Trends in the Treatment of Childhood Leukemia

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Introduction

The gratifying results now being obtained in the treatment of children with acute lymphocytic leukemia has had at least two major effects on the attitude of the medical community. First, these results have encouraged physicians to think of ALL as an eminentably treatable and, perhaps, curable disease, Second, physicians have become more aware of the obligation to avoid serious side effects that might compromise the otherwise good results. My purpose in speaking to you today is to review briefly some of the results obtained, mainly at our own institution, in the treatment of this disease and to point out some of the problems that have been encountered as result of treatment. Our data has been reported in some detail recently (19) so I will present only selected points rather than an exhausive review. Some of the results I will talk about today are preliminary and will require months or years before definitive conclusions can be made.

Materials and Methods

Definitions

Acute lymphocytic leukemia (ALL) is diagnosed on the basis of excessive numbers of lymphoblasts and/or "stem cells" in an aspirated bone marrow specimen. In practice, this diagnosis includes all children with leukemia that is not characterized by Auer rods or myelocytic or monocytic differentiation. Special cytochemical stains and histological specimens are sometimes helpful, but, ultimately, the diagnosis ist the concensus of at least three experienced investigators. Approximately 78 % of leukemia cases at this institution are diagnosed as ALL. Children with lymphoblastic or "stem cell" lymphosarcoma who had marrow involvement at diagnosis are considered to have ALI and are included in these studies.

Our definitions of remission, relapse and survival are described in detail elsewhere (15). Complete remission duration is the period free of all signs of ALL,

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whether hematologic, visceral or in the CNS. CNS leukemia is diagnosed by the observation of leukemia cells in a Wright-stained centrifugate of cerebrospinal fluid (CSF). The appearance of leukemia cells in the bone marrow signifies hematologic relapse.

Methods

A brief outline of the treatment plan for the first seven studies is shown in Table 1. This shows some of the variations on the theme of therapy that has been used over the years. Basically however, treatment entails four phases: 1) remission induction, 2) preventive CNS therapy, 3) continuation (maintenance) chemotherapy, and 4) cessation of therapy.

Table I: Outline of Protocols

Remission Induction (4 to 6 weeks)
- Prednisone
- Vincristine
- + Daunomycin in Study VI (2)
- + Asparaginase in Study VIII

Preventive CNS Therapy (2 1/2 to 4 weeks)
- 500–1200 rads Craniospinal in Studies I–III
- None in Study IV (16)
- 2400 rads Cranial + I. T. Methotrexate in Studies V (4), VII (1), VIII
- 2400 rads Craniospinal in Studies VI and VII

Continuation Chemotherapy (2 to 3 years)
- Mercaptopurine daily
- Methotrexate weekly
- Cyclophosphamide weekly
- + Vincristine weekly in Studies III, IV
- + Vincristine – Prednisone Pulses in Studies V, VI, VII

Cessation of Therapy after 2 to 3 years of Complete Remission (3)

Patients

These studies include a total of 549 children with ALL, of whom 363 entered studies I through VII, from 1962 through 1971. From 1972 to the present, 186 previously untreated children have entered study number VIII which is still under way. The initial features of a majority of these patients have been reported elsewhere (19).

Results

Remission Induction

Successful remission induction has been obtained in over 90 % of children with ALL. Vincristine and prednisone has been the treatment used in most of these studies and the addition of daunorubicin or asparaginase has not appreciably improved the remission induction rate. The reason for failure of patients to attain complete remission include: fatal infection in 2.5 %, usually due to gram-negative

sepsis in the first week of therapy; failure to respond to chemotherapy in 5 %; and leukemic pleocytosis in the cerebral spinal fluid on the day of first complete remission marrow in 1 %.

Preventive Central Nervous System Therapy

Attempts were made in earlier studies to prevent CNS leukemia from emerging by eradiating undetectable cells in the meninges early in remission. These early studies employed 500 or 1200 rads of craniospinal irradiation. However, these doses of irradiation did not reduce the frequency of CNS leukemia which terminated complete remission in 15 of 37 patients (18).

In 1967 it was decided that failure to prevent CNS leukemia in the earlier studies may have been due to inadequate dosage. Therefore, a study was designed in which 2400 rads of cranial radiation was given along with 5 doses of intrathecal methotrexate simultaneously (4). This form of treatment met with success since CNS leukemia terminated complete remission in only 3 of the 37 patients (19). Furthermore, over one-half of these patients remain in initial continuous complete remission for 6 years and have been off all therapy for three years.

