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Original Article

Intracranial Hemorrhage in Childhood Acute Leukemia: Incidence, Characteristics, and Contributing Factors

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Background: Among all cancers, hematologic malignancy has the highest rate of intracranial hemorrhage. However, there are limited data on intracranial hemorrhage in childhood acute leukemia. We aimed to determine the incidence, characteristics, and factors associated with intracranial hemorrhage in children with acute leukemia.

Methods: We reviewed a database of patients aged one month to 15 years diagnosed with acute leukemia during 2003 to 2016 at a hospital in Thailand. Characteristics of patients with intracranial hemorrhage were compared with those of patients without intracranial hemorrhage. Multiple logistic regression was used to determine the associated factors. We performed survival analyses to compare survival and hazard ratios between groups.

Results: There were 494 children with acute leukemia (acute lymphoblastic leukemia 367, acute myelogenous leukemia 127). Median age was 4.9 years (interquartile range 3.0 to 9.2). Follow-up duration was 2.1 years. Intracranial hemorrhage occurred in 12 patients whose median age was 12.5 years (interquartile range 7.5 to 13.3). Incidence rate of intracranial hemorrhage was 6.2 (acute lymphoblastic leukemia 5.1, acute myelogenous leukemia 12.9) per 1000 person-years. Case fatality rate of intracranial hemorrhage was 75%. Patients with early intracranial hemorrhage had prolonged international normalized ratio and higher white blood cell count, whereas patients with late intracranial hemorrhage had more concurrent systemic infections. Most cases of intracranial hemorrhage were intraparenchymal with perihematomal edema. Median survival was 24 days in the intracranial hemorrhage group compared with four years in the non-intracranial hemorrhage group. Risk of death from intracranial hemorrhage was 3.2 times higher than that of the non-intracranial hemorrhage group. Age at diagnosis, initial white blood cell count, and lactate dehydrogenase were associated with increased risk of intracranial hemorrhage.

Conclusions: Intracranial hemorrhage was common and often fatal in children with acute leukemia. Potential contributing factors differed by intracranial hemorrhage timing. Older age, white blood cell count, and lactate dehydrogenase were associated with high risk of intracranial hemorrhage.

Background

Hemorrhagic stroke in children is uncommon but often devastating. With a prevalence of two per 100,000 in the general pediatric population,[1] prevalence of hemorrhagic stroke increases to 1% in children with cancer.[2] Acute leukemia is the most common cancer in children, accounting for 30% of all pediatric cancers.[3] However, studies about intracranial hemorrhage (ICH) in children with leukemia are limited. The reported prevalence of ICH in children with acute leukemia ranges from 0.8% to 3.3%.[2,4-6] All previous studies reported a period prevalence, not an incidence rate.

In adults, there is a high incidence of ICH in individuals with acute myelogenous leukemia (AML), especially acute promyelocytic leukemia, which is associated with coagulopathy.[7,8] A US study

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used the National Inpatient Sample dataset to determine the contributing factors of ICH in 10,972 adult patients with AML. Associated factors found were urinary tract infection, secondary thrombocytopenia, and acute renal failure.[7] Several studies show that hyperleukocytosis (white blood cell [WBC] $\geq$100,000/mm^3) and prolonged prothrombin time (PT) are associated with ICH in adults with AML.[9-11] Brain autopsy of patients with leukemia with hyperleukocytosis who had ICH shows blast cell accumulation (i.e., leukostasis) in cerebral small vessels.[12]

Data on the epidemiology, characteristics, and contributing factors of ICH in children with leukemia are limited. Acute lymphoblastic leukemia (ALL) is much more common than AML in children than in adults.[13,14] Associated factors of ICH found in adults may not play a significant role in the pathophysiology of ICH in children. In a study in children with AML, hyperleukocytosis (WBC $\geq$100,000/mm^3) was associated with early death.[15] Thrombocytopenia and coagulopathy did not show significant association.

The differences in trends of pediatric cancer between the United States and Thailand suggest variation of etiologies and diagnostics.[16] AML incidence in Thailand has increased from 1990 to 2011, whereas the incidence in the United States is stable. Overall five-year survival of those with acute childhood leukemia in a Thai cohort (43%) is lower than that reported in the United States (79%).

