THE INCREASING INCIDENCE OF CENTRAL NERVOUS SYSTEM LEUKEMIA IN CHILDREN

(Children's Cancer Study Group A)

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The incidence of symptomatic CNS leukemia was studied in 209 children, all of whom were entered in a cooperative study during 1963–1964, and received the same chemotherapeutic agents. The overall incidence was 51%, and the median time for occurrence of the first episode was 9 months. The incidence was 56% in patients with acute lymphocytic leukemia (A.L.L.) and 25% in those with other forms of leukemia. CNS symptoms developed at a steady monthly rate of 3.8% for the first 24 months and then decreased to 2%. The rate for the first year was the same for all forms of leukemia; it was 4% in A.L.L. and 3.7% in the other forms combined. The overall median survival was 18 months—it was 21 months for patients with A.L.L. and 9 months for the other cell types. Life-table analysis showed a median survival of 8 months for patients who had developed CNS leukemia and 24 months for those free of the complication. Age, sex, hematologic status, and chemotherapy regimen did not influence the incidence. We conclude that the increasing survival of children with leukemia is the chief cause for the increased incidence of CNS leukemia noted by many investigators.

IT IS KNOWN THAT LEUKEMIA AFFECTS THE central nervous system (CNS) most often by the infiltration of the meninges with leukemic cells. The resulting clinical syndrome of increased intracranial pressure was fully defined, in 1957, by Gilbert and Rice,[4] Wells and Silver,[10] and Sullivan.[9] Subsequently, numerous authors have noted an increasing incidence of as much as 30-40%.[3, 8] Yet, to date, a true evaluation of incidence, morbidity, and therapeutic possibilities has not been available. Either the previous studies dealt with a relatively small number of patients or they encompassed patients collected over a long period of time when many developments in therapeutic regimens took place. Early recognition of this complication, increasing duration of survival, and type of treatment given may all influence the rate of occurrence. The following analysis of 209 children with acute leukemia, entered into a cooperative study conducted by Children's Cancer Study Group A** during a period of one year, provides some insight into the factors which influence the incidence of CNS infiltration.

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PATIENT SELECTION

A total of 224 children, 14 years or under, with all types of acute leukemia were studied between November 1, 1963 and November 15, 1964. All episodes of central nervous system (CNS) leukemia were suspected because of signs or symptoms of increased intracranial pressure. The diagnosis was confirmed by examination of the spinal fluid. The protocol did not require routine lumbar punctures on asymptomatic children (v.i.). Patients with symptomatology resulting from intracranial hemorrhage (an allied but different complication) are excluded from this analysis.

The study design and results of treatment have already been reported[6] and are summarized as follows:

All patients entered into the study were newly diagnosed and had received no treatment. The initial therapy was prednisone plus either

methotrexate* (MTX) or 6-mercaptopurine (6-MP). Patients in remission 42 days thereafter were again randomized into a cyclic or sequential group, all receiving the same 5 agents, viz., MTX, 6-MP, vincristine (VCR),† cyclophosphamide (CTX), and prednisone. The patients on the cyclic regimen changed drugs every 6 weeks. When the patient became resistant to all agents, he went off study, but most continued to receive other agents under the guidance of the same investigators. The post study phase of the disease in each patient is, therefore, included in the evaluation of CNS leukemia.

The study design allowed treatment of CNS manifestations by either intrathecal methotrexate or radiation therapy, and no attempt has been made to evaluate the relative merits of the treatments used. The criteria for evaluation of the patients' hematologic status are those customary in studies of this kind.[1]

STATISTICAL METHODS OF ANALYSIS

Special techniques are necessary in order to analyze data of this type. One of the problems that arise, from the statistical standpoint, is that there is a changing number of patients who *can* develop CNS disease for the first time. Since patients are continually dying, it is difficult to study what effect the duration of the leukemic state has on the risk of developing the complication. Also, the comparison of the survival experience of those who do and do not develop CNS manifestations is difficult because the likelihood of developing CNS leukemia depends, in part, on the length of time a patient lives. And, there are a few patients who were lost to follow-up at some time during their course of treatment. All these problems can be handled by a life-table method which is described by Cutler and Ederer.[2‡]

RESULTS

The charts of 209 of the 224 patients entered on the original study were suitable for evaluation. At the time data was compiled for the last time, information about the CNS status was known on all surviving patients. Fifteen patients were not suitable for analysis because 4 were lost to follow-up and 11 were eliminated from study because of deviations from protocol requirements.

