LEUKEMIA IN CHILDREN

THE CLINICAL AND THERAPEUTIC STUDIES OF 100 CASES

TAKASHI YOKOYAMA, YASUHIKO HIYOSHI
AND KINSUKE NAKAGAWA

*Department of Pediatrics and Child Health, Kurume University
School of Medicine, Kurume, 830, Japan*

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Clinical manifestations, laboratory data and results of therapeutic measures have been statistically studied on the 100 children whose clinical records were complete, in order to compare the therapeutic efficacy of the protocol and former ones.

INTRODUCTION

Cancer is now the number one cause of death from disease in children between 1 and 15 years of age. Acute leukemia is the most common malignancy, it occurs in nearly four per 100,000 children (Fernbach and Starling, 1975). Prior to the availability of chemotherapy for acute leukemia in children, the median time of survival from diagnosis to death was approximately three to four months. As new agents became available, survival gradually improved. Today, remission rate in excess of 90% are standard and expected, and as many as 50% of patients remain in complete continuous remission without hematologic or extramedullary relapse for more than five years following diagnosis (Miller, 1975). These advances have been the result of more effective chemotherapeutic regimens, better supportive care, and perhaps most significantly, the prevention of central nervous system leukemia.

PATIENTS AND METHODS

During 23 years through 1952 to 1975, 120 children with leukemia were hospitalized in Department of Pediatrics of Kurume University School of Medicine. We investigated the clinical records of 100 children except 20 whose records were incomplete. Survival rate was calculated by life table method.

RESULTS

1. Age distribution and sex difference of the incidence

The distribution of the children by age is shown in Fig. 1. The peak incidence is evident at three years of age and male to female ratio of 1.3 to 1.0, which are compatible with surveys by other authors.

2. Clinical manifestations

The clinical manifestation of acute

Fig. 1 Age distribution and sex difference.

leukemia in childhood are extremely varied and frequently nonspecific. Fever, pallor and anorexia, which resemble the signs of acute infection are the major symptoms at onset. The presenting signs and symptoms are the listed in Fig. 2. Anemia, mostly normocytic, normochromic in nature with Hb concentration less than 10g/dl, was present in 77 children at the time of diagnosis. Fever was noted in 62, bleeding in 32, including subcutaneous and submucosal bleeding and less frequent nosebleed. Bleeding, involved ocular fundi in 2. Hepatomegaly was noted in 27, splenomegaly in 24, lymphadenopathy in 22, and bone and joint pain in 5.

3. Types of leukemia and their incidence

Of the three main morphologic types

Fig. 2 Clinical signs and symptoms at first examination.

—acute leukemia, chronic myelocytic leukemia and chronic lymphocytic leukemia—the acute form is responsible for the majority of cases seen in childhood chronic myelocytic leukemia constitutes no more than 5 per cent of the cases; chronic lymphocytic leukemia has been entirely unknown in childhood. A few cases with unusual morphology (characterized as monocytic, eosinophi-

Abbreviations used

ALL : acute lymphoblastic leukemia
 AML : acute myeloblastic leukemia
 APL : acute promyelocytic leukemia
 AUL : acute undifferentiated leukemia

CML : chronic myelocytic leukemia
 CNS : central nervous system
 WBC : white blood cell counts

lic, mast cell, and reticuloendothelial) have been described. Acute forms of the disease may be classified as lymphocytic, undifferentiated, or myelocytic.

44 cases in this series seen through 1971 to 1975, the number of children with acute forms was 42 (95%) chronic form, 2 (5%), consisting of ALL 24 children (55%), AUL 9, (20%), AML 8, (18%), APL 1, (2%), CML 2, (5%).

TABLE 1

Types of leukemia and CNS involvement

Cellt ypes	No. of cases	No. of CNS involvement
ALL	24 (55%)	7 (29%)
AUL	9 (20%)	0
AML	8 (18%)	1 (13%)
APL	1 (2%)	0
CML	2 (5%)	0
Total	44	8

(1971~1975)

4. Relationship between the therapeutic protocol and outcome

The customs of various therapeutic protocols indifferent year periods are summerized in Fig. 2. The patients had been treated with symptomatic therapy only before 1954. Through 1955 to 1964, steroid hormone and 6-MP were the drugs used, and through 1965 to 1972, Vincristine (VCR), Prednisolone, Methotrexate (MTX), 6-MP and Cyclophosphamide were the drugs of choice. Systemic therapeutic approach has been employed with the protocol of Kyushu Childhood Leukemia Study Group (KCLSG) since 1972, when KCLSG was initiated. This protocol (protocol-721) consists of remisson induction with VCR and prednisolone, followed by vigorous maintenancetherapy with VCR, prednisolone, 6-MP and MTX. The programme

of maintenace therapy has been devided into two groups, namely Group-A and Group-B. The interim report showed more longer period of remisison in the Group-A, which has been developed into protocol 745-X, with a few modiffication in May, 1974 (Fujimoto, 1974).

