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Clinical features and survival pattern of central nervous system leukemia in children with acute lymphoblastic leukemia

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ABSTRACT. Infiltration of leukemic cells into the central nervous system (CNS) is one of the causes of neurological disorders in patients with acute lymphoblastic leukemia (ALL) that worsen the prognosis. This retrospective cohort study aimed to review the clinical manifestations of children with CNS leukemia, their survival pattern and the role of early CNS leukemial. The survival curve was developed by Kaplan-Meier method, while the comparison of survival curves was done with log-rank test. Among 128 new ALL patients, 23 (18.0%) patients suffered from CNS leukemia, while 13 (10.2%) suffered from early CNS leukemia and 10 (7.8%) suffered from relapsing CNS leukemia. CNS leukemia was more common in male, in those aged less than 2 years, in those with white blood cell (WBC) count above 50,000/µl, and in patients type FAB-L2 ALL. The clinical manifestations most commonly found were decrease of consciousness (61%), vomiting (48%), cranial nerve palsy (44%), seizures (39%), and headache (26%). Relapsing CNS leukemia was more common in high risk (12.5%) compared with standard risk leukemia (5.7%). Patients with early CNS leukemia had a lower survival rate than those without early CNS leukemia ($p = 0.0005$). The percentage of patients with early CNS leukemia surviving up to 3 years was 26%. We conclude that early CNS leukemia could cause low survival ALL patients. **[Paediatr Indones 2001; 41:247-252]**

***Keywords**: acute lymphoblastic leukemia, survival analysis, central nervous system, children*

NEUROLOGICAL DISORDERS IN LEUKEMIA CAN BE CAUSED BY infiltration of leukemic cells into central nervous system (CNS), CNS hemorrhage, CNS infection, toxic effects of chemotherapy, or adverse effects of radiation.[1,2] Infiltration of leukemic cells into nervous system could cause central and peripheral nervous system disorders, which may worsen the prognosis.[1,3] Early CNS leukemia occurs in 8% of patients at the time of the first diagnosis[4] while the percentage of relapsing CNS leukemia is 10%.[5] The 5 year survival of ALL patients was 71.0%[6] similar to the 4 year survival of 73.0%.[4] Report from Jakarta[7] shows that among 30 patients with ALL, 16 patients survive 5 years or more (53%), a figure lower than that of other series.[4,6]

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The prognostic factors that could influence the ALL patient's survival include age, sex, leukocyte and platelet count, hemoglobin level, the presence of organomegaly, infiltration to mediastinum, CNS leukemia, type of ALL, remission time, race, immunophenotype, chromosome abnormalities, and level of serum immunoglobulin.[8-11]

This retrospective cohort study aimed to find out the clinical and laboratory characteristics of pediatric patients with CNS leukemia, their survival pattern, and the correlation of early CNS leukemia and survival of patients with ALL treated at Cipto Mangunkusumo (CM) hospital.

Methods

This was a retrospective cohort study carried out at the Department of Child Health Faculty of Medicine

University of Indonesia-CM Hospital, starting from November 2000 to February 2001. During the 5 year period beginning in July 1st 1995 until June 30th 2001 there were 128 new ALL patients who fulfilled the study criteria. We included all ALL patients aged ≤ 18 years at the time of diagnosis and treated with the same protocol, but excluded patients who did not develop remission, those who received therapy outside the protocol, those who had their diagnosis changed to acute mieloblastic leukemia (AML), those whose diagnosis was not based on bone marrow aspiration, or those who had not their cerebrospinal fluid (CSF) examined.

