2002, a total of 240 patients of less than 16 years of age with untreated AML excluding children with Down syndrome and acute promyelocytic leukemia were registered by the Japanese childhood AML cooperative study group. Of these patients, 128 were boys and 112 were girls. Morphology subtyping by the French–American–British (FAB) system was performed at the treating institutions. CNS leukemia was diagnosed on the basis of >5 blast cells/μl in the CSF without blood contamination, and EMI was defined as leukemic infiltration in organs other than liver, spleen, and lymph nodes. Complete remission was defined as <5% blast cells in the bone marrow, normal hematopoiesis, the absence of blasts cells in the peripheral blood and disappearance of EMI. Relapse was defined as a return of leukemic blast cells in the bone marrow (>20%) and/or the return of EMI.

Treatment Protocol

The chemotherapy regimens (AML99 protocol) are outlined in Figure 1, excluding those for children with Down syndrome and acute promyelocytic leukemia; the drug doses and schedules are shown in Table I. Patients of less than 2 years of age or with WBC counts of $<100 \times 10^9$/L were treated with induction A therapy (etoposide 150 mg/m^2, days 1–5; cytosine arabinoside 200 mg/m^2, days 6–12; mitoxantrone 5 mg/m^2, days 6–10), and those over 2 years of age with WBC counts of $\geq 100 \times 10^9$/L were treated with induction B therapy (etoposide 100 mg/m^2, days 1–3; 200 mg/m^2, days 11–13; cytosine arabinoside 500 mg/m^2, days 4–6 and days

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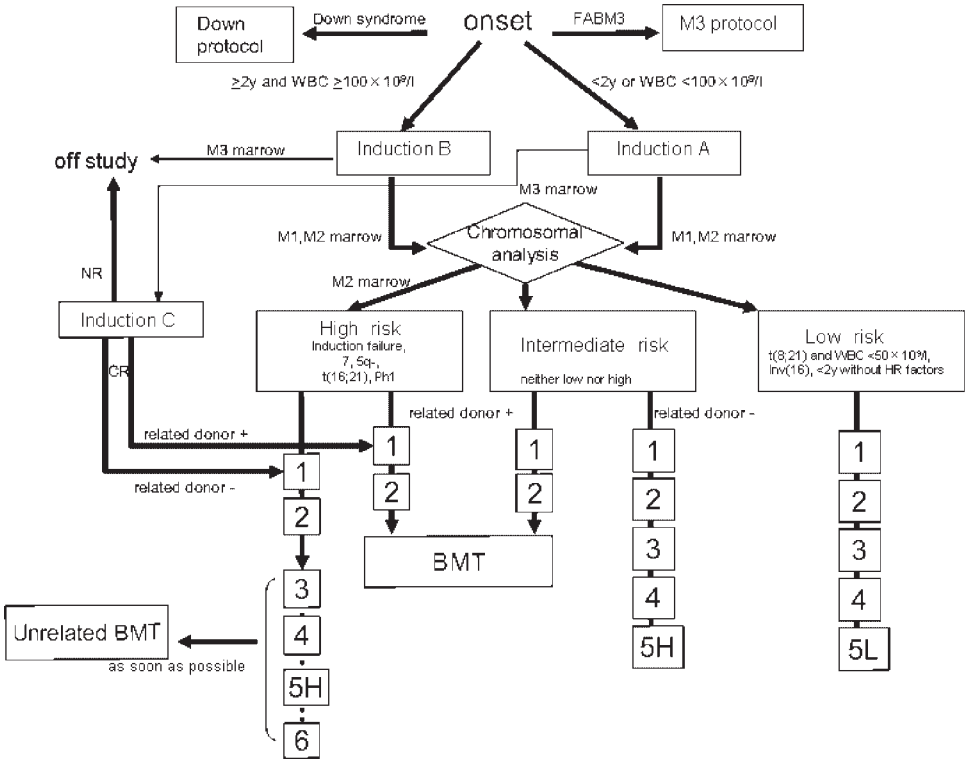

Fig. 1. Schema of the AML99 Study.

11–13; idarubicin, 8 mg/m^2, days 4–6). Patients with M3 marrow after induction A were treated with induction C (CA 500 mg/m^2 div, days 1–3, 8–10, IDA 8 mg/m^2 div, days 1–3, VP16 200 mg/m^2 div, days 8–10).

