Factors That Influence the Appearance of Central Nervous System Leukemia

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At present, central nervous system (CNS) leukemia is one of the principal causes for termination of complete remission in acute lymphocytic leukemia (ALL). The factors which influence the increase of CNS infiltration have been studied comparing different parameters (age, initial peripheral WBC count, type of leukemia, and presence or absence of initial organomegaly) to determine the leukemia population with highest risk of developing this syndrome. A total of 127 cases of acute lymphoid leukemia (ALL) (98 children and 29 adults) and 101 acute myelocytic leukemia (AML) (41 children and 60 adults), on the same treatment protocol from 1967 to 1970, were included in this study. The median survival and the rate of incidence of symptomatic CNS leukemia was 18 mo and 32% in ALL and 4 mo and 7% in AML. The incidence of CNS leukemia per month of survival was similar in both groups: 4 mo, 3% in AML and 4% in ALL, at 8 mo, 13% in both ALL and AML. The incidence of CNS leukemia was higher in children with ALL than in adults: 41% in children and 19% in adults at 20-mo survival. Organomegaly (spleen, liver and/or lymph nodes) as an early manifestation increased the risk of CNS involvement. The CNS infiltration was significantly greater in patients with high initial peripheral WBC count. The incidence of meningeal leukemia did not differ in ALL and AML. In conclusion, CNS leukemia infiltration was more frequent in children with initial organomegaly and high WBC count at the time of diagnosis.

DIAGNOSIS OF CENTRAL NERVOUS SYSTEM (CNS) infiltration in acute leukemia has been constantly increasing during the past few years. This complication has become one of the major problems in the management of this disease. Most studies on the clinical and pathological aspects of meningeal leukemia are reviews of large groups of cases seen over long periods of time and treated by a variety of therapeutic regimens. In an effort to determine which patients are more likely to develop CNS leukemia the GATLA (Grupo Argentino de Tratamiento de la Leucemia Aguda) studied 127 acute lymphocytic leukemias (ALL) and 101 acute myelocytic leukemias (AML). Both groups were treated by the same protocol. In

Supported in part by FUNDALEU (Fundacion para Combatir la Leucemia).
Publication of the GATLA (Grupo Argentino de Tratamiento de la Leucemia Aguda).
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order to evaluate the leukemic population with highest risk of CNS infiltration, different parameters (age, initial peripheral white blood cell count, leukemia cell type, and presence or absence of initial organ enlargement) were compared.

MATERIALS AND METHODS

A total of 228 acute leukemia patients were included in this study. They were followed during a period of 3 yr. from November 1967 to November 1970. Of these, 127 were ALL (98 children under 15 and 29 adults) and 101 AML (41 children and 60 adults). The therapeutic schedule was as follows: (a) induction: vincristine, daunorubicin, and prednisone; (b) maintenance: methotrexate and 6-mercaptopurine or methotrexate alone; and (c) consolidation: (every 6 mo) vincristine, daunorubicin, and prednisone. Of the 127 ALL, 84 had not been treated previously whereas 43 had already received treatment; of the 101 AML, 86 were new cases and 15 had received previous treatment.

In this retrospective study, diagnosis of meningeal leukemia was made whenever the cerebrospinal fluid obtained by lumbar puncture contained more than 10 mononuclear and/or blast cells per cu mm, in the absence of positive bacteriologic culture or gross blood contamination. Actually in the new protocols these criteria have changed. We now diagnose meningeal leukemia whenever we can demonstrate a blast by Wright’s stain and/or cytochemical techniques in the cerebrospinal fluid sediment, in the absence of blood contamination. This protocol did not require punctures on asymptomatic patients; however, these were immediately performed as soon as CNS involvement was suspected. CNS leukemia was treated by methotrexate intrathecally or $^{56}$Co (2400 R to cranium) or by a combination of both.

The life table method was used to establish the curve of incidence of CNS leukemia. Patients who died during interval without meningeal relapse were put in the same interval and column as those patients who were alive during this interval and withdrawn from observation without CNS relapse.

Patients who were lost to follow up during the interval and patients who had meningeal relapse (relapsing during the interval) were put as belonging to different categories.

RESULTS

The evaluation of the patients was carried out in May 1972. The median survival time in ALL was 18 mo and in AML 4.3 mo. CNS leukemia was observed in 41 (32%) ALL cases and seven (7%) AML patients.

The incidence of CNS leukemia per month of survival was as follows: in ALL patients, 4% at 4 mo, 13% at 8 mo, 29% at 16 mo, and 40% at 24 mo (Fig. 1); in AML patients, 3% at 4 mo and 13% at 8 mo.

