Treatment of Childhood Acute Lymphocytic Leukemia *

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Thank you for the honor of sharing in this memorial to Frederick Stohlman. The work I will report today represents the efforts of many physicians and scientists who have tried to understand and control childhood leukemia.

In North America and Europe acute lymphocytic leukemia (ALL) represents approximately 80 percent of childhood leukemia and 30 percent of childhood cancer. The disease usually occurs without warning in the well child who has been well cared for. It is characterized by fever, pallor, fatigue, malaise, bone pain, bleeding and enlarged viscera and lymph nodes. Without effective treatment the child soon dies of hemorrhage, infection or tumor encroachment. The diagnosis is made by examination of aspirated bone marrow.

In 1948 it was demonstrated that antifolate compounds produced clinical and hematological remissions in some children with ALL [10]. However, the remissions were only partial – cessation of treatment was followed by relapse in a few weeks, and temporary – relapse usually occurred within a few months despite continued administration of the drug. Subsequently, corticosteroids, mercaptopurine, vincristine and occasionally cyclophosphamide were demonstrated to induce remissions of a similar nature [11]. By 1961 it was possible to prolong the lives of children with ALL for a year or more but mortality remained near 100 percent. The major obstacles to cure were: drug resistance, initial and acquired; inadequate distribution of drugs to the leptomeninges resulting in primary meningeal relapse; treatment-related hematosuppression, immunosuppression and epithelial damage; and a pessimism about curing leukemia that imprisoned the wills of many physicians [15, 18].

The "total therapy" plan of treating ALL, initiated in 1962, embodied several innovative features: Combination chemotherapy for induction of remission and continuation treatment; reduction of leukemia cell mass to subclinical levels and restoration of hematopoiesis prior to antimetabolite

* This lecture is based on work performed at St. Jude Children's Research Hospital supported by National Cancer Institute grants CA 08480, CA 07594, CA 05176, CA 08151, by the American Cancer Society and by ALSAC. The work of the Midwest Children's Cancer Center is supported by National Cancer Institute grants CA 17997, CA 17700, CA 17851, by the American Cancer Society, the Faye McBeath Foundation and the Milwaukee Athletes Against Childhood Cancer.

therapy; meningeal irradiation early in remission to prevent meningeal relapse; cessation of chemotherapy after 2–3 years of continuous complete remission; and most important, a purpose to cure rather than palliate leukemia (Table 1) [15].

Early pilot studies suggested that the plan was feasible and useful [15]. Approximately $^{9}/_{10}$ths of the children experienced complete remission, hematological remissions were four times the usual length, and $^{1}/_{6}$th of the children remained in complete remission after treatment was stopped. However, the low doses of meningeal irradiation utilized were not effective in preventing meningeal relapse. In a later study the meningeal irradiation was increased and limited to the cranium and upper cervical area, and intrathecal methotrexate was administered during the irradiation period [2]. When followed by five-drug combination chemotherapy for 2½ to 3 years this treatment program resulted in a low frequency of meningeal relapse and ½ of the children are now surviving free of leukemia and off treatment for many years [19]. A comparative study proved that moderately high doses of preventive craniospinal meningeal irradiation reduced the risk of initial meningeal relapse 15fold and again led to one-half of the children surviving free of leukemia when they subsequently received three years of multiple drug chemotherapy [3]. At present meningeal irradiation is the only method demonstrated by long-term comparative study to prevent meningeal relapse both during chemotherapy and after its cessation [3,8,14,19,21].

Most of the children who survive continuously free of leukemia for five years and off treatment for two years are apparently cured. In Fig. 1 the initial continuous complete remission duration of 76 children entering complete remission in 1967 to 1970 are plotted on a semilogarithmic graph. All of the children received 2400 rads of cranial irradiation with simultaneous intrathecal methotrexate or 2400 rads of craniospinal irradiation early during complete remission. Subsequently they received multiple drug chemotherapy for 2½ to 3 years or until relapse or death during remission. As indicated, the complete remission duration curve forms a plateau after 4 to 5 years. All children represented in the plateau have been in complete remission for 8 to 10½ years and have been off treatment for 5 to 8 years. Except for the one child who relapsed after 5½ years of complete