CNS leukemia was diagnosed on the basis of the presence of CNS disorder with or without pathological cells in the CSF, or the presence of pathological cells in the CSF with or without CNS neurological disorders. The pathological cells in CSF (a positive CSF concentration test), was characterized by increased of mononuclear cells over 10/μl, and particularly when the number CSF pathological cells was more than 5/μl.[5,9] Early CNS leukemia was diagnosed if leukemic cells in CNS were found at the time of the diagnosis of leukemia, while relapsing CNS leukemia was diagnosed if leukemic cells in CNS were found in remission period.[12] Meningeal leukemia was defined as the presence of positive CSF concentration test, whereas cerebral leukemia refers to the presence of neurological disorders with a negative CSF concentration test. Remission was defined as the absence of signs and symptoms of the disease with normal peripheral blood pictures. Early remission was defined when the remission was reached within ≤ 4 weeks after the beginning of induction therapy. Late remission was a remission that was reached more than 4 weeks after the beginning of induction therapy.[9] Relapse was considered if there were obvious reoccurrence of clinical manifestations of leukemia, either indicated by peripheral blood and bone marrow examinations or from the other organ (extramedullar) examinations.[9] With high risk leukemia we meant leukemia with any of the following: leukocytes count of more than 50,000/μl, CNS infiltration, mediastinum infiltration, or type L3 ALL.[13]

The therapeutic regimen consisted of a combination of cytostatic vincristine 1.5 mg/m^2 TBS (total body surface)/week (IV, 6 times), dexamethasone 4 mg/m^2 TBS/day (PO), L-asparaginase 6,000 U/m^2 TBS 3 times /week (IV, 9 times), and daunorubicin 30 mg/m^2 TBS/week (IV, 4 times) as induction and 6-mercaptopurine 50 mg/m^2 TBS/day (PO) and MTX 30 mg/m^2 TBS/week (PO) as a maintenance. Prevention for CNS leukemia was carried out by a combination of metothrexate, dexamethasone, and Ara-C intratecally. For patients older than 2 years, cranial radiation of 1800 rad was given, and for patients younger than 2 years MTX 500 mg/m^2 TBS/week (IV, 4 times) was administered.

Survival analysis was performed by Kaplan-Meier method. A patients was labeled as censored if he or she was still alive at the time of the study, or could not be followed up (drop out or loss to follow up). Hypothesis test to determine survival differences was done by log-rank test.[14] Multivariate analysis by Cox regression model was carried out in order to find out the independent significant prognostic factor.[15] The significance value was predetermined at $p<0.05$; 95% confidence interval was supplied. We used computer programme SPSS release 7.0 for data management and analysis.[14,15]

Results

Out of 128 ALL patients, 23 (18%) had CNS leukemia, 1 patient with purulent meningitis, and 4 (3%) patients with CNS hemorrhage. Patient with purulent meningitis also suffered from CNS leukemia.

The characteristics of CNS leukemic patients

Table 1 shows that the incidence of CNS leukemia was more often in male (25%), with group of age below 2 years (21), leukocyte count more than 50,000/μl (33%), and in type L2 ALL (27%).

TABLE 1. CNS LEUKEMIA PATIENTS DISTRIBUTION BASED ON SEX, AGE, LEUKOCYTE COUNT, AND TYPE OF LLA

Characteristic	Number	
	LLA	CNS leukemia
Sex		
Male	81	20
Female	47	3
Age (yr)		
< 2	14	3
2 – 10	102	19
> 10	12	1
Leukocyte count (/μl)		
< 10.000	63	9
10.000 – 50.000	41	6
> 50.000	24	8
ALL type		
L1	101	17
L2	15	4
L3	12	2

Out of the 23 patients with CNS leukemia, decrease of consciousness was the most frequently found (14 patients), followed by vomiting, cranial nerve palsy, and seizures, which were found in 11, 10, and 9 patients, respectively.

Among 23 CNS leukemic patients, 17 patients showed meningeal leukemia (positive CSF concentration test) and 6 showed cerebral leukemia (negative CSF concentration test). CT scan examination was done in 4 patients, and MRI in 1 patient. CT scan demonstrated abnormal results in 4 patients, i.e., a pineal body tumor, atrophy and hygroma, mild atrophy. Patient who underwent MRI examination showed normal result. Among 128 ALL patients, 13 showed early CNS leukemia (8 of them died) and 10 with relapsing CNS leukemia (5 of them died). The causes of death in patients with CNS leukemia were CNS leukemia itself (8 patients), gastrointestinal tract hemorrhage (2 patients), sepsis (2 patients), and purulent meningitis (1 patient).

