ORIGINAL ARTICLE

Outcome of CNS Leukemia

by

A.H. MARKUM, M. ABDULSALAM, J. GATOT, I. WAHIDIYAT, S. MUSLICHAN

(Department of Child Health, Medical School, University of Indonesia, Jakarta)

Abstract

This study concerned the evaluation of CNS leukemia in relation with the necessity of maintenance prophylactic treatment of CNS leukemia, as well as prompt and intensive systemic therapy. It was performed on 77 cases of ALL hospitalized during 1974 — 1978, consisting of 44 boys and 33 girls.

All were treated with Oncovin and Prednisone as induction, 6MP and MTX as maintenance and in between intrathecal MTX and CNS irradiation. Of these 77 cases, 25 developed CNS leukemia, in which 12 cases had CNS involvement on first admission while the remaining 13 cases developed this involvement during the course of the illness with the onset ranging from 1½ — 29 mos.

Three parameters (organomegaly, WBC of 20.000/ml, age of 5 yrs) had been evaluated in relation with the occurrence of CNS leukemia and it appeared that only WBC count correlate significantly.

Our cases showed that when CNS leukemia was established at time of diagnosis the prognosis was very poor. Once a patient experienced CNS leukemia the chance to have another episode was high and it seems that maintenance prophylactic procedures of CNS leukemia is important. To prevent infiltration from the skull to the brain parenchym, it is important to start systemic treatment as early as possible.

*) This paper has been presented at the 3rd Asian Congress of Pediatrics, Bangkok, November 19 - 23, 1979.
Received 6th. October 1979.

Introduction

The progress in the treatment of acute leukemia in childhood, which leads to approximately 50% of five-year continuous disease-free survival rates (Frei et al., 1978; Hustu et al., 1973; Simone et al., 1972) has been achieved as the result of intensive treatment towards either the systemic or the CNS leukemia. On the other hand however, the mortality found in the remaining 50% of cases proved that adequate management is still beyond the scope of objectives, which is partially caused by the failure in treating CNS complication properly. The limited number of cytostatic which can be administered directly into the CNS, the deep located CNS foci, and probably the unknown natural history of CNS leukemia as well, seems to be some of the many factors that may cause this unsatisfactory result in facing CNS involvement.

Therefore, although CNS leukemia does not appear to be a direct cause of death with the exception of fatal cerebral leukemia-its prominent contribution in the treatment of leukemia should be taken into consideration, since leukemia foci in the CNS seems to have an important role in the pathogenesis of systemic relapse (Azzarelli and Roessmann, 1977; Evans et al., 1964; Pochedly, 1972).

Based on the above mentioned aspects of CNS leukemia, which may play a determinant factor in the outcome of acute leukemia, the purpose of this study will be directed towards the retrospective evaluation concerning the management of CNS leukemia, so as to identify whether the new regime of intervention should be developed in order to achieve the more successful result.

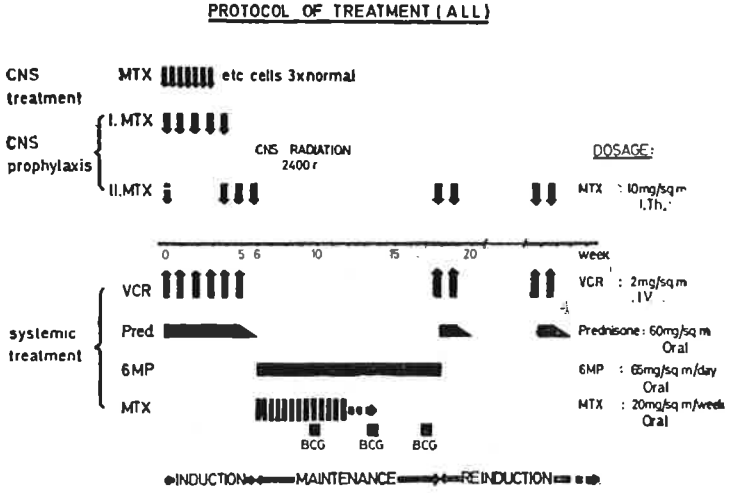
Material and methods

The material consisted of 44 boys and 33 girls with ALL, hospitalized during the last 5 years (1974-1978). Their age varied between 7½ months and 14 years. The diagnosis of ALL was confirmed by bone marrow examinations, while of CNS leukemia either by symptoms or by the finding of pathologic cells in the CSF.