Table 1. Plan of total therapy of acute lymphocytic leukemia 1962–75

Remission induction 4–6 weeks
To convert "late" leukemia into "early leukemia"
Prednisone + vincristine ± daunorubicin ± asparaginase
Preventive meningeal therapy 2–4 weeks
To eradicate arachnoid leukemia early in remission
cranial irradiation + intrathecal methotrexate or craniospinal irradiation
Continuation chemotherapy 2–3 years
To eliminate residual systemic leukemia
methotrexate + mercaptopurine + cyclophosphamide ± prednisone ± vincristine ± arabinosyl cytosine

remission all children in remission at 5 years remain so. This suggests that these children are biologically different from the children in the descending portion of the curve and that this difference represents biological cure of leukemia.

Since a plateau of continuous complete remission has been achieved the height of this plateau is now the criterion of success of curative treatment of ALL. Any new treatment or modification of treatment must be assessed with respect to this criterion. Since a plateau cannot be predicted or extrapolated statistically it is necessary to delay judgement about the curative value of treatment until actual experience demonstrates it.

The quality of survival for most children with ALL is satisfactory (Fig. 2, 3). Within a few weeks after initiation of treatment most children can return to normal activities such as school attendance and athletics [15,19,21]. Many children have 1–2 weeks of fever and somnolence approximately 6 weeks after cranial irradiation. All the children have various degrees of hematosuppression and immunosuppression, many exhibit inhibition of skeletal growth, and some demonstrate mucosal or skin disorders, elevation of hepatic enzymes in the serum, and macrocytic anemia. The children need to be monitored carefully to avoid excessive toxicity and to control infection. Trimethoprim and sulfamethoxazole is effective in preventing *Pneumocystis carinii* pneumonia in children at high risk [12].

After termination of chemotherapy an immunological rebound may occur with lymphocytosis of the bone marrow and rise in immunoglobulin levels [6]. Hematopoiesis recovers and elevated enzymes return to normal. Often growth and weight gain are accelerated and the children have increased energy and vitality [21]. Neuropsychological studies indicate that preschool children may experience impairment of short memory and

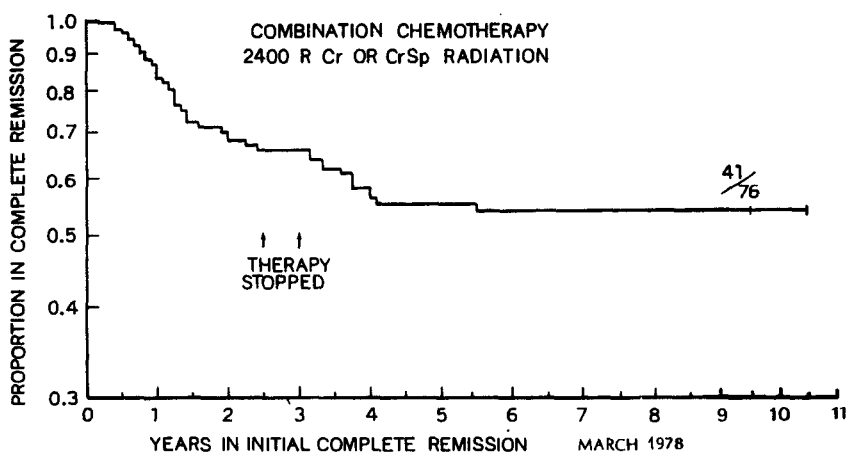

Fig. 1. This semilogarithmic graph describes the initial continuous complete remission duration of children who began receiving total therapy including preventive meningeal irradiation in 1967 to 1970. Treatment was stopped in all patients remaining in continuous complete remission after 2½ to 3 years. None of the children experienced initial meningeal relapse after cessation of therapy and only one child developed relapse after five years of complete remission. The level of this plateau of continuous complete remission is now the measure of curative value of treatment. It must be established by actual experience for each treatment plan or its modification