The 209 patients ranged in age from 2 months to 14 years at the time of diagnosis. The majority were between 1 and 7, with the peak at 3 years; 111 were boys. Acute lymphocytic and undifferentiated leukemia was diagnosed in 173 (82%), acute granulocytic or monomyelogenous leukemia in 32, and erythroleukemia in 4.

CNS leukemia occurred in 106 of 209 patients (51%), Fig. 1. Episodes were considered to be separate when symptoms cleared for more than one month following treatment. The total number of episodes was in excess of 280, with a mean of 2.6 per child and a range of 1–14. The age range of the children developing this complication was the same as that of the overall group and the peak incidence similarly was in children aged 3. Of the 106 patients developing CNS leukemia, 60 were boys; 97/173 had lymphocytic or undifferentiated leukemia, and 9/36 had other forms. Fifty-three patients were on the cyclic regimen, 52 on the sequential, and one (who died during induction) was on neither regimen.

CNS symptoms or signs first occurred at times ranging from the date of original diagnosis to 46 months thereafter; the median time was 9 months (Fig. 1).

The total number of patients contributed by each institution ranged from 6 to 34. The incidence of CNS leukemia by institution varied from 24% to 100%. These values are not significantly different from the mean (51%).

Figure 2 shows the total number of pa-

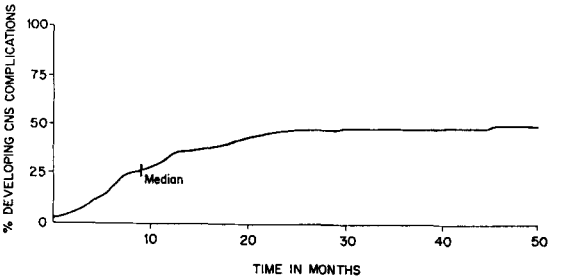

FIG. 1. Cumulative incidence of CNS complications in 209 children with leukemia.

* Methotrexate sodium—4-Amino-N[10]-methyl-pteroylglutamic acid sodium, Lederle Lab., Div. of American Cyanamid Co., Pearl River, N.Y.

† Vincristine sulfate—an alkaloid extracted from *Vinca rosea Linn.*, Eli Lilly & Co., Indianapolis, Ind.

‡ The authors would be pleased to supply details regarding the application of their method in this analysis.