The main points in treating ALL are as follows (fig. 1) : (1) Induction therapy , consisiting of weekly IV oncovin and daily oral prednisone administration as systemic treatment, and intrathecal MTX as well as craniospinal irradiation as prophylaxis or treatment of CNS leukemia. This induction therapy lasted for 6 weeks. Based on our previous study (Wahidiyat et al., 1972) that the first symptoms of CNS leukemia usually appeared after 4 weeks of hospitalization, our material was divided into 2 groups in order to look for the effect of early and late administration of MTX towards the occurrence of CNS involvement. In the first group, the so called "early CNS prophylaxis", the MTX was given at the time of diagnosis of systemic ALL, while in the "late prophylaxis" the MTX was administered after 4 weeks of systemic diagnosis. (2) Main-

tenance therapy consisted of oral MTX and 6-MP. (3) Reinduction treatment, which should be repeated every 3 month, consisted of drug administration similar to induction therapy, but lasted only for 2 weeks.

FIG. 1.



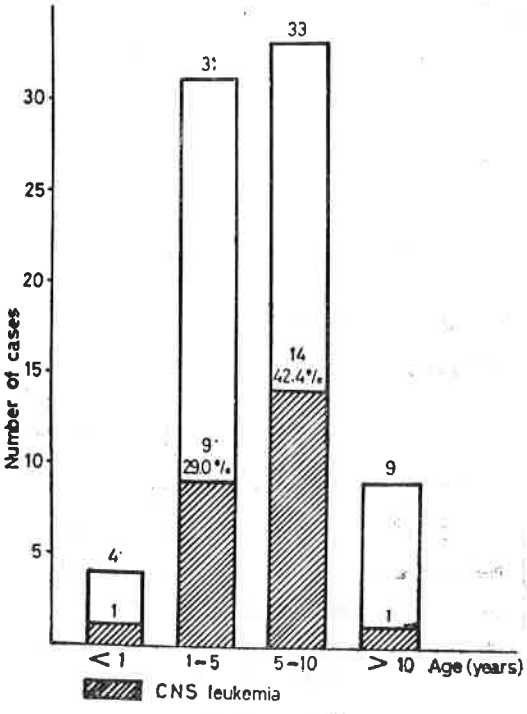
Cases expiring within 1 month of hospitalization were excluded from this study due to difficulties in evaluating the long term effect of CNS prophylaxis, since many factors as the cause of death will arise during this short period.

Results

The age distribution of systemic leukemia as well as CNS leukemia is shown in fig. 2. From this figure it can be noticed that 25 out of 77 cases (32.5%) suffered from CNS leukemia, detected either on the first systemic diagnosis (early CNS leukemia) or later during observation (late CNS leukemia).

The highest incidence of CNS involvement occurred in the age group of 5 - 10 years. The majority of cases had symptoms of meningeal leukemia, while only 5 cases suffered from cerebral leukemia.

FIG 2 : *Age distribution of systemic and CNS leukemia*



It is further noted that 12 out of 25 CNS leukemia cases belonged to the early CNS leukemia, while the remaining 13 were cases of the late CNS leukemia with the interval between first systemic diagnosis and CNS involvement varying between 1½ — 29 months (table 2). The incidence of CNS leukemia, based on this differentiation, is listed in table 1. The overall incidence, including early and late CNS leukemia is 35,2%. However, the figure of 25.5% illustrates the real incidence of our cases, in which the beneficial effect of CNS prophylaxis can be evaluated.

TABLE 1 : *Incidence of CNS Leukemia*

	ALL	CNS Involvement	% CNS Involvement
Total cases	77	25	35.2
Number of cases with prophylaxis	51	13	25.5
Number of cases without prophylaxis (1972)	19	10	52.6

Clinical data presented in table 2 shows that cases with late CNS leukemia appear to have a longer mean period of survival of 18.0 months compared to the mean survival period in early CNS leukemia of 8.5 months ($p < 0.05$). After 3 years of observation the incidence of CNS relapse in late CNS leukemia is more than 50% (7 out of 13 cases); this figure could not be compared to that of early CNS leukemia cases because of the early death of cases belonging to this group. However, the overal incidence of relapse is 45.0%.

TABLE 2: *Survival period and incidence of CNS relapse in „Early" and „Late" CNS involvement*

	Early CNS involvement (12 cases)	Late CNS involvement (13 cases)
Interval systemic diagnosis → CNS involvement (month)	0	1½ — 29
Survival period (month)	8.5 (0 — 46)	18.0 (4 — 52)
Cases with CNS relapsed	2/7 (5 died before 1 month)	7/13
% of CNS relapse	9/20 ——→	45.0%

Regarding the time for intrathecal MTX administration, no conclusive evidence can be taken of whether early prophylaxis gives better results than late prophylaxis (table 3). It means that MTX prophylaxis may be given either directly on the first few days or on the 4th week of hospitalization. Nevertheless, it is also clearly indicated from this table that MTX prophylaxis may have some beneficial effect if compared to our previous study (Wahidiyat et al,. 1972) which served as control group without MTX prophylaxis.