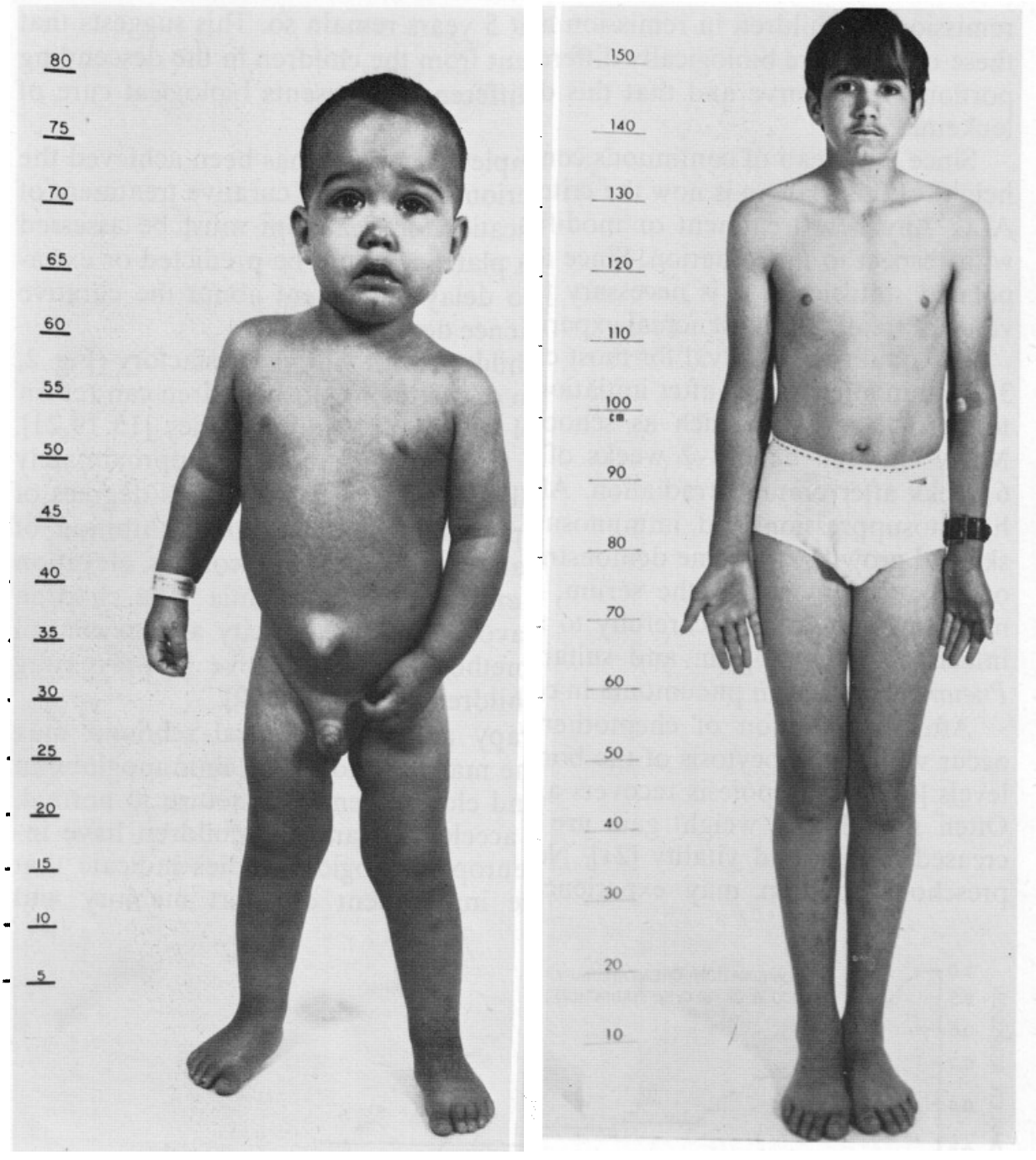

Fig. 2. Patient J.E. was admitted with ALL in August 1964 at age 1½ years. He survives continuously free of leukemia for 14 years and off therapy 11 years while enjoying normal growth, development and function

mathematical ability [9]. Early detection of these defects is important to allow remedial measures and to minimize school difficulties.