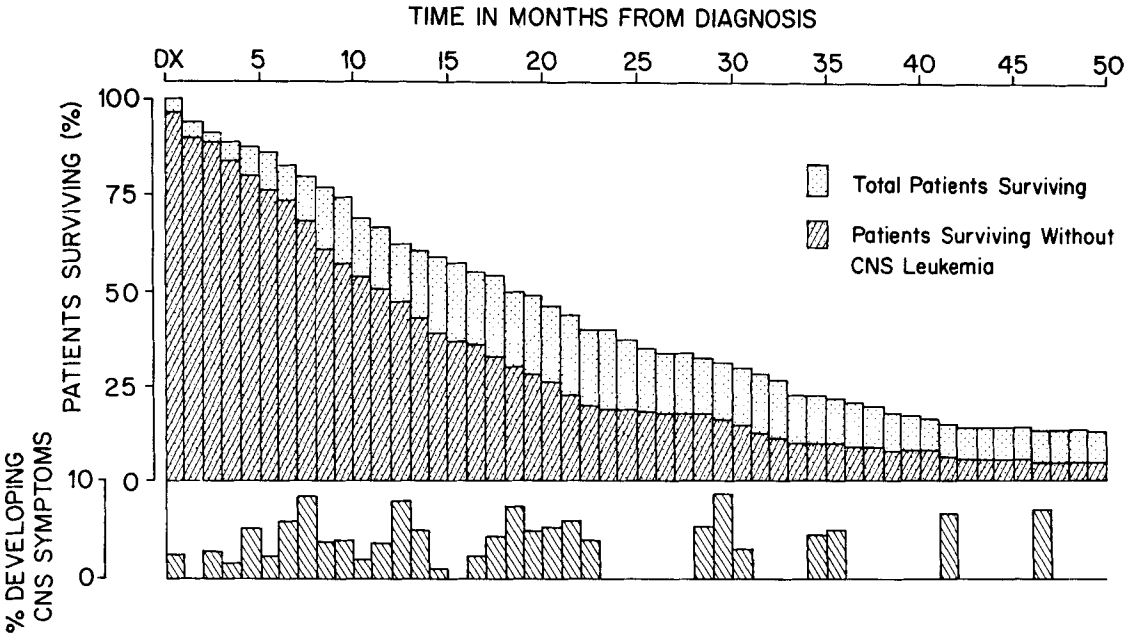

FIG. 2. The upper bar graph shows both the overall percentage of patients surviving and those free of CNS leukemia. The lower graph gives the percentage developing CNS symptoms for the first time. This ratio is based on the number of patients surviving who have not yet developed the complication (lower half of the upper graph).

tients surviving each month and the percentage of those who have not yet developed meningeal leukemia. It can be seen that half of the patients survive 18 months and, from 24 months onward, approximately half of the remaining patients have developed at least one episode of CNS leukemia. The lower part of the graph shows, for each month of survival, the percentage of patients still at risk who first develop CNS leukemia. The rate for the first 24 months is 3.8% per month; for the second 2 years, the rate is 2% per month. The highest incidence was 3/34 patients or 8.8% occurring at month 29.

Essentially, the same number of episodes occurred in both treatment groups; there was a total of 148 episodes in the patients on the cyclic regimen and 131 episodes in those on sequential therapy. Initial and subsequent attacks of meningeal leukemia occurred on all 5 agents, including prednisone. In 46 episodes in the sequential group, where the patients' hematologic status was recorded, 26 episodes (56%) occurred during remission.

Although the incidence of CNS symptoms was greater in those children with lymphocytic leukemia than in those with other forms of the disease, the monthly rate was the same for all types. Fifty-six percent of patients with lymphocytic and 25% with myeloid, monocytic, or erythroleukemia developed CNS disease; the rate for the former was 4% and for the latter 3.7% per month for the first 12 months. The survival time of this group was approximately half that of the patients with acute lymphocytic leukemia (v.i.).

The median survival of 209 patients was 18 months; the range was from less than one month to greater than 48 months (Fig. 2). At preparation of this report, 26 patients had survived for 48 months and 12 had not yet developed CNS symptoms. Patients with lymphocytic leukemia survived a median of 21 months and those with nonlymphocytic morphology, 8.5 months. The median survival of all patients developing CNS complications was 21 months; it was 13 months for those who did not develop CNS leukemia. The median survival from the first episode of CNS leukemia to death was 7.5 months—the mean was 11 months and the range was from less than one to 46 months.

The development of CNS leukemia is related to patient survival. Therefore, a life-

table type analysis was used to calculate the probability of developing the complication. The method employed permitted analysis of the date for any time period without reference to the number of patients who had died previously. Figure 3 depicts the monthly cumulative incidence of CNS leukemia arrived at by life-table analysis plotted on a simi-log scale. It can be predicted that 50% of patients who survive 18 months and 75% of the patients who survive 4 years will have developed CNS symptoms by that time. It can be seen from this figure that, apart from an initial lag, the rate appears fairly constant for approximately 24 months when it decreases. Averaged in 2-year blocks, the 3.8% incidence in the first 2 years is approximately twice that of the second 2-year period (2.0%).

The crude survival data includes the bias that the longer a patient with leukemia lives, the greater the chance he will develop a CNS complication. In order to evaluate the effect of CNS leukemia on survival, life-table analysis of the data was used to calculate 2 hypothetical survival curves—one for patients developing CNS disease and another for those who do not. These 2 curves are presented in Fig. 4. It can be seen that the trend obtained by analysis of the crude data is reversed. In this prediction, patients who do not develop CNS disease should live a median of 24 months and those who do develop disease, a median of 8 months.