TABLE 3 : *CNS involvement in relation to the time of MTX administration*

	MTX (+)	MTX (+)	MTX (—) 1972
MTX administration on week	1 → 5	4 → 6	—
CNS onset (month)	1½ — 28	4	1 — 12
% of CNS involvement	12/43 = 27.9%	1/8 = 12.5%	52.6%

The long term effect of MTX on the occurrence of CNS leukemia is obviously illustrated in fig. 3, that 50% of cases remained free of CNS involvement after 2 years of observation and then dropped to 27.8% after 3 years of follow up.

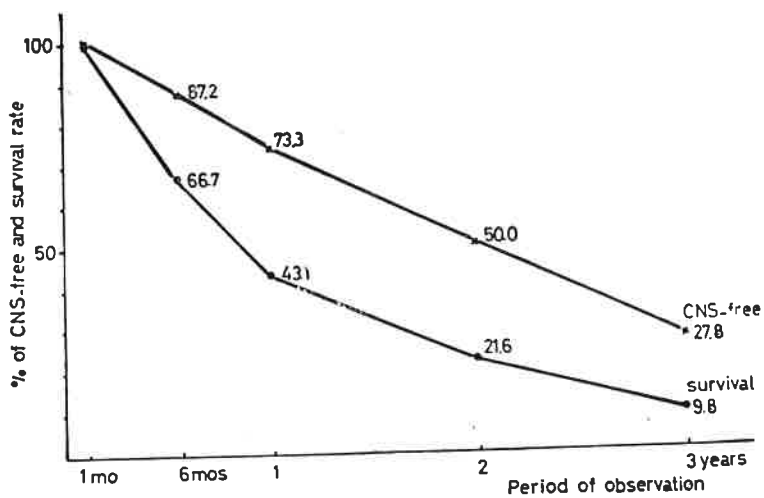


FIG. 3 : *Percentage of CNS free and survival rate*

Table 4 represents the relationship between certain initial data and the occurrence of CNS leukemia. It seems that the possibility to have CNS leukemia is greater in cases showing a number of WBC of more than 20.000/mm^3. On the other hand organomegaly and the age of children used as prediction factors for CNS involvement, did not appear to be correlated statistically.

TABLE 4 : *The occurrence of CNS leukemia in relation to several factors*

Observation	CNS (+)	CNS (—)	Remarks
Organomegaly (+)	17 (36.2%)	30	$P > 0.05$
Organomegaly (—)	8 (26.7%)	22	
WBC $<$ 20.000/cmm	11 (22.9%)	37	$P < 0.05$
WBC $\geq$ 20.000/cmm	14 (48.9%)	15	
Age $<$ 5 years	9 (20.3%)	31	$P > 0.05$
Age $\geq$ 5 years	16 (43.2%)	21	

Discussion

It has been widely reported that with increased prolongation in survival, a progressive increased incidence of CNS leukemia occurred, which eventually exceeded 50% in cases without CNS prophylaxis (Frei et al., 1978; Melhorn et al., 1970; Pochedly et al., 1972; Wahidiyat et al., 1972). A marked contribution to progress in the treatment of ALL is the development of CNS prophylaxis which can reduce the incidence of CNS leukemia to 5 - 10% (Aur et al., 1973; Hustu et al., 1973; Price and Jamieson et al., 1975). This figure is higher in this study (25.5%), which may be due to irregular or delayed visit in some cases, since the programme of treatment seems to be similar compared to other investigators. Nevertheless, to some extent CNS prophylaxis does delay the onset of CNS involvement, but does not provide complete eradication of this disorder (Bernard et al., 1972; Evans et al., 1964; Holland and Glidewell, 1972). This problem becomes the first major barrier in an attempt to obtain an increased rate of survival and complete cure of childhood ALL.

Of other interest in the field of CNS leukemia is the occurrence of relapse (Markum et al., 1977) which is still observed in spite of intensive CNS prophylaxis. As presented in this study (table 2), 7 out of 13 cases who were initially free of CNS involvement and got prophylacted treatment with intrathecal MTX as well as cerebral irradiation, developed CNS relapses during the course of their illness. It can be predicted therefore that approximately 50% of our children once suffered from CNS complication would develop another episode of CNS leukemia.

