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ACUTE LYMPHOCYTIC LEUKEMIA -- A REVIEW

A Review of the Cases of Acute Lymphocytic Leukemia
Seen at the University of Nebraska
College of Medicine Hospital from 1955 - 1966

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Acute lymphocytic leukemia is peculiar to the acute leukemias. Unlike acute myelocytic and monocytic leukemia it afflicts primarily children and young adults.⁵ With the advent of modern treatment methods it has twice the remission rate and three times the mean survival of other acute leukemias.⁶

Prior to the introduction of steroids and folic acid antagonists in the 1940's untreated acute lymphocytic leukemia had an average survival of 4 months. With improved symptomatic therapy the average survival increased to 9 months. Later with the introduction of 6-mercaptopurine in the 1950's complete hematologic and clinical remissions became common with subsequent increased average survival to 11.5 months.⁵

To date there is no standardized treatment regimen, although there are a number of effective chemotherapeutic agents. Numerous reports are present in the literature advocating new treatment programs utilizing existing drugs. These programs are usually attendant upon a particular theory as to the most effective method of leukemic cell suppression or eradication. Foremost among these are the "VAMP" intensive chemotherapy program of Freireich et al,² "composite cyclic therapy" of Zuelzer,⁶ and the "sequential chemotherapy" program of Mangalik et al.³

Although at present no cures can be demonstrated, long term survival is not uncommon. This increased survival is directly related to the effectiveness of remission induction and maintenance of that remission.¹ Multiple remissions are possible but at present the disease is considered to be ultimately fatal with the development of leukemic cell resistance to available chemotherapeutic agents.

Of the currently advocated treatment programs, Zuelzer's "composite cyclic therapy" has yielded survival figures comparable to any present in the literature. It should be mentioned however that his is a select group

in that cases are limited to children under ten years of age. This program employs prednisone and 6-mercaptopurine for remission induction and cyclic maintenance therapy with 6-mercaptopurine and methotrexate.⁶

This review will analyze those cases of acute lymphocytic leukemia treated at the University of Nebraska College of Medicine Hospital from 1955 - 1966 and compare treatment results to Zuelzer's study of cases from 1955 - 1963.

Materials and Methods

All cases of acute lymphocytic leukemia treated at the University Hospital from 1955 - 1966 are included in this review. Cases were found from a master file in the hematology department. Data was compiled from code sheets prepared by technicians for a computer program of analysis currently in development by the hematology department at the University.⁴ Vital data, e.g. the diagnosis, were verified from the patient's records.

The diagnosis in each case was made by the hematology staff from the peripheral blood smear and bone marrow considered diagnostic for acute lymphocytic leukemia. Two cases of lymphosarcoma with terminal leukemic phase were excluded.

Survival was measured from diagnosis to death and expressed to the nearest whole month. Those cases still living (4) or lost to follow-up (1) were considered dead at the completion of the study or on the date lost to follow-up in computation of survival figures.

Time spent in the University Hospital, "hospital days" or HD, was determined in each case. Morbidity index (MI), a term coined for this review, is the ratio of HD to survival in days and may be expressed as per cent. It is used as an indication of relative morbidity as is reflected by the necessity of hospitalization.

Drugs used in each case throughout the course of the disease are simply listed in table 1. In general the treatment program from 1955 - 1960 consisted of

Table 1. -- Summary of All Cases of Acute Lymphocytic Leukemia Treated at the University Hospital, 1955 - 1966.

Init.	1st Seen	Age (Yrs.)	Survival (Months)	HD	MI	Drugs Used
J.D.A.	8/55	7	9	37	.1	*Pu,P
J. S.	10/55	7	13	34	.09	A,P
D. D.	2/56	1	2	49	.8	P,A
J. N.	3/56	57	5	32	.2	Pu,f
R. P.	11/56	17	1	50	1.	P,Pu
M. D.	1/57	5	2	56	.9	A,P
D.S.Y.	6/57	3	1	7	.2	A
B. A.	7/57	57	0	7	1.	P
C. W.	8/57	3	4	20	.2	P
W. M.	3/58	56	2	45	.8	Pu,P
G. H.	9/58	41	9	56	.2	*Pu,P
M. F.	7/59	16	10	59	.2	*Pu,P,M
C. B.	10/59	2	16	70	.1	Pu,P,D
T. D.	4/60	3	7	28	.1	*P,Pu
<u>D. W.</u>	<u>12/60</u>	<u>- 23 -</u>	<u>2</u>	<u>23</u>	<u>.4</u>	<u>*Pu,P</u>
C. G.	9/61	73	6	43	.2	Pu,P,M
M. H.	9/61	76	1	24	.8	Pu
D. E.	1/63	5	47**	55	.04	*Pu,M,P,V,C,f
J. M.	10/63	20	1	87	1.	Pu,P,M
D. H.	10/63	4	7	28	.1	P,M,Pu,V
L. E.	4/64	5	22	6	.009	Pu,P,M,V,f
A. H.	12/64	5	35**	10	.01	*Pu,P,M,V,f
J. B.	12/64	9	8	48	.2	*Pu,P,M,Vb,V
C. S.	3/65	2	21**	14	.02	Pu,M,P
R. T.	9/65	43	1	44	1.	M,Pu,P,V
D. M.	2/66	5	10**	15	.05	*Pu,M,P
M. E.	5/66	9	7**	15	.07	Pu,M,P
L. M.	8/66	37	5**	23	.2	Pu,M,P