We analyzed data from nearly 500 Thai children with acute leukemia with statistical approaches not used in the previous studies i.e., incidence rate and survival analysis. Knowing the subpopulation that is at risk may help in finding secondary prevention of ICH.

Objectives

The aim of this study was to evaluate the clinical characteristics of patients with ICH and risk factors that might be associated with development of ICH in children with acute leukemia.

Study population

Leukemia case identification

We reviewed the database of the Pediatric Oncology Unit, Songklanagarind Hospital, Thailand. This hospital is a referral center for individuals with cancer in southern Thailand. Patients aged one month to 15 years diagnosed with acute leukemia between January 1, 2003, and December 31, 2016, were identified. This study was approved by the ethical committee of Faculty of Medicine, Prince of Songkla University. Acute leukemia was confirmed and categorized using French-American-British classification.[17] Only individuals with ALL and AML, which are the two most common acute childhood leukemias, were included in this study.

ICH ascertainment

Diagnosis of ICH was documented by brain imaging. Traumatic brain injuries and ICH related to brain surgery were excluded. Bleeding types (intraparenchymal, subarachnoid, subdural hemorrhage) and locations (lobar, basal ganglia, thalamus, brainstem, cerebellum) were interpreted by certified radiologists.

Operational definition

The date of leukemia diagnosis was defined as the date of documented diagnosis by pediatric oncologists in the medical record. Follow-up time was defined as the duration from date of leukemia diagnosis to the date of last follow-up or date of ICH occurrence. Early ICH was defined as the duration from the date of leukemia diagnosis to the date of ICH less than or equal to seven days. Time to death was the duration between the date of the ICH event and the death date. Hyperleukocytosis was defined as WBC $\geq$100,000/mm^3. Tumor lysis syndrome was defined using laboratory criteria of classification system by Cairo and Bishop.[18]

Statistical analyses

Analysis of incidence density rate of ICH

The incidence rate of ICH (per 1000 person-years) was estimated using the number of patients with ICH divided by the summation of duration of follow-up of all subjects in the study sample.

Descriptive analyses

Demographic data and clinical characteristics were compared between groups of patients with and without ICH. Chi-square test, Fisher's exact test, and rank sum test were performed depending on the data distribution.

Analysis of survival

Survival was summarized using Kaplan-Meier estimates. Median survival with 95% confidence intervals was provided for ICH occurrence. Survival was censored at the date of the last follow-up for all subjects who were still living. We compared survival rates between patients with ICH and without ICH using the log rank test.

Analysis of factors associated with ICH

Multiple logistic regression was used to determine factors associated with ICH. Variables that showed a P value < 0.2 in the bivariate analysis were adjusted in the multivariate analysis. All statistical analyses were performed using R program.[19] P value < 0.05 was considered statistically significant.

Results

Patient characteristics

There were 537 patients with acute leukemia during the study period. After we excluded patients with other underlying diseases and traumatic ICH, 494 patients (367 ALL, 127 AML) were included in the analysis. Median age at leukemia diagnosis was approximately 4.9 years with ratio of male to female being 3:2 (Table 1). The most common subtypes of ALL and AML were L2 and M5, respectively. About one-fifth of the patients presented with hyperleukocytosis (WBC $\geq$100,000/mm^3). The median follow-up time of the study population was 2.1 (interquartile range 0.4-3.3) years. Half of the patients died within study period. Applying a survival analysis, the median survival of our study population was 3.7 (95% confidence interval [CI]: 2.9-6.5) years.

Characteristics of patients with ICH

Of the 494 patients with leukemia, 12 patients developed spontaneous ICH. The incidence density rate was calculated using data from 10 patients with ICH because two patients developed ICH a few days before the leukemia diagnosis. Our study included 1618 person-years of observation. The incidence density rate of ICH was 6.2 per 1000 person-years (ALL 5.1, AML 12.9 per 1000 person-years). Table 1 shows bivariate analysis comparing clinical features between patients with and without ICH. Age of patients with ICH was 12.5 years, which was greater than that of patients who did not have ICH. Initial WBC count, percent of peripheral blast cells, and level of lactate dehydrogenase (LDH) in patients with ICH were significantly greater than in patients without ICH. Although