The incidence of CNS relapse in this study seems to be rather high compared to data found by other investigators. In cases following intrathecal MTX prophylaxis alone, the incidence of CNS relapse is reported around 15 - 47% (Bernard et al., 1972; Evans et al., 1964; Holland and Glidewell et al., 1972; Sullivan et al., 1971; Sullivan et al., 1975), which may be significantly reduced to 2 - 8% by introducing a combination of intrathecal MTX and adequate cerebral irradiation (Dritschilo et al., 1976; Frei et al., 1971; Sullivan et al., 1975).

These data suggest that poor prognosis may be expected in cases suffering from CNS involvement regardless whether these children have got prophylaxis, since leukemic foci in the CNS is thought to be the source of hematologic relapse (Azzarelli and Roessmann, 1977; Evans et al., 1964; Pochedly et al., 1972). As shown in Fig. 3 the high incidence of CNS relapse in this study is followed by a decreasing rate of survival as well as percentage of CNS leukemia-free cases after longer period of observation. The situation of CNS relapse should be considered as the second major obstacle in the way to eradicate CNS complication completely.

The pathogenesis of CNS infiltration seems to be an important aspect in preventing the occurrence of CNS leukemia. Azzarelli and Roessmann (1977) noted that CNS involvement occurs as a direct infiltration of leukemia cells from the bones of the skull into the brain parenchyma by way of perivenous adventitial tissue. If this is the case, the main point which should be taken into consideration is the early and intensive treatment of initial systemic attack as an effort to prevent the above mentioned pathway of brain infiltration.

It is apparent therefore, that 2 major aspects of total eradication of CNS leukemia should be improved: (1) To reduce completely the incidence of CNS complication, (2) To prevent the occurrence of CNS relapses. Both problems arise as a result of either inadequate CNS prophylaxis or treatment, which probably is caused by (1) Limited number of effective drugs which can cross blood-brain barrier or injectable intrathecally. (2) Deep seated leukemic foci which is very hard to be penetrated by present method of treatment. (3) Other poorly understood factors concerning the natural history of CNS leukemia. Regarding the favourable result in treating systemic ALL, it is suggested that the

procedure in facing CNS involvement should be similar to that of hematologic disorders, which at least should consist of induction, maintenance and reinduction, either by intrathecal or if possible by intravenous route, besides the routine craniospinal irradiation. The effectiveness of performing maintenance therapy in CNS leukemia has been reported by Sullivan et al. (1975) and Morgan et al. (1977), where prolongation of CNS remission and bone marrow remission have been achieved by introducing intrathecal methotrexate periodically. It is the main intention indeed that an intensive effort should be accomplished directed towards the development of compounds that may be able to pass the blood-brain barrier easily, so as to permit treatment of meningeal leukemia with systemically administered compounds (Sullivan et al., 1971).

Although the number of cases in this study is small, we have the impression that the time of prophylactic MTX administration seems to have no influence upon the occurrence of CNS involvement (table 3), provided the spinal fluid is free of pathologic cells on the first systemic diagnosis. Based on this finding as well as on the previous experience (Wahidiyat et al., 1972) MTX prophylaxis may be given at any time up to the 4th week of hospitalization. In case of limited MTX supply this finding can be suggested in order to avoid early MTX treatment for cases who died within 4 weeks of hospitalization. Late intrathecal MTX prophylaxis has also been performed by other investigators (Dritschilo et al., 1976; Hustu et al., 1973) with an excellent result, in which MTX is given after systemic remission has been obtained.

Regarding the prediction factors which may relate to the occurrence of CNS leukemia, the present data shows that the incidence of CNS involvement is significantly greater in cases having WBC count higher than 20.000/mm^3 (table 4). This finding is consistent to that of other investigators but differs from the data reported by other authors (Hardisty and Norman, 1967). However, in contrast to the WBC count, there is likely no relationship between the presence of organomegaly or the age of children and the appearance of CNS leukemia.

Summary and conclusions

1. The failure to obtain a better result of complete cure in ALL so far, is partially caused by the failure of preventing and treating CNS complication, as proved by the fact that high incidence and relapse of CNS leukemia still exist in spite of intensive procedures currently performed.

Therefore, the authors are of the opinion that systemic treatment should be performed as early as possible and CNS prophylaxis should be given in a more intensive and continuous way, similar to that of systemic attack.

2. More careful attention should be carried out in cases whose WBC count is higher than 20.000/mm^3, where the

chance to suffer from CNS complication seems to be greater.

3. Intrathecal MTX administration is not necessarily given on the first days of hospitalization, but may be delayed up to the 4th week, provided no leukemic cells was detected on initial CSF examination.