The appearance of CNS leukemia in ALL (Fig. 1) was higher in children than in adults, the difference between the two curves was significant at 20 mo ($p < 0.01$).

The incidence of CNS leukemia in patients with initial organomegaly (liver, spleen and/or lymph node enlargement present at time of diagnosis) was higher...
Fig. 2. Incidence of CNS leukemia in relation to initial WBC count in acute lymphoblastic leukemia.

(46\textsuperscript{o}o) compared with those without initial organomegaly (25\textsuperscript{o}o) at 20 mo, respectively; confrontation with these two curves showed a significant difference ($p < 0.05$).

Patients with WBC count greater than 50,000 at time of diagnosis have had higher incidence of CNS leukemia (Fig. 2). We can see that the higher the initial WBC count is, the higher is the incidence of meningeal relapse. There was a statistically significant difference between patients with WBC count less than 10,000/cu mm and the group with initial WBC above 50,000/cu mm ($p < 0.05$). Comparison between the other curves did not show significant difference.

The interrelationship between three factors—age, early organomegaly, and initial WBC count—was determined. There was no significant difference between the age and organomegaly or age and WBC counts. As for the WBC count, there was a statistically significant difference ($p < 0.01$) between the groups with and without organomegaly.

DISCUSSION

The proportion of patients with acute leukemia developing manifestations of CNS involvement has increased markedly during the last two decades.

Evans,\textsuperscript{1} in a study of 921 children over a period of 14 yr (1947–60), found that the proportion of patients with manifestation of CNS involvement rose from approximately 4\textsuperscript{o}o in the early years of her review, to 40\textsuperscript{o}o in patients diagnosed during 1960. The same author,\textsuperscript{2} in a similar group of 209 children studied during 1963–64, found an over-all incidence of 51\textsuperscript{o}o. The incidence was 56\textsuperscript{o}o in patients with ALL and 25\textsuperscript{o}o in those with other types of leukemia. CNS leukemia symptoms developed at a steady monthly rate of 3.8\textsuperscript{o}o for the first 24 mo and then decreased to 2\textsuperscript{o}o, suggesting that the increase of incidence is largely due to increased length of survival. Nies et al.,\textsuperscript{4} in a similar study at the National Cancer Institute found, during 1953–58, an incidence of 25\textsuperscript{o}o in ALL and 4\textsuperscript{o}o in patients with AML; during 1961–63, meningeal leukemia was recognized in 42\textsuperscript{o}o of patients with ALL and 12\textsuperscript{o}o of patients with AML. They commented that the increased incidence between series was primarily due to the increased number of lumbar punctures performed in the later group on patients without major CNS symptoms, and also to their longer life span.

In the present study, the over-all incidence of CNS infiltration was 32\textsuperscript{o}o in ALL and 7\textsuperscript{o}o in AML. The monthly rate of incidence was similar in both
groups: 1.6\% during the first 10 mo after diagnosis; this result is consistent with other studies.\(^2\) Therefore, it is believed that the increase in survival in ALL during the last years and the increase of lumbar punctures performed on asymptomatic patients (due to greater awareness of the possibility of meningeal infiltration) are mainly responsible for the increase in diagnosis of CNS.

The incidence of CNS relapse was higher in children than in adults, 41\% and 19\% at 20 mo, respectively (\(p < 0.01\)).

The enlargement of lymph nodes, spleen, or liver, present at the time of diagnosis, increased the incidence of meningeal leukemia. At 10 mo survival, 21\% of the patients with initial organomegaly and 18\% without initial organomegaly had developed CNS leukemia; moreover, after 20 mo survival, 46\% and 25\%, respectively, showed CNS infiltration (\(p < 0.05\)).

The present data show that there is a relationship between the incidence of CNS leukemia and the initial peripheral WBC count. Patients with a WBC count of more than 50,000/cu mm had a significantly greater incidence of CNS involvement than patients with WBC count of less than 10,000 cu mm: 59\% versus 15\% at 20 mo (\(p < 0.05\)). Recently, Melhorn et al.\(^7\) reported similar results in a group of 47 children with acute leukemia. On this point it is worth mentioning that a correlation between WBC count and survival has been shown in earlier studies.\(^8-10\)

From the results of this study, it can be inferred that the risk of CNS leukemia is higher in children and in patients with early organomegaly or initial high WBC count. The patients in whom these factors are combined may be considered a high-risk population to develop meningeal leukemia.

In spite of the fact that we can identify patients with "high risk" for developing CNS leukemia, the data now available suggest that CNS prophylactic treatment is effective.\(^11\) Therefore, it should be given to all patients, because even those with favorable initial parameters may develop CNS leukemia.

REFERENCES


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