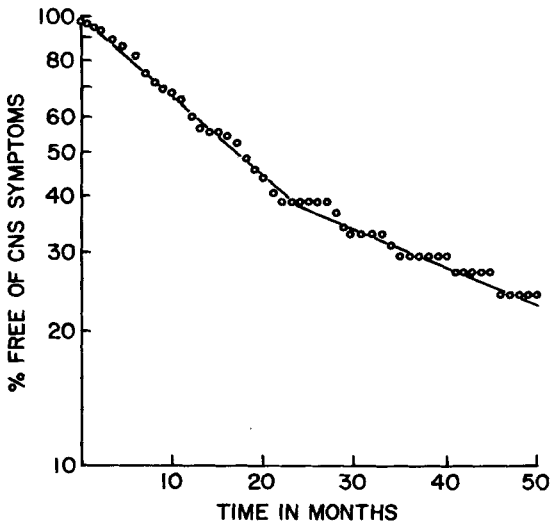

FIG. 3. The ordinate gives the probability that a patient living x months will not have developed CNS symptoms. Fifty percent of the patients living at 18 months will develop the complication. The rate of incidence appears to change at 24 months.

DISCUSSION

Is the reported increasing incidence of CNS leukemia due to a prolongation of survival, is it because the complication is being recognized more often, or is it a consequence of the new drugs being employed?

In nearly 1,000 patients diagnosed between 1948 and 1960, the incidence of CNS leukemia increased from 3–40%, and the median survival rose from 4–12 months.[3] This suggests that increased survival does influence the incidence of CNS infiltration. Hyman et al. noted CNS symptoms were uncommon in the first 3 months when the incidence rose sharply with a median at 7 months after diagnosis.[6] Hardisty reported a group of 29 patients who developed CNS leukemia between 2 and 41 months after the time of diagnosis. His data suggested a fairly steady rate of incidence during the course of disease.[5] Nies compares 2 groups of patients diagnosed between 1953 and 1958 and between 1961 and 1963; the median survival for the former was 9 months and for the latter, 13 months.[8] The incidence of symptomatic CNS disease was not different in the 2 groups, but diagnosis of the complication was more frequent in the second period because routine lumbar punctures were done and abnormalities detected in asymptomatic patients. Examination of the CSF was not done routinely in the first series. Thus, increased awareness is no doubt contributing to the higher incidence figures being reported.

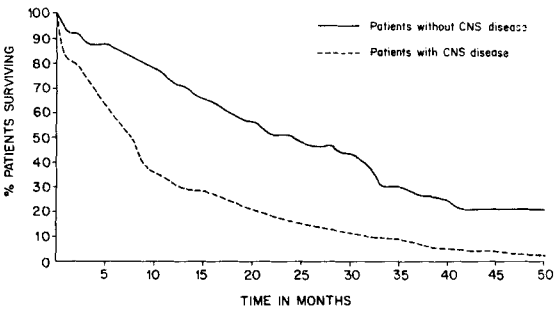

FIG. 4. Life-table analysis showing the probability of dying with and without previous CNS disease. The monthly death rate is calculated as the percentage of patients at risk (i.e., living that month with or without CNS infiltration) who die that month.

Most chemical agents used in the treatment of leukemia appear in the spinal fluid in insignificant concentrations. This is true also for the 2 agents introduced more recently: cyclophosphamide and vincristine. Therefore, the longer hematologic control made possible by the newer drugs has not led to control of the disease in the meninges.

The records reviewed in the present study had 2 advantages in helping to answer some of the questions raised above: 1. they belonged to a large number of children placed on study during a relatively short time period, and 2. all received the same chemotherapy. Even the children who completed the original treatment protocol and survived for a significant period of time thereafter were treated in a comparable fashion, the majority receiving cytosine arabinoside and daunomycin.

Fifty-one percent of all patients developed CNS complications, an incidence higher than in any previously reported study. The monthly rate of 3.8% is constant for the first 24 months, suggesting that the increased incidence is largely due to the increased length of survival. It can be seen in Fig. 3 that there is an initial lag in the curve which agrees with the results noted by Hyman, that the incidence was less during the 3 months after diagnosis. This could, perhaps, result from the fact that most patients, and all those in this study, received corticosteroids for the first 6 weeks of their course and therapeutic doses of cortisone may have decreased the CNS infiltration. The steady rate of occurrence from diagnosis to 24 months also suggests that the pathology of this complication is not different in the advanced patient than in one newly diagnosed. Of interest is the fact that after 24 months, the rate decreased. There are several possible explanations; the more susceptible patients have died or there has been an increase of some protective factor against CNS involvement.