REFERENCES

1. AUR, R.J.A.; HUSTU, H.O.; VERZOSA, M.S.; WOOD, A. and SIMONE, J.V. : Comparison of two methods of preventing central nervous system leukemia. Blood 42 : 349 (1973).
2. AZZARELLI, B. and ROESSMANN, U.: Pathogenesis of central nervous system infiltration in acute leukemia. Arch. Pathol. Lab. Med. 101 : 203 (1977).
3. BERNARD, J.; JACQUILIAT, Cl and WEIL, M. : Treatment of the acute leukemias. Semin. Hematol. 9 : 181 (1972).
4. DRITSCHILO, A.; CASSADY, J.; CAMITTA, B.; JAFFE, N.; FURMAN, L. and TRAGGIS, D. : The role of irradiation in central nervous system treatment and prophylaxis for acute lymphoblastic leukemia. Cancer 37 : 2729 (1976).
5. EVANS, A.E.; D'ANGIO, G.J. and MITUS, A. : Central nervous system complications of children with acute leukemia. J. Pediatr. 64 : 94 (1964).
6. EVANS, A.E.; GILBERT, E.S. and ZANDSTRA, R. : The increasing incidence of CNS leukemia in children. Cancer 26 : 404 (1970).
7. FREI, E.III; SALIAN, S.; WEINSTEIN, H.; MAYER, R.; ROSENTHAL, D.; CANELLOS, G. and NATHAN, D.: Advances in the treatment of acute leukemia. 17th ISH and 15th ISBT Congress, Paris 23-29 July 1978.
8. GALTON, D.A.G. and SPIERS, A.S.D.: Progress in the leukemias. Progr. Hemat. 7 : 343 (1971).
9. HARDISTY, R.M. and NORMAN, P.M.: Meningeal leukemia. Arch. Dis. Child. 42 : 441 (1967) .
10. HOLLAND, J.F. and GLIDEWELL, O.: Chemotherapy of acute lymphocytic leukemia of childhood. Cancer 30 : 1480 (1972).
11. HUSTU, H.O.; AUR, R.J.A.; VERZOSA, M.S.; SIMONE, J.V. and PINKEL, D. : Prevention of central nervous system leukemia by irradiation. Cancer 32 : 585 (1973).
12. MARKUM, A.H.; WAHIDIYAT, I.; ABDULSALAM, M.; MUSLICHAN, S. and GATOT, D.: Refractory meningeal leukemia. Nat. Congr. Hemat. Blood Transf. Surabaya, October 1977.
13. MELHORN, D.K.; GROSS, S.; FISHER, B.J. and NEWMAN, A.J. : Studies on the use of prophylactic intrathecal amethopterin in childhood leukemia. Blood 36 : 55 (1970).
14. MORGAN, E.; DONALDSON, M.H. and MEADOWS, A.T. : The value of maintenance therapy following treatment of central nervous system leukemia. Cancer 40 : 1005 (1977).
15. POCHEDLY, C. : Management of CNS leukemia in childhood. An outline of

current concepts. Clin. Pediatr. 11 : 503 (1972).

16. PRICE, R.A. and JAMIESON, P.A. : The CNS in childhood leukemia. Cancer 35 : 306 (1975).

17. SIMONE, J.; AUR, R.J.A.; HUSTU, H.O. and PINKEL, D. : "Total therapy" studies of acute lymphocytic leukemia in children. Current results and prospects for cure. Cancer 30 : 1488 (1972).

18. SULLIVAN, M.P.; VIETTI, T.J.; HAGGARD, M.E.; DONALDSON, M.H.; KRALL, J.M. and GEHAN, E.A. : Remission maintenance therapy for meningeal leukemia. Intrathecal methotrexate vs. intravenous bis Nitrosourea. Blood 38 : 680 (1971).

19. SULLIVAN, M.P.; HUMPHREY, G.B.; VIETTI, T.J.; HAGGARD, M.E. and LEE, E. : Superiority of conventional intrathecal methotrexate therapy, unmaintained, or radiotherapy (2000 - 2500 rads tumor dose) in treatment for meningeal leukemia. Cancer 35 : 1066 (1975).

20. WAHIDIYAT, I.; MARKUM, A.H.; ABDULSALAM, M.; MUSLICHAN, S. and ODANG, O. : "Prophylactic" treatment of meningeal leukemia in children by intrathecal methotrexate. Acta. Haemat. 47 : 81 (1972).

21. WEST, R.J.; GRAHAM-POLE, J.; HARDISTY, R.M. and PIKE, M.C. : Factors in pathogenesis of central-nervous-system leukemia. Brit. med. J. 3 : 311 (1972).