*Prior chemotherapy
 **Living as of 12/66
 HD= hospital days
 MI= morbidity index
 Pu=6-mercaptopurine
 A=aminopterin
 M=Methotrexate
 P=prednisone
 V=vincristine
 Vb=vinblastine
 C=cytotoxin
 D=drug A
 f=folic acid

attempted remission induction with 6-mercaptopurine or aminopterin often with subsequent utilization of a glyco-steroid. From 1960 - 1966 it generally consisted of combination therapy with prednisone, methotrexate, and 6-mercaptopurine for remission induction and essentially "sequential" use of methotrexate, 6-mercaptopurine, and prednisone for remission maintenance. Treatment variations were made dependant upon the course of the disease in each case.

Survival and epidemiologic data were analyzed and tabulated. Survival figures were compared to Zuelzer's study.

Results

All data collected is shown in table 1. There were 28 cases of acute lymphocytic leukemia seen in the period 1955 - 1966. These were divided into two groups for purposes of survival comparison, group 1 (1955 - 1960) and group 2 (1961 - 1966). Male to female ratio was 2.1. With the exception of one negro all patients were caucasian. Age range was 1 - 73 years with a mean age of 21 years and a median age of 14 years. Over half of the patients were under 10 years of age when first seen (fig. 1).

The mean overall survival was 9.1 months with a median of 4 months and a range of 0 - 47 months. For group 1 the mean survival was 5.5 months and the median 4 months with a range of 0 - 10 months. For group 2 the mean survival was 13.2 months and the median 7 months with a range of 1 - 47 months. It is interesting to note that even with current treatment methods survival is quite variable. The difference in survival between groups 1 and 2 shows that improved treatment methods often with the same chemotherapeutic agents prolonged life. Moreover the three patients with the longest survival were still living at completion of the study.

When survival figures were determined for those patients under 10 years of age (as in Zuelzer's study), the mean survival was 13.2 months and the median 8 - 10 months.

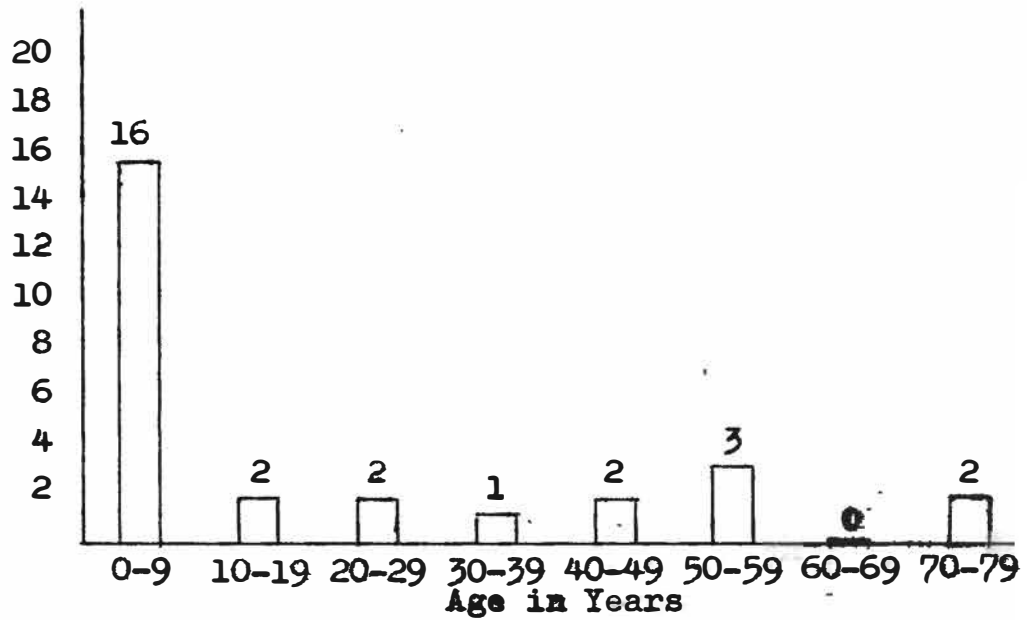


Fig. 1 -- Age distribution of 28 patients with acute lymphocytic leukemia when first seen at University Hospital, 1955 - 1966.