TABLE 1.
Characteristics of Patients by ICH

Characteristics	All Patients N = 494	ICH N = 12	Non-ICH N = 482	*P*
Age (y), median (IQR)	4.9 (3.0-9.2)	12.5 (7.5-13.3)	4.8 (2.9-9.2)	<0.01
Male	290 (58.7)	7 (58.3)	283 (58.7)	1
ALL (n = 367)				0.39
L1	61 (16.6)	2 (25.0)	59 (16.4)	
L2	282 (76.8)	5 (62.5)	277 (76.9)	
L3	25 (6.8)	1 (12.5)	24 (6.7)	
AML (n = 127)				0.80
M1	8 (6.3)	0 (0)	8 (6.5)	
M2	4 (3.1)	0 (0)	4 (3.3)	
M3	2 (1.6)	0 (0)	2 (1.6)	
M4	17 (13.4)	1 (25.0)	16 (13.0)	
M5	46 (36.2)	1 (25.0)	45 (36.6)	
M6	4 (3.1)	0 (0)	4 (3.3)	
M7	14 (11.0)	0 (0)	14 (11.4)	
Unknown	32 (25.2)	2 (50.0)	30 (24.4)	
Clinical bleeding				
Skin bleeding	289 (58.5)	5 (41.7)	284 (58.9)	0.25
Gum bleeding	79 (16.0)	3 (25.0)	76 (15.8)	0.42
Initial laboratory				
Hct, mean (S.D.)	22.3 (7.07)	23.3 (5.2)	22.3 (7.1)	0.63
Hb, median (IQR)	7.2 (5.6-9.1)	7.7 (6.4-8.5)	7.2 (5.6-9.1)	0.53
WBC, median (IQR)	19,350 (6,302-82,105)	374,925 (17,810-480,530)	19,145 (6,255-77,910)	0.02
WBC ≥100,000	107 (21.7)	7 (58.3)	100 (20.7)	0.01
Platelet × 1000, median (IQR)	39 (19-84)	65 (51-82)	38 (18.3-84)	0.13
Platelet < 35,000	231 (46.8)	2 (16.7)	229 (47.5)	0.07
LDH, median (IQR)	1140 (653-2,711)	4140 (2,413-11,799)	1113 (648-2,543)	<0.01
Tumor lysis syndrome	97 (19.6)	4 (33.3)	93 (19.3)	0.26
Blast (%), median (IQR)	53 (15.3-85.0)	96.0 (30.8-97.0)	51.5 (15.0-84.8)	0.01
Death	249 (50.4)	9 (75.0)	240 (49.8)	0.15

Abbreviations:
AML = Acute myelogenous leukemia
Hb = Hemoglobin
Hct = Hematocrit
IQR = Interquartile range
LDH = Lactate dehydrogenase
WBC = white blood cell

the proportions of gum bleeding and tumor lysis syndrome were higher in the ICH group, the differences were not statistically significant.

ICH features

Twelve ICH cases were documented by brain imaging. Types and locations of ICH are shown in Table 2. Most patients (11 of 12) had multiple bleeding sites. Hematomas were commonly intraparenchymal at the gray-white junction of cerebral hemispheres (lobar ICH). Another prominent finding was severe cerebral edema, which led to rapid brain herniation in eight of 12 cases. Deep gray nuclei bleeding was observed in three cases, one of which was related to invasive aspergillosis. Regarding cancer treatment, ICH happened before receiving chemotherapy in four patients. Most of the treated cases developed ICH during the induction period.

Table 2 demonstrates the clinical characteristics of the 12 individual patients with ICH. ICH occurred at a median of 18 (interquartile range 3.8 to 177.8) days after the diagnosis of leukemia, and about 40% presented within seven days (early ICH). Two patients had ICH before the leukemia diagnosis, and one had leukemia and ICH diagnosed on the same day. Nine of the 12 patients with ICH died within the study period, and seven of them died within 30 days of the ICH event.

Survival analysis (Fig 1) shows shorter survival in the ICH group, with a median survival time of 24 days (95% CI: cannot be calculated due to small sample size) after diagnosis compared with 4.0 (95% CI: 3.1-6.5) years in the non-ICH group. The probability of death in patients with ICH was about three times higher than that of the non-ICH group (hazard ratio [HR]: 3.17, 95% CI: 1.63-6.19, *P*-value < 0.01).