The AML99 study was planned to test the concept of risk-stratified treatment. Patients were stratified into three risk categories: low (inv(16), t(8;21) and WBC $<50 \times 10^9$/L; age <2 years old, without HR factors), high (-7, 5q$-$, Ph1, t(16;21), remission failure), and intermediate (neither low nor high risk). The basic framework of AML99 involved prospective enrollment of patients for risk-adapted therapy. Low risk (LR) patients were treated exclusively with chemotherapy regardless of the availability of a donor for HSCT, whereas all high-risk (HR) patients were treated with hematological stem cell transplantation (HSCT). Intermediate risk (IR) patients with an HLA-matched donor were treated with HSCT and those without a donor were treated with chemotherapy. Patients with Down syndrome and acute promyelocytic leukemia were treated using the AML99 Down protocol and AML99 M3 protocol, respectively. Determination of CR was made after induction therapy and course 1.

Statistical Analysis

A *t* test or chi-squire test was used to compare patients with and without EMI. Analysis of overall survival and event-free survival (EFS) were performed using the Kaplan–Meier method, with differences compared by log-rank test. Multivariate analysis stepwise regression was performed to explore the independent effects of variables that showed a significant influence in univariate analysis. Statistical analyses were performed using Dr. SPSS II for Windows (release 11.0.1J, SPSS Japan Inc.).

RESULTS

EMI was a complication in 56 of the 240 AML patients (23.3%). The presenting clinical and hematological features of patients with EMI are summarized and compared with those of patients without EMI in Table II. The median age in each group was not significantly different. Patients with EMI had a higher initial WBC count and a higher proportion of M4/M5 morphological variants (57.1 vs. 27.7%). Cytogenetically, patients with EMI had a higher population of inv16 and 11q23 abnormalities.

EMI was noted at a single site in 49 (87.5%) out of the 56 patients, whereas the remaining 7 patients (12.3%) had EMI at multiple sites. Among the patients with a single site of EMI, there were 13 cases of skin infiltration, 7 of gingival involvement, 7 of CNS leukemia, 5 of bone involvement, and 4 of orbital tumor. The seven patients with EMI at multiple

TABLE I. AML99 Study: Chemotherapy

Drugs	Dose/Route	Duration
Induction A		
VP16	150 mg/m^2 div	Days 1–5
CA	200 mg/m^2 div	Days 6–12
MIT	5 mg/m^2 div	Days 6–10
Triple it		Day 6
Induction B		
VP16	100 mg/m^2 div	Days 1–3
CA	500 mg/m^2 div	Days 4–6, 11–13
IDA	8 mg/m^2 div	Days 1–3
VP16	200 mg/m^2 div	Days 11–13
Triple it		Day 4
Induction C		
CA	500 mg/m^2 div	Days 1–3, 8–10
IDA	8 mg/m^2 div	Days 1–3
VP16	200 mg/m^2 div	Days 8–10
Triple it		Day 1
Course 1, 4		
VP16	100 mg/m^2 div	Days 1–5
CA	3 g/m^2 × 2 div	Days 1–3
IDA	10 mg/m^2 div	Day 1
triple it		Day 1
Course 2, 5H		
VP16	150 mg/m^2 div	Days 1–3
CA	200 mg/m^2 div	Days 4–8
MIT	5 mg/m^2 div	Days 4–6
Triple it		Day 1
Course 3, 5L		
VP16	100 mg/m^2 div	Days 1–5
CA	2 g/m^2 × 2 div	Days 1–5
Triple it		Day 1
Course 6		
VP16	200 mg/m^2	Day 1–3, 8–10
CA	500 mg/m^2	Day 1–3, 8–10
Triple it		Day 1

Triple it: under 1 y MTX 5 mg, CA 10 mg, HDC 10 mg; 1 y MTX 7.5 mg, CA 15 mg, HDC 15 mg; 2 y MTX 10 mg, CA 20 mg, HDC 20 mg; over 2 y MTX 12.5 mg, CA 25 mg, HDC 25 mg.
VP16, etoposide; CA, cytosine arabinoside; MIT, mitoxantrone; IDA, idarubicin; HDC, hydrocortisone; MTX, methotrexate.

sites included five cases of CNS leukemia, two of gingival involvement and two of testicular tumor. The presenting clinical and hematological features of patients in the EMI subgroups are shown in Table III. Although patients with CNS leukemia and multiple site infiltration were lower in age, the difference was not statistically significant. Cases with gingival involvement and skin infiltration showed a higher relative occurrence of monoblastic leukemia (M4/M5), and cases with EMI associated with CNS leukemia had a higher initial WBC count than with EMI at other sites.