Table 2 shows that the percentage of relapsing CNS leukemia in high risk ALL patients (12.5%) was much more than in standard risk ALL patients (5.7%).

TABLE 2. RELAPSE CNS LEUKEMIA DISTRIBUTION BASED ON HIGH AND STANDARD RISK FACTORS

Risk factor	Number of LLA	Number of relapse CNS leukemia	%
Standard risk	88	5	5.7
High risk	40	5	12.5

Correlation between clinical characteristics, laboratory examinations, and survival

Survival analyses based on various clinical and laboratory findings were analyzed by Kaplan-Meier method and also log-rank test. It shows that on univariate analysis, out of several factors analyzed (early CNS leukemia, remission rate, sex, age group, hepatomegly, splenomegaly, and lymphadenopathy) prognostic factors that related significantly to survival were early CNS leukemia and splenomegaly. On multivariate analysis using Cox regression model in order to find out the independent significant prognostic factors, both early CNS leukemia ($p=0.0005$) and splenomegaly ($p=0.507$) had a significant correlation with survival (data not shown).

Separate survival curves were constructed based on the presence of mediastinal infiltration, hemoglobin level, leukocyte count, platelet count, and type of ALL (types I, II, III). No laboratory value was proven to be significantly associated with survival.

Survival pattern of CNS leukemic patients

Figure 1 shows the cumulative 5 year-survival in ALL patients (1822 days), i.e., 42.5%. Figure 2 shows a significant survival difference between patients with and without early CNS leukemia ($p < 0.0001$). The 3 year survival of ALL patients with early CNS leukemia (1049 days) was 25.9% while 5 year survival rate of ALL patients without early CNS leukemia (1822 days) was 47.0%. The longest survival time of patients with early CNS leukemia was 1050 days. In Figure 3, we could see that the 4 year survival of ALL patients suffering from CNS relapse leukemia (1346 days) was 36.0%. The 5 year survival of ALL patients without early and CNS relapse leukemia (1822 days) was 51.3%.

Discussion

Limitation of this study

As in all retrospective studies, this study implies certain biases, especially information bias, because the analysis relied on the completeness of data on medical record. Besides, some of the diagnosis of CNS leukemia, CNS hemorrhage and infection were hard to determine as a consequence of the lack of supporting data. As a consequence, not all prognostic factors affecting survival could be analyzed.

ALL patients distribution based on CNS leukemia

Our findings on the prevalence of CNS leukemia, early CNS leukemia, and relapsing CNS leukemia are not quite different from the previous studies reporting 5-8% patients with early CNS leukemia and 5-10% patients with were relapsing CNS leukemia.[1,4,13] In this study, the percentage of early CNS and CNS relapse leukemia were lower than the outcome from Markum et al. revealing 15.5% early CNS leukemia and 25.5% relapse CNS from 55 patients in remission. The difference could be due to the differences in management and some of the patients late for

treatment

The characteristics of CNS leukemia

Our study showed that the CNS leukemia distribution was most frequently found in less than 2 years of age and in leukocyte count over 50,000/µl. This result was consistent with the previous study that the CNS leukemia was mostly found in the age group less than 2 years old and in a child having high leukocyte count.[9,16]