Figure 2 and Table 3 compare the potential contributing factors of ICH by timing. Figure 2 illustrates that patients with early ICH (within seven days after leukemia diagnosis) had higher WBC, LDH, and percent of blast cells than those in the late ICH group, although this was not statistically significant. Age, tumor lysis syndrome, and platelet count at diagnosis are similar between early and late ICH groups.

A statistically significant difference was noted in two factors (i.e., septicemia and international normalized ratio [INR]) during the ICH event. Most patients with late ICH had concurrent bacteremia or systemic aspergillosis, whereas no patient with early ICH had a documented organism. The INR of patients with early ICH was greater than that of patients in the late ICH group. Eighty percent of early ICH cases had prolonged PT (INR greater than 1.5), whereas the late ICH cases had normal INR during the ICH event. Platelet count during ICH showed no difference. Among all patients with ICH, there was only one patient with platelet count less than 20,000/mm^3.

Clinical characteristics associated with ICH

Potential contributing factors at the leukemia diagnosis were analyzed by multivariate analysis (Table 4). Multiple logistic regression shows that age, initial WBC, and LDH were associated with higher risk of ICH. Gender, types of leukemia, initial platelet count, percent of blast cells, and tumor lysis syndrome showed no association.

TABLE 2.
Clinical Characteristics of Individuals With ICH (Sorted by Time to Event)

ID	Sex	Dx Age (y)	Type	Time to Event (d)	Chemo	Initial Labs		WBC	Immediate Findings Before or During ICH				ICH Site(s)	Time to Death (d)
						WBC	Platelet		Platelet	PTT	INR	Bacteremia		
1	Male	14.6	ALL (L3)	−3	Never	800,000	90,000	800,000 (N 3)	61,000	38	2	NG	Bilat-F-P, Rt. thalamus, pons, H	0
2	Male	7.3	AML (unknown)	−1	Never	2210	39,000	2210 (N 26)	39,000	35	1.6	NG	Rt. F, Rt. BGG, IVH, H	16
3	Male	12.1	ALL (L1)	0	Never	758,810	86,000	758,810 (N1)	68,000	40	2.5	NG	Bilat-F, Lt cerebellum, H	10
4	Male	8.8	AML (M4)	5	Induct	475,380	79,000	635,240 (N 2)	54,000	70	2.7	NG	Bilat-F-P, Rt T	6
5	Female	14.8	ALL (L1)	6	Induct	495,980	64,000	4480 (N 50)	35,000	20	1	*Acinetobacter* spp.	Lt. T-P, IVH, H	23
6	Female	7.5	ALL (L2)	18	Induct	20,680	65,000	770 (TLTD)	82,000	34	1.2	*Aeromonas* spp.	Rt. F-P, Rt SDH	25
7	Male	13.2	AML (unknown)	18	Never	9200	81,000	21,300 (N 0)	40,000	36	1.48	NG (severe sepsis)	Rt. P, SDH, H	18
8	Female	13.1	ALL (L2)	31	Induct	21,040	279,000	340 (TLTD)	131,000	31	0.9	*Pseudomonas* spp.	Rt. F-P, Lt. midbrain	NA*
9	Male	12.9	ALL (L2)	102	Consolidate	396,890	55,000	2300 (N38.7)	ND	ND	ND	NG (pulmonary aspergilloma)	Diffuse microhemorrhage bilat hemispheres	262
10	Female	13.8	AML (M5)	405	Complete	406,100	66,000	236,450 (N 1)	16,000	23	1	Enterobacter	Rt. T-O, H	432
11	Female	2.6	ALL (L2)	455	Induct	352,960	25,000	24,350 (N 60)	45,000	29	1.1	*Klebsiella* spp. Pulmonary aspergillosis	Rt F-P-O/cingulate, SAH, H	NA*
12	Male	2.3	ALL (L2)	4791	Complete	2,600	13,000	3490 (N 60)	234,000	31	1.3	NG (pulmonary aspergillosis)	Lt. thalamus/midbrain/ cerebellum, Rt. F-P, IVH, H	NA*

Abbreviations:
BGG = Basal ganglia
Bilat = Bilateral
F = Frontal
H = Herniation
ICH = Intracerebral hemorrhage
INR = International normalized ratio
IVH = Intraventricular hemorrhage
Lt. = Left
N = Neutrophil
ND = Not done
NG = No growth
O = Occipital
P = Parietal
PTT = Partial thromboplastin time
Rt. = Right
SAH = Subarachnoid hemorrhage
SDH = Subdural hemorrhage
T = Temporal
TLTD = Too low to differentiate
* Survived

Discussion

The incidence of ICH in our patients was much higher than that in the general pediatric population. Most bleeding was multifocal and intraparenchymal. The mortality rate of ICH was high, and most patients with ICH died within a short period. Older age, high initial WBC count, and LDH level were associated with an increased risk of ICH.