In the 240 patients, the CR rate with induction chemotherapy was lower in patients with EMI (85.7 vs. 95.7%, $P < 0.05$). However, overall survival did not differ between patients with or without EMI (77.3 vs. 77.6%), and although EFS was lower in patients with EMI, it was not statistically different from those without EMI (Table IV). In patients with EMI, those having WBC counts $>100 \times 10^9$/L at diagnosis had a lower EFS, and the difference from EMI patients with lower WBC counts was statistically significant ($P = 0.0052$) (Fig. 2). EFS was also significantly lower in children with CNS leukemia, compared with those without EMI or with myeloblastoma.

DISCUSSION

The frequency of EMI at diagnosis in childhood AML varies in literature reports from 7 to 49%. The Children's Cancer Group (CCG) Study 2891 reported that extramedullary disease of any type occurred in 160 of 580 (27.6%) patients [16]. The Pediatric Oncology Group (POG) Study 8498 reported non-central nervous system extramedullary disease in 21 of 285 (7.4%) patients and Study 8821 reported 51 of 492 (10.4%) patients with this condition [9]. The BFM-78, BFM-83, and BFM-87 studies reported extramedullary organ involvement, defined as leukemic infiltration in organs other than the liver, spleen and central nervous system, in 33 of 84 (39.3%) patients younger than 2 years of age, and in 103 of 398 (25.9%) patients over 2 years of age [17].

The prognostic significance of EMI in AML at presentation and even the definition of EMI remain controversial; while some authors consider CNS leukemia or hepatosplenomegaly to be EMI, others do not [1,18]. The outcome of children with AML who initially present with EMI is generally thought to be poor [9–13], and gingival infiltration and CNS leukemia have been reported to be prognostic factors in childhood AML [10,19]. On the other hand, several reports suggest the presence of EMI at diagnosis has no significant effect on EFS [2,14,15]. In our study, patients with EMI accounted for 23.3% of the entire AML population, in concordance with past reports. Moreover, many patients with EMI had high WBC counts and cases of M4/M5. Although the complete remission rate of patients with EMI was lower than for other patients, this did not influence the survival rate and EFS, and hence did not change the prognosis. However, the prognosis of cases with CNS leukemia and high WBC counts was poor, and patients with EMI and WBC counts $>100 \times 10^9$/L at diagnosis had a particularly low EFS.

In childhood AML, patients with high WBC counts have a poor prognosis [2,9]. We analyzed the prognosis of AML patients using two factors: the presence of EMI and a WBC count $>100 \times 10^9$/L at diagnosis. Although patients with EMI and a WBC count $>100 \times 10^9$/L at diagnosis had a lower EFS (23.8%), patients in the other three groups (i.e., those with EMI and a WBC count $\leq 100 \times 10^9$/L; those without EMI and with a WBC count $>100 \times 10^9$/L; and those without EMI and a WBC counts $\leq 100 \times 10^9$/L) had

TABLE II. Comparison Between Patients With and Without EMI

	EMI (+) (n = 56)	EMI (−) (n = 184)	
Age (years)			
Median (range)	4.1 (7 d–15.4 y)	6.9 (2 m–15.8 y)	NS
Gender (M/F)	32/24	88/96	NS
WBC ($\times 10^9$/L)(range)	28.7 (2.5–365.0)	20.3 (0.8–621.0)	$P < 0.05$
FAB			
M0	2 (3.6%)	8 (4.3%)	NS
M1	10 (17.9%)	26 (14.1%)	NS
M2	11 (19.6%)	73 (39.7%)	$P < 0.05$
M4/M5	32 (57.1%)	51 (27.7%)	$P < 0.05$
M6	0 (0%)	3 (1.6%)	NS
M7	1 (1.8%)	19 (10.3%)	$P < 0.05$
Chromosome			
t(8;21)	11 (19.6%)	60 (32.6%)	NS
inv16	5 (8.9%)	7 (3.8%)	NS
11q23	19 (33.9%)	23 (12.5%)	$P < 0.05$
Induction therapy			
A	48 (85.7%)	166 (90.2%)	NS
B	8 (14.3%)	18 (9.8%)	NS
Complete remission	48 (85.7%)	176 (95.6%)	$P < 0.05$
HR	7 (12.5%)	18 (9.8%)	NS
IR	15 (26.8%)	77 (41.8%)	$P < 0.05$
LR	27 (48.2%)	83 (45.1%)	NS