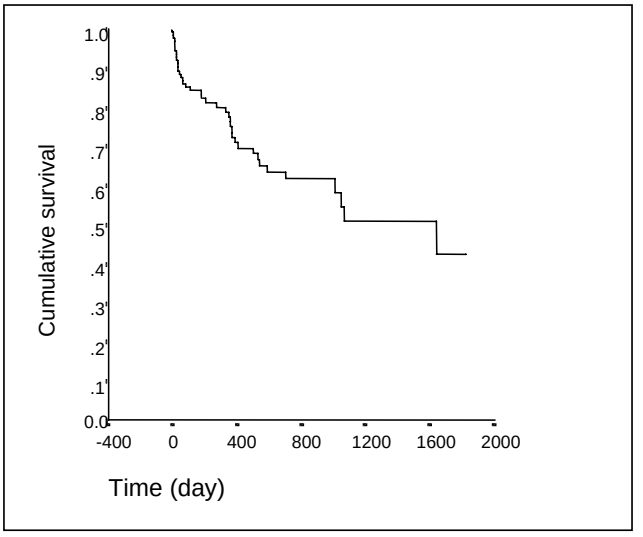

Figure 1. Survival curve of ALL patients

The most frequently found neurological disorders in CNS leukemia were decrease of consciousness, vomiting, cranial nerves palsy, seizures, and headache. In the previous studies, the symptoms of increased intracranial pressure, such as vomiting, headache, lethargy, were the most frequent symptoms, while cranial nerves palsy, convulsion, and nuchal rigidity were rare to be found.[17,18] The differences in this study could be the result of incompleted history, from which more obvious symptoms and signs, such as decrease of consciousness, seizures, and cranial nerves palsy, could be easily known.

The percentage of patients with meningeal leukemia in our study was higher than those with cerebral leukemia. This result was in favor with a previous study.[16] Result of CT scan and MRI examination in 5 patients with CNS leukemia demonstrated that there were 2 patients with a normal result and 3 other patients not showing a typical image of CNS leukemia. This result was consistent with the literature explaining that the infiltration of leukemic cells into CNS was rarely detected by CT scan.[1,19] Postmortem biopsy examination could determine the presence of leukemic cell infiltration into CNS.[20]

Our series shows that the percentage of relapsing CNS leukemia was higher in high risk ALL patients than in standard risk ALL patients. The same result was also found in the previous study showing that relapsing CNS leukemia was more frequently found in the high risk ALL patients (8.2%) than in standard risks ALL patients (2.5%).[12]

The percentage of mortality in those patients with early CNS leukemia was higher than in relapsing CNS relapse leukemia. In this study, the mortality of CNS leukemia was mostly due to the CNS leukemia itself. This observation was consistent with the literature explaining that CNS leukemia has a bad prognosis, where once leukemic cells infiltrate the CNS, their hidden presence cannot be reached by chemotherapy either orally or parenterally.[5,21,22]

Correlation between early CNS leukemia and survival

Among all prognostic factors analyzed, only early CNS leukemia had a significant correlation with survival. This result was consistent with the previous study reporting that there was a significant correlation between early CNS leukemia and survival, so it means that early CNS leukemia had a bad prognosis.[11] However, Rivera et al.[4] did not find a significant

Figure 2. Survival curve of patient with and without early CNS leukemia

correlation between early CNS leukemia and survival. Prognostic factors affecting survival in the previous study were more than in this study. This could be as a result of limitation, where not all of prognostic factors, such as race, immunoglobulin, chromosome abnormalities, and immunophenotype could be analyzed in this study.

Survival patterns of ALL and CNS leukemia patients

The 5-year survival of ALL patients in this study was 42.5%. Chessells et al.[6] found that the 5-year survival of ALL patients was 71.0%, whereas Rivera et al.[4] reported the 4 year survival of ALL patients was 73.0%. The survival we found in this study was lower than that of Chessells and Rivera. This difference was due to the number of early CNS leukemia in this study was much more than Rivera study and the prognostic factors of early CNS leukemia affected the survival of ALL patients. Multivariate analysis in Rivera's study against prognostic factors resulted a not significant association between early CNS leukemia and survival. The 3 year survival of early CNS leukemic patients (25.9%) was lower than 4 year survival in the Rivera study4 (54.0%).