The most important observation from our study is that there appears to be a bimodal pattern of ICH incidence (early and late ICH) in pediatric patients with leukemia, and we identified the potential contributing factors for the ICH, which differed by ICH timing. More details of these apparent associations are provided below.

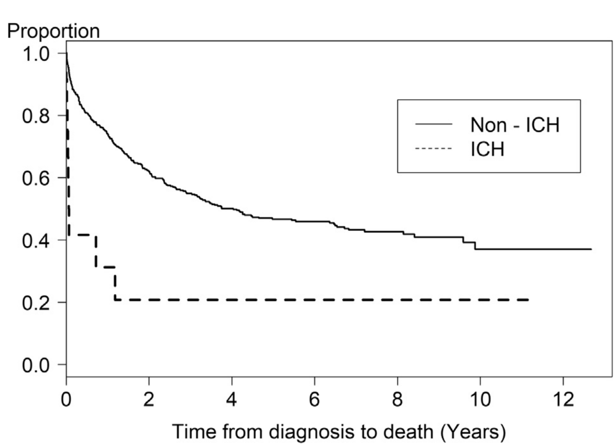

FIGURE 1. Survivals of patients with acute leukemia by ICH.

Epidemiology of ICH

The incidence density rate of ICH at 6.2 per 1000 person-years in our study was much higher than that in other pediatric populations, for which it is 1 to 3 per 100,000 person-years.[1,20] We chose to report the incidence density rate instead of prevalence because the time at risk of each patient varied. Thus, we could not compare our incidence rate with those of previous studies, which reported prevalence.[2,6] Similar to previous reports, we found a higher incidence of ICH in patients with AML compared with those with ALL.[15] AML has been known for higher risk for ICH in adult studies, especially in acute promyelocytic leukemia (M3 subtype), which is associated with coagulopathy.[7,21,22] However, less than 2%