TABLE III. Patient Characteristics in the EMI Subgroups and in Patients Without EMI

	No EMI	Myeloblastoma	Gingival infiltration	CNS leukemia	Skin infiltration	Multiple sites
Number of patients	184	22	7	7	13	7
Gender (M/F)	88/96	13/9	4/3	3/4	7/6	5/2
Age	6.90	4.87	6.90	1.87	6.14	1.87
<2 y	28	3	0	4	5	5
FAB						
M4/M5	51	8	6	3	11	4
Other	133	14	1	4	2	3
WBC($\times 10^9$/L)	20.3*	17.8*	84.0*	91.1*	55.4*	11.5

*$P < 0.05$.

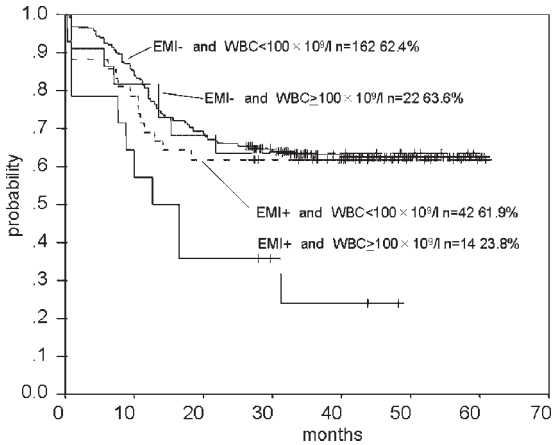

Fig. 2. Kaplan–Meier estimate of event-free survival for patients with and without extramedullary infiltration at diagnosis. In patients with EMI, those having WBC counts $>100 \times 10^9$/L at diagnosis had a lower EFS compared of no EMI with WBC counts $<100 \times 10^9$/L ($P = 0.0021$), no EMI with WBC counts $\geq 100 \times 10^9$/L ($P = 0.0351$) and EMI with WBC counts $<100 \times 10^9$/L ($P = 0.0303$).

a surprisingly similar EFS of 61.9, 63.6, and 62.4%, respectively. This suggests that the WBC count does not contribute to the prognosis of childhood AML in the absence of EMI. It is of note that the WBC count is often used as a factor for the selection of treatment, but our results suggest that WBC should not be used as a single prognostic factor. This reason is not clear. We conclude that CNS leukemia and EMI together with a WBC count of $>100 \times 10^9$/L at diagnosis of AML are HR factors for relapse and that alternative treatment approaches should be explored.

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TABLE IV. Three-Year Estimates of Event-Free Survival (EFS) in Patients With Acute Myelogenous Leukemia

Risk factor	No. of patients	Percentage EFS	*P* value
Gender			
Male	128	60.5 ± 4.4	0.9879
Female	112	60.2 ± 4.7	
Age			
<2	45	43.4 ± 7.6	0.0362
2–10	116	65.5 ± 4.4	
10–16	79	62.8 ± 5.5	
WBC count			
<50	175	61.7 ± 3.7	0.2806
50–100	29	65.5 ± 8.8	
>100	36	49.7 ± 8.4	
FAB			
M4/M5	83	54.0 ± 5.5	0.1668
Other	157	63.8 ± 3.9	
Cytogenetic findings			
t(8;21) or inv(16)	82	79.1 ± 4.5	0.0001
Other	158	50.6 ± 4.0	
EMI			
No EMI	184	62.5 ± 3.6	0.1174
EMI	56	53.3 ± 6.7	
EMI with WBC > 100×10^9/L	14	23.8 ± 12.9	0.0052
No EMI or EMI with WBC < 100×10^9/L	226	60.0 ± 3.5	
Myeloblastoma	22	72.7 ± 9.5	0.0467
Gingival infiltration	7	42.8 ± 18.7	
CNS leukemia	7	28.6 ± 17.1	
Skin infiltration	13	52.8 ± 14.1	
Multiple sites	7	—	

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