Protocol 721, A and B have been employed for the treatment of peroxidase reaction-negative acute leukemia since 1972, with 4 exceptional cases to which the protocol was not applied. Patients with peroxidase reaction-positive acute leukemia was treated mainly with Mini-COAP therapy. The mean time period by which 50% survial rate was reached was two months in four patients before 1954, 5.5 months in 32 through 1955 to 1964, and 6.5 months in 28 through 1965 to 1971. After 1972, among the patients treated independently from the protocol, the mean periods of 50 % survial rate were 10.5 months in four patients with peroxidase reaction-negative leu-

Fig. 3 Survival rate of acute leukemia.

Fig. 4 Protocol 721.

Fig. 5 Protocol 745-X.

kemia and 10.5 months in eight patients with peroxidase reaction-positive leukemia. In four patients treated on the basis of protocol 721-B, the mean period of 50% survival rate was 16 months, while that of 20 patients on the protocol 721-A was over 40 months. Protocol 721-A has induced complete remission in all of 20 patients at the initial episode without any serious side effect, and made maintenance therapy possible without hospitalization.

5. CNS leukemia

The CNS leukemia, which has been increasing in frequency together with improving survival period, is most predominantly encountered in ALL, and it has been reported that the incidence in CNS involvement was as high as 45 to 70 % of all ALL. Cases in earlier period when prophylactic CNS therapy was not considered.

The incidence of CNS involvement was more predominant in ALL also in

this series; seven patients out of 24 with ALL and 1 patient in eight with AML. The CNS involvement was demonstrated in the six patients during the period when they were in remission. MTX 12 mg/m² and hydrocortison 12 mg/m² have been injected intrathecally as the preventive measure against CNS involvement. Less frequent incidence of CNS involvement has been reported with the combined therapy of intrathecal injection with MTX and skull irradiation (2,400 rads) (Hustu, 1973).

6. White blood cell count at the time of diagnosis and prognosis

The white blood cell counts at the time of initial diagnosis varied from 1,100/cmm to 592,000/cmm and 22 % of the patients had WBC less than 5,000/cmm. In 59 patients with initial WBC less than 20,000/cmm, 17 (28.8 %) survival over 18 months, while in 41 patients WBC over 20,000/cmm no patients survived more than 18 months, demonstrating a poor prognosis of the latter group.

It has been reported that over 90 % of the longterm survivors had an initial WBC and initial peripheral blast count of less than 20,000/cmm and 10,000/cmm respectively (Till et al, 1973).

7. Cause of death

Post mortem evaluations were performed on 23 children died between 1970 and 1975. Of these, seven died of intracranial bleeding, eight of infection and eight of unknown causes. Among eight children with infections disease, five developed septicaemia with causative agents as showed in Table 2.

One of the three patients who eventually had varicella was in remission and the other two were in relapse.

TABLE 2
Causes of death

Intracranial bleeding	7
Sepsis E.coli	3
Klebsiella	1
Cryptococcus	1
Varicella	3
Unknown	8
Total	23

(1970~1975)

COMMENTS

Age of onset, sex difference and clinical manifestations were identical with those reported in previous literatures. We have employed the same therapeutic measures as for ALL to AUL, since the latter, which is difficult to differentiate either of myelocytic or lymphocytic origin and highly sensitive to steroid hormone and antineoplastic agents. The majority of AUL is undifferentiated myeloblastic leukemia in nature and no difference has been noted between the two types of leukemia from the view of therapeutic plans. The protocol 721-A has achieved more excellent therapeutic results as compared with any other therapeutic programmes for the childhood leukemia with negative peroxidase reaction. We are now executing protocol 765.

The initial WBC was one of the strongest prognostic indicators, and the children with an initial WBC greater than 20,000/cmm had a poor prognosis.

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