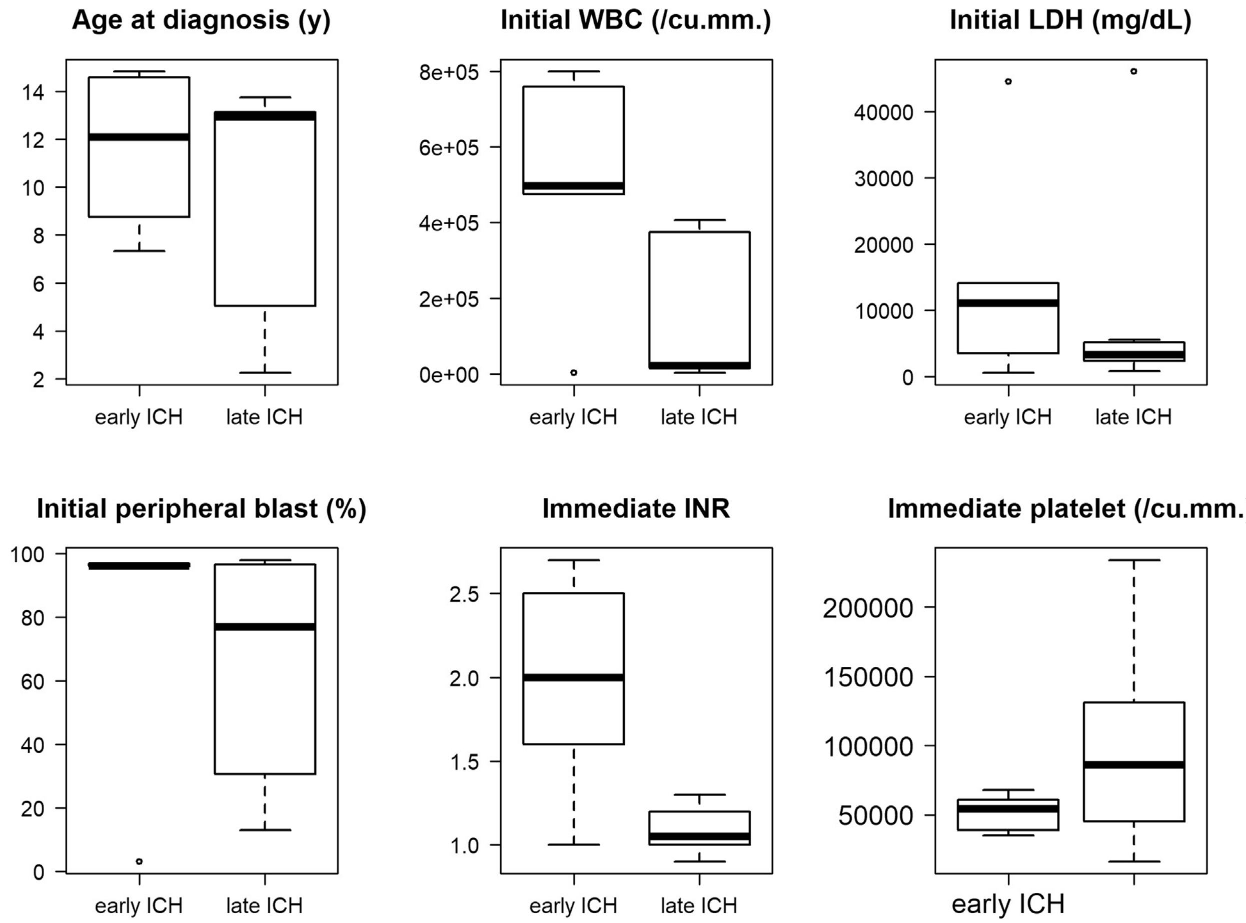

FIGURE 2. Box and whisker plots compare continuous variables by timing of ICH.

of our patients had acute promyelocytic leukemia, and none of them had ICH.

Features of ICH

In our study, all cases of early ICH with an INR greater than 1.5 had large multifocal intraparenchymal hematomas and severe perihematomal edema. However, brain imaging in patients with late ICH shows various findings. Imaging of ICH in adults with AML illustrates multifocal distribution in about 40%, and the locations are at supratentorium, basal ganglion, and cerebellum in 80%, 17%, and 10%, respectively.[10] The intraparenchymal location and the large volume of hematoma suggest the impact of coagulation defect rather than thrombocytopenia.[23]

High case fatality rate of ICH

Our study confirmed that hemorrhagic stroke in patients with acute leukemia was highly fatal, especially if ICH presented early. The mortality rate of pediatric stroke from various causes varied from 7% to 52%,[1,20,24-27] whereas our study showed a 75% fatality rate. The case fatality rate was 100% in our patients with early ICH. Multifocal and bilateral hemispheric hematomas suggest a systemic pathology in nature. Extensive involvement and expanding lesions due to coagulopathy may make ICH in patients with leukemia more severe than a localized bleeding found in vascular anomalies, which are the most common causes of pediatric stroke.

Potential contributors of ICH in childhood acute leukemia

Factors associated with an increased risk of ICH were older age, higher initial WBC count, and higher LDH level. These three factors are associated with a worse prognosis for individuals with childhood leukemia.[28] However, the exact mechanism by which these factors might contribute to higher risk of ICH is unclear. ICH may be related to cancer treatment itself,[5] but almost 40% of patients had ICH before initiation of chemotherapy.

We noticed the bimodal timing of ICH occurrence and explored whether the contributors were different between early and late ICH. We observed that the contributing factor of early ICH appears to be leukostasis related with abnormal hemostasis, whereas in late ICH systemic inflammation might play a key role.