Reports of abnormal computerized cranial tomography, of paraventricular calcifications and of serious functional neurological defects have caused concern [13,17]. The evidence suggests that clinical meningeal leukemia, high doses of parenteral methotrexate following cranial irradiation and intercurrent infectious encephalitis may be responsible for many of

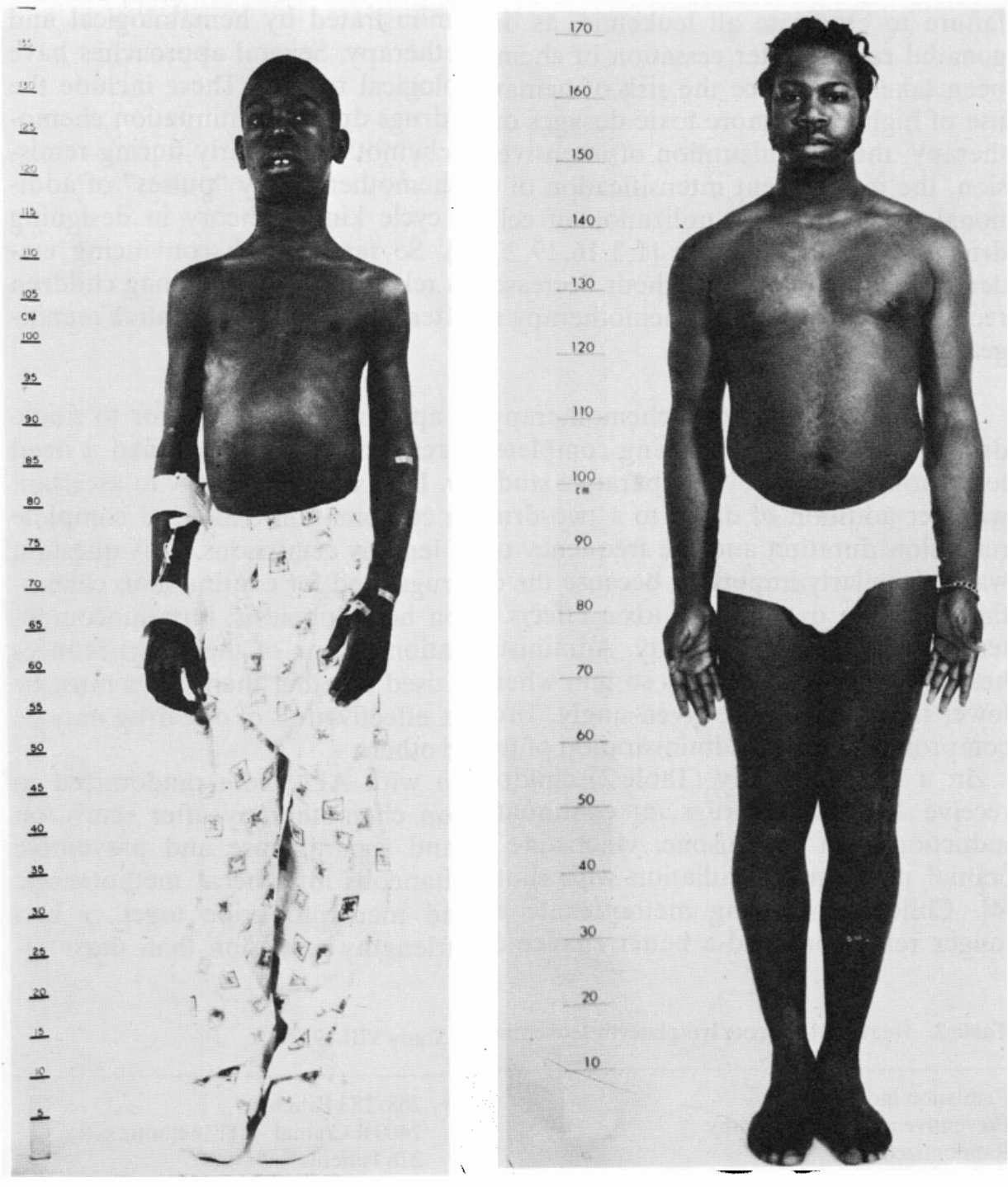

Fig. 3. Patient F.G., age 13 years, had an initial white blood cell count of 225,000 per cu mm. He has developed from adolescent to adult while continuously free of leukemia for 10 years. He has not received treatment for eight years

these problems. Also to be considered, however, are other neurotoxic drugs such as vincristine, asparaginase and prednisone, and the most common cause of cerebral atrophy in young children, protein-calorie malnutrition, a frequent concomitant of leukemia and its treatment.