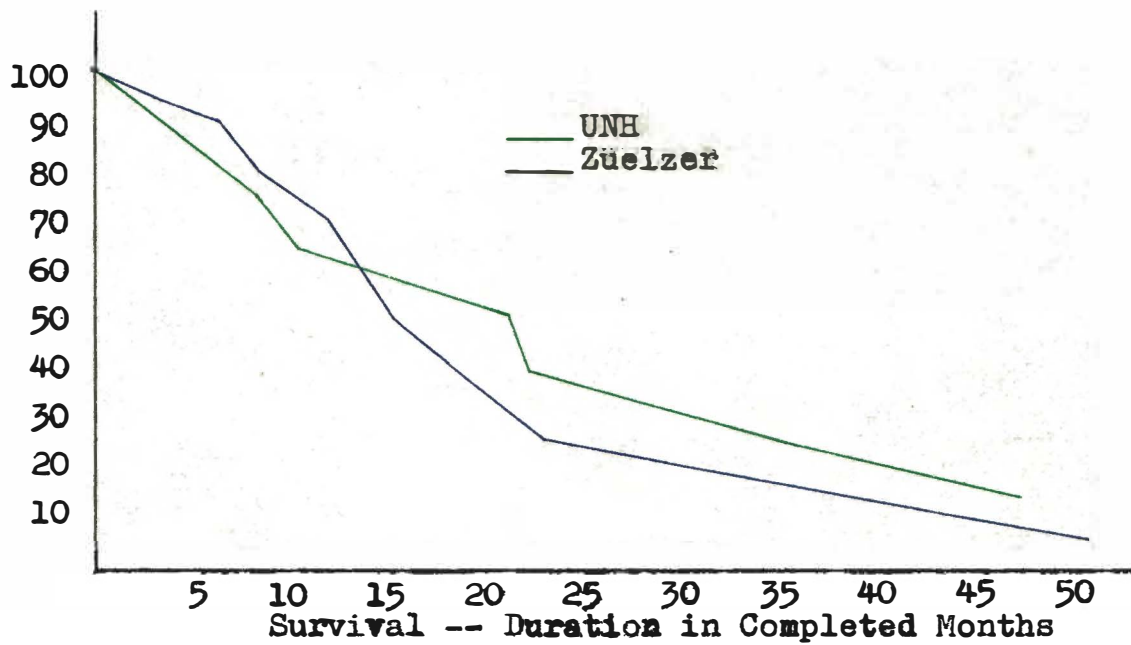


Fig. 3 -- Per cent survival of patients under age 10 with acute lymphocytic leukemia at University Hospital, 1961 - 1966. (Compared to Zuelzer, 1955 - 1963)

Moreover, the mean survival of children in group 2 alone was 19.6 months with a median of 10 - 21 months. Comparable figures for Zuelzer's study were a mean survival of 15.8 months with a median of 14.2 months.⁶ The per cent survival of the children in group 2 plotted against the duration of survival is shown in fig. 2 -- compared to Zuelzer's study.

The mean survival of adults (over age 15) was 3.6 months and that of children was 13.2 months, thus demonstrating the well known superior response to treatment in children.

In the majority of cases time from onset of symptoms to diagnosis was less than 2 months. Those cases where diagnosis was delayed tended to do poorly. In most cases onset of treatment was coincident with diagnosis.

The mean morbidity index for group 1 was 40% and that of group 2 was 30%. Those individuals with the longest survivals tended to have the lowest MI. Thus, the longer life was often useful because the individual was returned to his home. Also with treatment there was often obvious increased comfort and feeling of well-being even without prolonged survival.

Discussion

It is shown by this review that improved treatment methods have resulted in improved survival of those patients afflicted with acute lymphocytic leukemia. Although no 5 year survivals can be demonstrated and cure is probably non-existent at present, long-term survival is possible as shown by three cases surviving 4, 3, and 2 years. The longest survivor had aplastic anemia two years prior to the onset of leukemia, therefore his overall survival might conceivably be 6 years.

Survival figures for children (under age 10) seen from 1961 - 1966 are comparable to Zuelzer's with a mean survival even greater. No significant difference can be demonstrated between the cyclic therapy by Zuelzer and the sequential program at the University of Nebraska Hospital as to survival benefit.

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