Early ICH: hyperleukocytosis and coagulopathy

Hyperleukocytosis has been associated with ICH and mortality in several adult studies.[9-11] Our findings are consistent with a previous study by Wald et al.,[15] who showed that patients who experienced an early death died from ICH and had hyperleukocytosis. From our bivariate analysis, prolonged INR and initial WBC count were significantly higher in the early ICH group. Four of

TABLE 3.
Comparison Between Early ICH (Within Seven Days After Leukemia Diagnosis) and Late ICH (Later Than Seven Days)

Characteristics	All (n = 12)	Early ICH (n = 5)	Late ICH (n = 7)	*P*
Age mean (S.D.)	10.2 (4.5)	11.5 (3.4)	9.3 (5.2)	0.43
Age at diagnosis				0.18
≤ 5 y	2 (16.7)	0 (0)	2 (28.6)	
6-10 y	3 (25.0)	2 (40)	1 (14.3)	
11-14 y	5 (41.7)	1 (20)	4 (57.1)	
>14 y	2 (16.7)	2 (40)	0 (0)	
Male	7 (58.3)	4 (80)	3 (42.9)	0.29
Types				1
ALL	8 (66.7)	3 (60)	5 (71.4)	
AML	4 (33.3)	2 (40)	2 (28.6)	
At diagnosis (initial lab)				
WBC median (IQR)	374,925 (17,810-480,530)	495,980 (475,380-758,810)	21,040 (14,940-374,925)	0.09
Hyperleukocytosis (WBC >100,000)	7 (58.3)	4 (80)	3 (42.9)	0.29
Blast median (IQR)	96 (31-97)	96 (96-97)	64 (31-96)	0.60
LDH median (IQR)	4140 (2412-11,799)	11,039 (3550-14,080)	3270 (2375-5170)	0.52
Tumor lysis syndrome	4 (33.3)	1 (20)	3 (42.9)	0.58
Platelet median (IQR)	65,500 (51,000-82,250)	79,000 (64,000-86,000)	65,000 (40,000-73,500)	0.52
Platelet ≤35,000	2 (16.7)	0	2 (28.6)	0.47
Platelet ≤20,000	1 (8.3)	0	1 (14.3)	1
During ICH (immediate lab)				
Septicemia	7 (58.3)	0	7 (87.5)	<0.01
Platelet median (IQR)	61,000 (42,000-86,000)	54,000 (39,000-61,000)	86,000 (54,250-120,750)	0.24
INR median (IQR)	1.2 (1-1.8)	2 (1.6-2.5)	1.1 (1-1.2)	0.05

Abbreviations:
ALL = Acute lymphoblastic leukemia
AML = Acute myelogenous leukemia
INR = International normalized ratio
IQR = Interquartile range
LDH = Lactate dehydrogenase
WBC = White blood cell

five patients with early ICH had initial WBC greater than 450,000/mm^3 while all of them had platelet count greater than 35,000/mm^3. Leukocytosis and coagulopathy are also associated factors with ICH in adult patients with acute leukemia.[29] We conclude that leukostasis played the main role for the early ICH cases.

Leukemic infiltration of the brain tissue has been confirmed by autopsies of patients with hyperleukocytosis and ICH.[15] Leukostasis (also called symptomatic hyperleukocytosis) is a pathologic diagnosis when WBCs accumulate in microcirculation.[12] Clinically, it is characterized by highly elevated blast cells with symptoms of reduced tissue perfusion, e.g., respiratory distress or neurological disturbances. The occurrence of ICH during blastic hyperleukocytosis was previously reported in two children with acute leukemia. This report demonstrated multifocal T2-hyperintense MRI lesions in bilateral white matter. Brain biopsy of one patient revealed petechial hemorrhages and macrophagic cellular infiltration in the white matter.[30]

AML has more frequent leukostasis than ALL owing to the larger and lesser deformable blasts compared with lymphoblasts. Besides the overcrowded blasts in the capillaries, cytokine release induces direct endothelial cell damage of blood vessels.[31] Expression of specific adhesion molecules may be more important than the number of blasts to determine the occurrence of leukostasis,[32] so leukostasis might occur in patients without hyperleukocytosis. In our patients with early ICH, all but one had hyperleukocytosis. We found a significant association between hyperleukocytosis and early ICH, but we could not confirm leukostasis by pathologic evidence.