The two most important reasons why children still die of ALL are drug resistance, as manifest by hematological relapse during chemotherapy, and

failure to eradicate all leukemia, as demonstrated by hematological and gonadal relapse after cessation of chemotherapy. Several approaches have been taken to reduce the risk of hematological relapse. These include the use of higher and more toxic dosages of drugs during continuation chemotherapy, the administration of intensive chemotherapy early during remission, the intermittent intensification of chemotherapy by "pulses" of additional drugs, and the utilization of cell cycle kinetic theory in designing drug treatment schedules [1,3,16,19,20]. So far we lack convincing evidence that any of these methods decreases relapse frequency among children receiving multiple agent chemotherapy after appropriate preventive meningeal treatment.

Although combination chemotherapy appeared to be superior to single drug treatment for continuing complete remission, there remained a need to demonstrate this by comparative study. It was also necessary to ascertain whether addition of drugs to a two-drug combination enhanced complete remission duration and the frequency of lengthy remissions. This question was particularly important because the drugs used for continuation chemotherapy have overlapping toxic effects on hematopoiesis, immunocompetence and epithelial integrity. Administration of one of the drugs reduces host tolerance to the others so that when used together their doses must be lower than if they were given singly. Thus, effectiveness of one drug may be compromised by the administration of the others.

In a 1972–75 study (Table 2) children with ALL were randomized to receive 1, 2, 3 or 4 drugs for continuation chemotherapy after remission induction with prednisone, vincristine and asparaginase and preventive cranial meningeal irradiation with simultaneous intrathecal methotrexate [4]. Children receiving methotrexate and mercaptopurine together had longer remissions and a better chance of lengthy remission than those re-

Table 2. Treatment of acute lymphocytic leukemia. Study VIII 1972–75

Remission induction	268/283 Patients			
Preventive meningeal therapy	2400 R Cranial + IT methotrexate			
Randomized	228 Patients			
	M	MMp	MMpC	MMpCA
No. Patients	20	68	70	70
Relapses	15	24	32	28
Died in complete remission	1	0	4	5
Continuous complete remission	4	44	34	37
Off therapy in continuous complete remission	4	37	26	28

In this comparative study remission was induced with prednisone, vincristine and asparaginase and followed by preventive cranial meningeal irradiation with simultaneous intrathecal methotrexate. Patients were assigned at random to one of four regimens: methotrexate alone (M), methotrexate and mercaptopurine (MMp), methotrexate, mercaptopurine and cyclophosphamide (MMpC), or methotrexate, mercaptopurine, cyclophosphamide and arabinosyl cytosine (MMpCA). The results indicate superior efficacy for the MMp combination.

ceiving methotrexate alone. On the other hand, patients receiving cyclophosphamide or cyclophosphamide and arabinosyl cytosine in addition to methotrexate and mercaptopurine tended to have shorter remissions and fewer lengthy remissions than those in the two-drug group. These results indicate that addition of simultaneous cyclophosphamide or cyclophosphamide and arabinosyl cytosine did not improve the efficacy of the methotrexate and mercaptopurine combination. Whether a cyclic or sequential schedule of two two-drug combinations might prove superior needs to be determined.

The morbidity and mortality of the one, three and four-drug regimens were greater than those of the two-drug combination (Table 3). Children on methotrexate alone received two to three times higher doses of this drug than those receiving the combinations. Nine out of 20 suffered leukoencephalopathy during initial complete remission while none of the other 218 children developed evidence of this complication during initial remission. In the three- and four-drug groups immunosuppression was more pronounced and was accompanied by higher risk of varicella-Zoster infection and *Pneumocystis carinii* pneumonia, more frequent hospitalizations and deaths during complete remission. Thus the most efficacious treatment regimen also had the least morbidity.