Moreover, Pollock et al.[23] observed that colored patients had a worse survival than white patients. This could be as a result in the worse response of therapy in colored skin, due to high dihydrofolate reductase level.[23,24] Oakhill et al.[24] found that ALL prognosis in Asian children living in The United Kingdom was worse than that in white children. This result could be caused by a low socioeconomic status and nutrition, and also by a complicated communication between the patient family and the doctors while carrying out the treatment.

Those factors mentioned above might result in the low survival rate of ALL patients in CM Hospital, because the population in this study was colored skin race living in developing country, and most of them were in the low socioeconomic status. Besides all of those factors, there were other factors that might cause the low survival of ALL patients in CM hospital, such as race, chromosome abnormalities, immunophenotype, and immunoglobulin level, which were not examined in this study due to the lack of facilities.

In conclusion, we found that early CNS leukemia was proven to cause low survival of ALL patients in CM hospital. Futher study should be carried out with a more complete supporting examination data in a prospective study in order to get a more accurate results. The study should include other prognostic factors affecting survival, such as race, chromosome abnormalities, immunophenotype, immunoglobulin level, parent education degree, economic status, and nutrition status, which were not yet analyzed in this study.

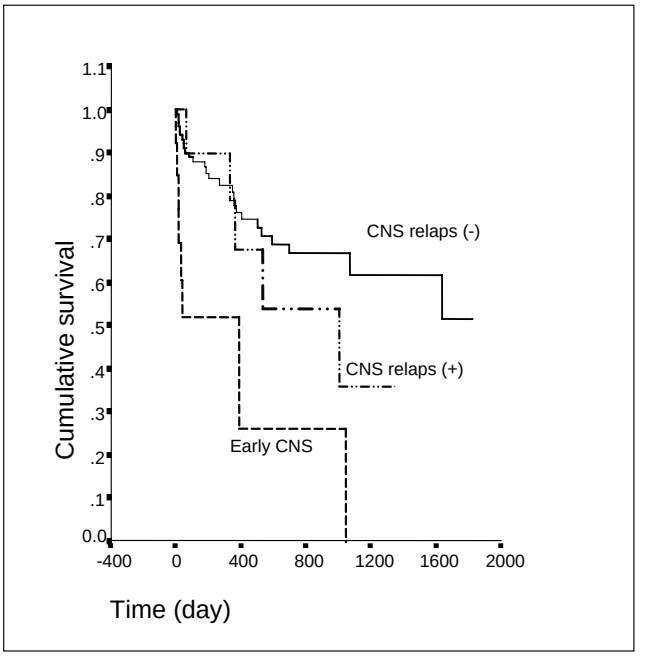

Figure 3. Survival curve of patient with early CNS leukemia, CNS relapse, and without CNS involvement

References

1. **Menkes JH, Hurvitz CG, Mcdiarmid SV, Williams RG**. Neurologic manifestations of systemic disease. In: Menkes JH, editors. Textbook of child neurology. Baltimore: Williams & Wilkins, 1995. p. 903-7.
2. **Campbell RHA, Marshall WC, Chessels JM**. Neurological complications of childhood leukemia. Arch Dis Child 1997; 52:850-8.
3. **Abdulsalam M**. Diagnosis dan penanggulangan leukemia akut pada anak. In: Wahidiyat I Abdulsalam M, editors. Hematologi anak. Pendidikan tambahan berkala ilmu kesehatan anak. Jakarta: FKUI, 1982; 55-64.
4. **Rivera GK, Raimondi SC, Hancock ML, Behm FG, Pui CH, Abromowitch M, et al**. Improved outcome in childhood acute lymphoblastic leukemia with reinforced early treatment and rotational combination chemotherapy.