TABLE 4.
Factors at Diagnosis Associated With ICH

Characteristics	Crude OR	95% CI	Adjusted OR	95% CI	*P* (LR)
Age (y)	1.26	1.09-1.45	1.19	1.02-1.40	0.02
Female	1.01	0.32-3.23	1.07	0.29-3.99	0.92
AML (ref = ALL)	1.46	0.43-4.93	2.45	0.53-11.38	0.26
Initial laboratory					
WBC (×1000/mm^3)	1.0042	1.0022-1.0061	1.0049	1.002-1.0077	0.001
Platelet (×1000/mm^3)	1.0005	0.9952-1.0058	1.0025	0.9969-1.0081	0.45
Blast cells (%)	1.0187	0.9991-1.0386	0.9929	0.9679-1.0185	0.58
LDH (×100 U/L)	1.0084	1.0041-1.0128	1.0077	1.0021-1.0133	0.01
Tumor lysis syndrome	2.13	0.63-7.21	0.86	0.18-4.16	0.55

Abbreviations:
ALL = Acute lymphoblastic leukemia
AML = Acute myelogenous leukemia
CI = Confidence interval
LDH = Lactate dehydrogenase
OR = Odds ratio
P (LR) = *P*-value by likelihood ratio test
WBC = White blood cell

Patients with leukemia may have prolonged partial thromboplastin time (PTT) from disseminated intravascular coagulation (DIC) and hyperfibrinolysis.[33] However, our study found that prolonged INR contributed to early ICH, but prolonged PTT did not. A similar finding is seen in a study in adult patients with leukemia. Patients with ALL had significantly longer PT, but similar PTT compared with normal controls.[34] It is unclear what underlies this discrepancy of hemostatic parameters. Coagulopathy may present at the diagnosis of acute leukemia. A study reported coagulopathy for 14% and 3% in children with ALL and AML before treatment.[35] By and large, the mechanism of coagulopathy in pretreated acute leukemia is not well understood. The only well-known leukemia subtype that is associated with coagulopathy is acute promyelocytic leukemia.[8]

Late ICH: systemic inflammation

Seven of eight patients with late ICH had concurrent bacteremia or pulmonary aspergillosis. Although another one with late ICH did not have a positive hemoculture, that patient had clinical severe sepsis documented by the physician. Infection can induce consumptive coagulopathy through a systemic inflammatory response. However, our patients had normal PTT during the event, so DIC was unlikely. We postulated that bleeding in late ICH was an inflammatory bleeding. Systemic infection increased permeability of vessels including intracranial vessels.[36] Thrombocytopenic mice showed organ bleeding only when the organ was inflamed, not in normal condition. The inflammatory bleeding recovered easily after platelet replacement, and the author concluded that platelets helped maintain vascular integrity during the inflammation.[37]

Thrombocytopenia played little role in ICH.[15] We found only one patient with hemorrhage with a platelet count less than $20,000/mm^3$ at the time of the stroke. Our findings confirmed that additional factors are required to provoke bleeding in thrombocytopenic patients. Merely having severe thrombocytopenia was insufficient to cause stroke.

Limitations

First, our incidence rates might be underestimated. This study was hospital-based, so survivorship bias was possible. As ICH was highly fatal, patients with ICH might die before getting a diagnosis of acute leukemia.

Second, the multivariate analysis should be interpreted with some caution. We had access to only baseline clinical characteristics of the patients, but the baseline characteristics might be of little value to predict ICH that occurs late. Some laboratory investigations (e.g., coagulogram and hemoculture) were performed when clinically indicated. Other than baseline, though, we could not select a proper time point for the non-ICH group to compare with the ICH group in our multivariate analysis. However, we discovered some important findings when we analyzed among the ICH cases by timing of the occurrence.

Strengths

Owing to the scarcity of data about ICH in childhood acute leukemia, our study adds important information and addresses several knowledge gaps. We applied statistical approaches to estimate the incidence and survival of ICH. The subgroup analysis among the ICH cases helped us define two separate groups (early versus late) and discover new contributing factors of ICH. This study also addressed the association of systemic infection and ICH for the first time.

Recommendations

Several trials to prevent early ICH in patients with hyperleukocytosis have been conducted, with little evidence of efficacy.[38,39] Owing to the narrow therapeutic window for treatment in early ICH, we suggest increasing our attention on the secondary prevention of late ICH. Unresolved questions are why bacteremia without DIC was associated with ICH and whether we should correct hemostatic parameters more aggressively when patients with leukemia have systemic infection. More research on the effects of systemic infection on the intracranial bleeding should be done in the future.

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