The most significant opportunity for improving the treatment of ALL in the past five years has been its biological and clinical classification by immunological cell surface markers (Table 4) [5,7]. This allows species identification of the leukemia cells, the first step toward developing specific cytocidal or cytostatic therapy. This may also provide further specific biological and chemical correlates of sensitivity and resistance of ALL cells to current drugs and may lead to new concepts of control of ALL. For example, the relatively good prognosis of common type ALL could be related to increased glucocorticoid receptors on the common type leukemic lymphoblasts [22]. Other speculations for the good prognosis of common type ALL include: its origin in the bone marrow where drug diffusion is probably superior than in the visceral masses characteristic of thymic cell and B-cell ALL; its low mitotic rate and less DNA synthesis, which might reduce the risk of mutation to drug resistance; its lower number of leu-

Table 3. Morbidity during initial complete remission. Study VIII

	M	MMp	MMpC	MMpCA
No. Patients	20	68	70	70
Cases of Leukoencephalopathy	9	0	0	0
Cases of Pneumocystis pneumonia	0	1	7	19
Cases of Varicella-Zoster	0	8	16	17
Total No. Hospitalizations	13	25	49	72

See table 2 legend for explanation of abbreviations. The two-drug regimen was accompanied by the least morbidity during initial complete remission. This suggests that efficacy and morbidity of a chemotherapy regimen may be unrelated.

kemia cells and therefore greater susceptibility to chemical eradication and less possibility of a drug resistant variant; the better stimulation of normal lymphocytes by common type lymphoblasts in mixed leucocyte cultures and therefore greater susceptibility to a theoretical immune control. Another speculation is that common type ALL is a developmental disorder of lymphocytes. Children normally experience rapid lymphocytic proliferation from age two to six years, the most frequent age for common type ALL. Is it possible that factors controlling lymphocytic proliferation after age six years contribute to control of common type ALL? Does leukemia therapy simply repress common type lymphoblast replication until normal controls take over as the child becomes older?

Table 4. Immunologic classification, childhood lymphocytic leukemia

	Common	Null	T cell	B cell
Frequency	60%	15%	22%	3%
Sex, Age	M = F, 2–6 yrs.	?	M, > 8 yrs.	?
Origin	Marrow	?	Thymus	Alimentary
Mitotic Rate	Low	?	High	High
Initial white blood cell count	Low	High	High	Low or High
Remission	Long	Less	Less	Least
Surface immunoglobulin	—	—	—	+
Erythrocyte rosettes	—	—	+	—
Thymic antigens	—	—	+	—
Common ALL antigen	+	—	—	+
Ia antigen	+	±	—	+

This tentative classification of ALL is based on immunological cell surface markers of the leukemic lymphoblasts. For valid determination of species, leukemic lymphoblasts of the bone marrow need to be studied prior to chemotherapy. The table was prepared by Dr. Luis Borella.

Summary

ALL in children cannot be considered incurable. Approximately one-half of children receiving modern therapy survive free of leukemia 5–10 years after cessation of treatment and at little or no risk of relapse.

The value of any treatment program must be measured by the proportion of children surviving free of leukemia off therapy and at little or no risk of relapse, that is, the proportion that is apparently cured. This cannot be projected or extrapolated from preliminary data.

The classification of ALL into biological species by immunological markers may lead to the development of more specific and effective treatment as well as to better understanding of its origin and nature.

Most important, it must be emphasized that the majority of children in the world do not benefit from advances in treatment of ALL because of their complexity, hazards, expense and inaccessibility. Therapeutic research needs to be directed away from more complex, expensive technology such as bone marrow transplantation and sophisticated radiotherapy. Effort

should be concentrated on understanding the fundamental biology of children's ALL and on its practical application for specific, effective, simple, safe and cheap treatment. In this way we can assure that all children in the world will benefit from our science and we can best fulfill our obligations as scientists and physicians.

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