The reported incidence of CNS leukemia varied widely between institutions though, presumably, the investigators were equally aware of the significance of this complication. The 6 children at the institution reporting a 100% incidence received routine lumbar punctures as part of their care and some of their "episodes" of CNS leukemia were on the basis of CSF findings only. From this, one might conclude that all children would be found to have some degree of CNS infiltration if routine lumbar punctures were done but, in fact, this is not so. Several of the long-term survivors in this study who had not developed CNS symptoms had lumbar punctures which revealed normal spinal fluid. An additional factor influencing high incidence in this institution was the unusually long median survival of these 6 patients, which was 36 months. The authors considered that the wide range of incidence was the result of chance and allows the patients from all institutions to be analyzed as a single group.

The incidence of CNS symptoms varied in the different morphological types. Most of the patients (82%) had acute undifferentiated or lymphocytic leukemia, and the incidence in this group was 56%. CNS leukemia developed in 25% (9/36) of the patients with leukemia of other types, but at the same monthly rate. The lower incidence is probably related to the decreased overall survival of 8.5 months, compared to 21 months in the patients with lymphocytic leukemia.

No influence of specific chemotherapy on the development of CNS leukemia could be seen in this study. The patients on the cyclic regimen had frequent changes of drug and those on sequential treatment had MTX or 6-MP as either the first or the final agent. Initial and subsequent episodes occurred during therapy with all 5 agents, and there was no difference in the 2 treatment groups. It is interesting to note that approximately the same number of episodes occurred while patients were receiving prednisone. Corticosteroids cross the blood brain barrier and, thus, are sometimes used in the treatment of CNS leukemia. The dose of the prednisone used for the maintenance phase of this study was approximately a third of that normally used for induction of remission. The lower consequent concentration in the CSF may be a factor in the incidence reported here.

The development of CNS symptoms is usually thought to indicate a poor prognosis. If the 7.5 month median survival after the first episode is added to the 9 months, which is the median time of incidence, the 16.5-month total is shorter than the overall 21-month survival of patients with CNS disease. A better way to estimate the effect of this complication on prognosis is by life-table analysis, which shows that the median survival predicted for those who develop CNS

symptoms is 8 months; for those who do not, the projected figure becomes 24 months. The results of such an analysis do not allow one to conclude that the development of CNS leukemia is the sole cause for the poor survival and that a median survival of 24 months would prevail if CNS leukemia were eliminated. Conceivably, persistence of the leukemic infiltration does provide a source of cells to reseed the bone marrow and precipitate a hematologic relapse. Such is the basis for the studies employing "sanctuary" therapy. It, therefore, appears that attempts to eradicate leukemic infiltration of the central nervous system by vigorous treatment with intrathecal medications, radiotherapy, or a combination of the 2 might lead to prolonged survival.

APPENDIX
(Children's Cancer Study Group A)

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C	University of Wisconsin	Dr. L. Gilbert Thatcher	CA 05436
D	*Children's Orthopedic Hospital, Seattle, Wash.	Dr. John R. Hartmann	CA 04936
E	University of Chicago	Dr. Audrey E. Evans	CA 01300
F	Children's Hospital, Washington, D. C.	Dr. Sanford Leikin	CA 03888
G	Children's Memorial Hospital	Dr. Wayne Borges and Dr. Mila Pierce	CA 07336
H	Children's Hospital, Los Angeles, Calif.	Dr. Denman Hammond and Dr. Charles A. Brubaker	CA 02649
I	Children's Hospital, Columbus, Ohio	Dr. William A. Newton, Jr.	CA 03750
J	Babies' Hospital, N. Y.	Dr. James A. Wolff	CA 03526
K	Children's Hospital, Pittsburgh, Pa.	Dr. Vincent Albo	CA 07439
M	Children's Hospital, Denver, Colo.	Dr. Eugene C. Beatty, Jr.	CY 3179
N	University of Minnesota	Dr. William Krivit	CA 07306
P	St. Christopher's Hospital, Philadelphia, Pa.	Dr. A. E. McElfresh	

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