Central Nervous System Therapy and Combination Chemotherapy of Childhood Lymphocytic Leukemia

By Rlomes J. A. Aur, Joseph Simone, H. Omar Hustu, Thomas Walters, Luis Borella, Charles Pratt and Donald Pinkel

In earlier combination chemotherapy regimens for childhood acute lymphocytic leukemia, nervous system leukemia terminated complete remission in over half the patients in a median time of 11 months. In the present study, cranial radiation (2400 R, ^{60}Co) and intrathecal methotrexate given early in remission were added to combination chemotherapy in an attempt to prevent or delay central nervous system relapse and termination of complete remission. Of 35 consecutive children with previously untreated acute lymphocytic leukemia, 20 of 30 who attained remission and received all initial phases of therapy have been in continuous complete remission for 23 to 30 months. Complete remission was terminated by nervous system relapse in three patients and by hematological relapse in five. Two patients died in complete remission of viral infections and others experienced reversible drug toxicity. We conclude that this combined therapy reduces the incidence of nervous system relapse in the first 2 years and prolongs complete remission.

Since 1962 we have employed multiple agent combination therapy in the treatment of children with acute lymphocytic leukemia. The purpose has been to achieve prolonged continuous complete remission and to establish a significant 5-year cure rate for this disease. Of 41 patients with previously untreated acute lymphocytic leukemia entered into early studies (1962–1965), 37 experienced complete remission and seven...
remain in continuous complete remission for 5 years or more and have been off all therapy for 2 to 3½ years. Thus, a 17 per cent 5-year leukemia-free remission rate has been achieved.5

In these studies complete remission has been most often terminated by nervous system leukemia occurring in the presence of hematological remission. The present therapy scheme was designed to explore the possibility that nervous system leukemia and thus early termination of complete remission could be prevented by administering a moderately high dose of cranial radio therapy along with intrathecal methotrexate early during complete remission.

This study has been in progress for more than 2 years. It is reported at this time because the results are currently superior to those of any previous treatment program.

MATERIALS AND METHODS

Patients
Thirty-five children with acute lymphocytic leukemia were registered consecutively in this study (Protocol V) from December 1967 to July 1968. Patients were admitted to the study as soon as the diagnosis was confirmed if they had no prior therapy except for blood transfusions or less than 7 days of corticosteroids. The ages ranged in the 18 boys (three black) from 2 years and 4 months to 15 years and 10 months, and in the 17 girls from 2 years and 1 month to 10 years and 8 months. The median age of all 35 patients was 4 years and 7 months.

Diagnosis
At this hospital a diagnosis of acute lymphocytic leukemia is made when lymphoblasts or "stem cells" predominate in the bone marrow. In effect, childhood leukemia is considered lymphocytic unless cells are characterized by unequivocal Auer rods and/or definite myelocytic or monocytic differentiation.

A diagnosis of central nervous system leukemia is made when leukemic blast cells are found in the Wright-stained centrifugate of a 2- to 5-ml. sample of spinal fluid. Whenever the cellular morphology is questionable, another sample is obtained in a few days. Because lumbar punctures are performed routinely at 10-week intervals, the diagnosis is made most often before the appearance of papilledema, headaches, vomiting, or other signs of increased intracranial pressure.

Definition of Terms
Complete remission duration is the time between the first complete remission marrow and the first sign of relapse, whether hematological, nervous system, or visceral. This definition differs from the one currently used by many investigators who do not consider complete remissions terminated when meningeal relapse occurs.6,7

Hematological remission duration is the time between the first complete remission marrow and first evidence of marrow relapse. Thus, hematological remission duration includes periods of central nervous system or other disease outside of the marrow. This definition corresponds to that termed complete remission duration by other investigators.6,7