The efficacy of preventive CNS irradiation was tested in a randomized control study before the results of the previous study were known (2). Patients were randomized to receive or not to receive 2400 rads craniospinal irradiation without intrathecal methotrexate. CNS leukemia terminated complete remission in only 2 of 45 patients who received preventive irradiation. However, CNS leukemia terminated complete remission in 33 of 49 patients who did not receive preventive irradiation. This study provided further evidence that CNS leukemia could indeed be prevented with adequate doses of irradiation. Another feature of this study was to determine whether CNS irradiation at the same dosage level would be as effective if given at the first sign of CNS relapse. Therefore, the 33 patients who developed CNS leukemia were given therapeutic craniospinal irradiation. Although the CSF was cleared of leukemic cells in all 33 patients, this second complete remission was terminated by recurrence of CNS leukemia in 13 patients and by simultaneous hematological and CNS relapse in 2. Only 9 of the 33 have had a lengthy second complete remission.

In a subsequent study, patients were randomized to receive either 2400 rads cranial irradiation with simultaneous intrathecal methotrexate or 2400 rads craniospinal irradiation (1). The results showed no significant difference between in the rate of CNS relapse with either form of therapy, which confirmed the historical controls of the two preceding studies.

Continuation (Maintenance) Chemotherapy.

In the above studies, patients received mercaptopurine daily and methotexate and cyclophosphamide weekly during the continuation phase of chemotherapy. A controlled study (16) has shown that these agents must be given in maximum tolerated dosage to achieve optimal results. Variations on this basic regimen have included the addition of vincristine once a week or periodic brief courses of rincristine plus prednisone.

With the overall improvement in results, it became important to try to learn the relative contribution of CNS therapy and continuation chemotherapy. The

earlier studies, with apparently ineffective CNS therapy, had yielded a 17 % long-term leukemia-free survival rate. This had been improved to approximately 50 % in the studies using the higher dose of preventive CNS irradiation (19). In view of the major contribution of adequate CNS therapy, it was not known whether such aggressive chemotherapy during remission was necessary in view of its toxicity with a disturbing proportion of patients dying during initial continuous complete remission (21). An attempt to improve the therapeutic index of continuation chemotherapy by reducing toxicity was the major purpose behind the design of Total Therapy Study VIII. The preliminary results of this study are given here with the understanding that they are not definitive at this point, but do yield some important observations even at this early date.

The principal goal of Study VIII is to learn how the therapeutic index of chemotherapy during remission might be improved. Combination chemotherapy has been used to take advantage of different modes of action and lack of cross-resistance. The value of combination chemotherapy for inducing remission was established in 1951 with cortisone and methotrexate (6) and subsequently for other combinations (7, 8). Combinations of two or more drugs have also been given for continuing remission. For example, most of our studies employed a combination of mercaptopurine, methotrexate, and cyclophosphamide. There have been controlled studies of the cyclic (rotation of several drugs, one at a time) versus sequential (single drugs, each until relapse) chemotherapy (5, 12) and of the addition of one or another drug to a basic regimen (13). Controlled studies of different drug combinations began with the classical study by Acute Leukemia Group B (7a). The first controlled study of single versus combination chemotherapy, also performed by Group B, later showed that median durations of remission in childhood ALL were the same with mercatopurine, methotrexate, or both agents given simultaneously in the same dosages as in the single drug regimes (7). Since then, improved remission durations have been obtained in some studies using multiple-drug therapy (8, 20) leading to increasingly complex, multiple-drug regimens. For example, the L-2 protocol from Memorial Hospital employs eight drugs in cycles designed to take maximum advantage of estimated cellular kinetics (9).

However, individual drugs are not equally effective for prolonging remission of childhood ALL (8). Intermittent methotrexate is better than mercaptopurine and either is better than cyclophosphamide. Vincristine, cytosine arabinoside, daunomycin, asparaginase and other agents apparently are less effective. Most of these agents have overlapping toxicity, particularly myelosuppression and immunosuppression, often lowering the tolerable dosage limits of each drug in a multiple-drug regimen. In any given schedule, the effectiveness of single (8) or multiple (16) drugs is related to dosage. Thus, the critical question emerges: Does the advantage of multiple agent chemotherapy outweigh the disadvantage of dosage reduction of the more effective agents? An affirmative answer could lead one to employ all available agents (as many as six or ten) while a negative answer could lead to use of only the most effective agent (methotrexate) in maximum-tolerated dosage. Study VIII was designed to answer this question.