Lancet 1991; 337:61-6.
5. **Cohen ME, Duffner PK**. Tumors of the brain and spinal cord including leukemic involvement.. In: Swaiman KF, editor. Pediatric neurology principles and practice. 2nd ed. St Louis: Mosby; 1994. p. 931-5.
6. **Chessells JM, Bailey C, Richards SM**. Intensification treatment and survival in all children with lymphoblastic leukemia: results of UK Medical Research Council Trial UKALL X. Medical Research Council Working on Childhood Leukemia. Lancet 1995; 345:143-8.
7. **Abdulsalam M, Zacharia J, Setianingsih I**. Kasus leukemia limfoblastik akut pada anak dengan masa hidup 5 tahun. Presented at Kongres Nasional Ilmu Kesehatan anak X (the 10 th National Congress of Pediatrics), Semarang, June 13-17, 1993.
8. **Horibe K, Hara J, Yagi K, Tawa A, Komada Y, Oda M, et al**. Prognostic factors in childhood acute lymphoblastic leukemia in Japan. Int J Hematol 2000; 72:61-8.
9. **Niemeyer CM, Sallan S**E. Acute lymphoblastic leukemia. In: Nathan DG, Oski FA, editors. Hematology of infancy and childhood. Philadelphia: Saunders, 1993. p. 1249-73.
10. **Poplack DG, Reaman G**. Acute lymphoblastic leukemia in childhood. Pediatr Clin North Am 1988; 35:903-32.
11. **Ekert H**. Clinical paediatric haematology and oncology. Melbourne: Anderson, 1982.p. 52-70.
12. **Gelber RD, Sallan SE, Cohen HJ, Donnelly M, Dalton V,Tobia F, et al**. Central nervous system treatment in childhood acute lymphoblastic leukemia. Cancer 1993; 72:261-70.
13. **Behrendt H, Leeuwen EF, Schuwirth C, Verkes RJ, Hermans J, Vanderberg A, et al**. The significance of an isolated central nervous system relapse, occurring as first relapse in children with acute lymphoblastic leukemia. Cancer 1989; 63:2066-72
14. **Sastroasmoro S, Firmansyah A, Said M, Akib AP Siregar SP**. Analisis kesintasan. In: Sastroasmoro S, Ismael S, editors. Dasar-dasar metodologi penelitian klinis. Jakarta: Binarupa aksara, 1995; 95-108.
15. **Saunders BD,. Trapp RG**. Basic and clinical biostatistics. Norwalk: Appleton & Lange, 1990. p.186-206.
16. **Markum AH, Abdulsalam M, Gatot J, Wahidayat I, Muslichan S.** Outcome of CNS leukemia. Paediatr Indones 1980; 20:57–67.
17. **Bleyer WA**. Central nervous system leukemia. In: Whittaker JA, Delamose IW, editors. Principles and practice of pediatric oncology. 2nd ed . Philadelphia: JB Lippincott Company, 1990. p. 1009-11.
18. **Hardisty RM, Norman PM**. Meningeal leukaemia. Arch Dis Child 1967; 42:441-7.
19. **Aicardi J**. Tumours of the CNS and other space occupying lesions. In: Aicardi J, editor. Disease of the nervous system in childhood. London: Mac Keith Press, 1992. p. 817-22.
20. **Bray PF**. Neurology in pediatrics. Chicago: Yearbook Medical, 1969. p. 263-5.
21. **Mellinger JF.** Central nervous system involvement in childhood lymphoblastic leukemia. In: Swaiman KF, Wright FS, editors. The practice of pediatric neurology; 2nd ed . St. Louis: Mosby, 1982. p. 817-9.
22. **Price RA, Johnson WW**. The central nervous system in childhood leukemia: I. the arachnoid. Cancer 1973; 3:520-33.
23. **Pollock BH, DeBaun MR, Camitta BM, Shuster JJ, Ravindranath Y, Pullen DJ, et al**. Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: A Pediatric Oncology Group Study. J Clin Oncol 2000; 18:813-23.
24. **Oakhill A, Mann JR**. Poor prognosis of acute lymphoblastic leukemia in Asian children living in The United Kingdom. BMJ 1983; 286:839-41.