After successful remission induction and preventive CNS therapy, patients are randomized to receive one, two, three, or four drugs simultaneously during remission. The prescribed dosages are starting points only and in each regimen drug

dosages are adjusted to the maximum tolerated by the patient. Upward or downward dosage adjustments are made proportionately for all prescribed drugs. To obtain valid conclusions it is essential that the dose-limiting toxicity be of comparable degrees in each group to avoid the "half-dosage effect" seen in Study IV (16). The principal guide for dosage for dosage adjustment ist maintenance of the leukocyte count between 2000 and 3500/mm^3. Dosage reductions allowed for other predetermined degrees of toxicity, fever or infection are the same for all groups.

The preliminary results of Study VIII are given here mainly to illustrate the points of rationale and must not be viewed as conclusive at this early date. In the 33 months since beginning this study, 180 patients attained complete remission and received preventive CNS therapy. Thirty were given additional initial therapy due to the presence of features (CNS involved at diagnosis, mediastinal involvement, failure to attain remission after 4 weeks) associated with a poor prognosis and were not randomized. All received three drug maintenance. The remaining 150 were randomized to receive (1) methotrexate alone; (2) methotrexate + mercaptopurine; (3) methotrexate + mercaptopurine + cyclophosphamide; (4) methotrexate + mercaptopurine + cyclophosphamide + cytosine arabinoside. All agents except mercaptopurine were given by vein weekly.

At this time, the frequency of relapse has been approximately the same among patients receiving two drugs (6 of 44), three drugs (10 of 45) or four drugs (3 of 41 plus two deaths in remission). With methotrexate alone, 14 of 20 have relapsed and one patient died in initial remission. These early results show no systematic assocation of efficacy with the number of drugs but apparently indicate the superiority of multiple agents over methotrexate alone.

The smaller number of patients in the group receiving methotrexate alone is the result of discontinuing randomization to that arm of the study. This action was taken because the relapse rate was higher but, more importantly, a serious side effect was observed in this group. Eight of the twenty patients developed a neurological syndrome, not associated with CNS leukemia. It was characterized by disturbances of gait, speech and motor function. This syndrome was progressive and fatal in one child and left permanent residual damage in several others. The pathological lesion was found to be a severe leukoencepholopathy with myelin degeneration. This syndrome usually occurred in patients who had been receiving more than 50 mg per meter squared of methotrexate weekly for 6 months or more. A more detailed analysis of this problem is underway and will be reported in the near future. For the time being however, no patient who has received brain irradiation will be given more than 50 mg per meter squared per week of methotrexate by vein at this institution. This observation should serve to caution other investigators who are giving high doses of methotrexate to patients who had CNS irradiation.

Discussion

The efficacy and dangers of combined modality therapy of childhood ALL are reflected in these studies. The search by many investigative groups for more effective and less toxic modalities and combinations of therapy is illustrated by the scope of a few current studies. A recent Medical Research Council Study (28) has shown

that CNS leukemia is effectively prevented by craniospinal irradiation with intrathecal methotrexate. A review of previous trials (25) and the anatomical nature of arachnoid leukemia (31) have led us to conclude that intrathecal methotrexate alone does not effectively prevent CNS leukemia. However, studies by Group B (10) and the Sothwest Oncology Group now in progress, as well as the L-2 Protocol at Memorial Hospital (9), should yield more information on the preventive value of intrathecal methotrexate. Since systemic chemotherapy in maximum-tolerated dosage delayed the onset of CNS leukemia in Study IV (11, 15, 16), the definitive results with even more aggressive systemic chemotherapy in the L-2 Protocol (9) will be of interest. Another approach under study by Children's Cancer Study Group A is a test of the value of extending irradiation of the CNS to include other organs such as liver, spleen, kidneys and gonads.

The question of when to stop therapy is an important one. It has been our practice to stop therapy after two to three years of complete remission. Our experience with this approach has been published recently (3).

Despite improvement in therapy, many old problems remain unsolved and new problems have emerged. Both patient and physician take little satisfaction in a longer survival unless it is of satisfactory quality, but, we must remind ourselves that the most important negative influence on quality of survival is the leukemia itself. By any standard of comparison, the cost of relapse and its complications in human and monetary resources far exceeds that of therapy. Nonetheless, the evolution of studies for childhood ALL demonstrates a keen awareness of the responsibility to minimize undesirable effects of therapy. This requires even more careful design of studies because with combined modality therapy, the side effects may not be due to a single agent but to the unfortunate synergism of several agents.

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