Time to central nervous system leukemia is the period between the first complete remission marrow and the first evidence of central nervous system leukemia. Survival is the period between diagnosis of leukemia and death. It should be emphasized that complete remission refers to the initial continuous remission free of all evidence of leukemia, and that hematological remission refers to the initial continuous remission free of hematological evidence of leukemia. Five-year leukemia-free remission contrasts with 5-year survival which means that the patient has lived 5 years since diagnosis regardless of leukemic status.5
Table 1.—Outline of Therapeutic Regimen With Dosage Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Therapy Details</th>
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</thead>
<tbody>
<tr>
<td>Remission induction</td>
<td>Prednisone: 40 mg./sq. m./day in three or four divided doses</td>
</tr>
<tr>
<td></td>
<td>Vincristine: 1.5 mg./sq. m./wk. intravenously</td>
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<tr>
<td>Intensive chemotherapy</td>
<td>6-mercaptopurine: 1000 mg./sq. m./day intravenously for 3 days, followed by</td>
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<tr>
<td></td>
<td>Methotrexate: 10 mg./sq. m./day intravenously for 3 days, followed by</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide: 600 mg./sq. m. intravenously for 1 day</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>2400 R 60Co radiotherapy to cranium and, simultaneously,</td>
</tr>
<tr>
<td></td>
<td>Methotrexate: 12 mg./sq. m. intrathecally twice weekly for five doses</td>
</tr>
<tr>
<td>Continuation therapy</td>
<td>6-mercaptopurine: 50 mg./sq. m. once a day by mouth</td>
</tr>
<tr>
<td></td>
<td>Methotrexate: 20 mg./sq. m. once a week intravenously</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide: 200 mg./sq. m. once a week intravenously</td>
</tr>
<tr>
<td>The following therapy</td>
<td>Prednisone: 40 mg./sq. m./day by mouth for 15 days</td>
</tr>
<tr>
<td></td>
<td>Vincristine: 1.5 mg./sq. m./week intravenously for three doses</td>
</tr>
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* Complete protocol available on request.

**Therapeutic Regimen**

An outline of therapy with dosage guidelines is shown in Table 1. Informed parental consent was obtained before the start of therapy and before radiation. Weekly vincristine and daily prednisone were used to induce remission. If successful, patients were given high-dose intravenous chemotherapy daily for 1 week: 6-mercaptopurine on each of the first 3 days, methotrexate on each of the next 3 days and cyclophosphamide on the final day. On completion of this phase, central nervous system therapy was begun. The skull was irradiated through opposing lateral ports using a cobalt-60 unit. A tissue dose of 2400 R was delivered in 15 fractions over 2½ weeks with concurrent administration of methotrexate intrathecally, 12 mg. per square meter twice weekly for five doses. Following radiation, combination chemotherapy consisted of 6-mercaptopurine daily by mouth, methotrexate and cyclophosphamide weekly intravenously, and a 15-day course of prednisone and vincristine every 10 weeks.

**Modification of Chemotherapy**

Patients received maximum tolerated doses of each agent. Doses were increased if the total leukocyte count was consistently above 3000 per cubic millimeter. Doses of all agents were reduced to one-half if the leukocyte count was between 1000 and 2000 per cubic millimeter and full doses restored when the count rose above 3000 per cubic millimeter. All agents were stopped for severe leukopenia (less than 1000/cu. mm.), mucosal ulceration, severe vomiting or diarrhea, and in the presence of fever persisting longer than 2 days. Chemotherapy was restored when toxicity or infection resolved. If there was evidence of hemorrhagic cystitis, cyclophosphamide was to be stopped until the symptoms cleared, at which time it would be restored at full dosage with more precautions for proper hydration. A second episode of hemorrhagic cystitis was to be an indication for permanent cessation of cyclophosphamide. Chemotherapy was reduced whenever necessary to permit completion of cranial radiotherapy within the designated period.

**RESULTS**

Complete remission was successfully attained in 32 of the 35 patients (91%)
Fig. 1.—Per cent of patients remaining in complete remission in the present study (Protocol V) compared to earlier studies. Complete remission duration is the time from first complete remission marrow to first sign of relapse, whether hematological or meningeal. This differs from the definition of other investigators who do not consider meningeal relapse as terminating complete remission (see text). The numbers in parentheses represent the patients in continuous complete remission as of June 30, 1970. The broken lines represent the current span of complete remission durations in each protocol. A total of 126 previously untreated children with acute lymphocytic leukemia entered these studies and 114 (90%) attained remission. In Protocol IV, 42 of 45 who attained remission were randomized to receive half-dosage or full-dosage combination chemotherapy. (Central nervous system therapy given early in remission.)

entering this study. The median time from start of therapy to remission was 27 days, with a range of 19 to 33 days. Two of the three remission induction failures were in black children. Only one of the three black children entering the study attained remission. This is consistent with our experience that black children with leukemia do not respond to therapy as well as white children. A 13-year-old boy attained remission but expired 10 days later of fulminating pseudomonas sepsis and peritonitis related to preexisting intestinal perforation. Autopsy failed to show histological evidence of leukemia.

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During the phase of intensive intravenous chemotherapy, a 2-year-old girl developed varicella necessitating interruption of leukemia therapy for 3 weeks. Consequently, the phase of cranial radiation and intrathecal methotrexate was omitted and continuation chemotherapy begun when the varicella resolved. She has remained in continuous complete remission for 25 months.

Cranial radiotherapy and intrathecal methotrexate were tolerated without serious difficulty by all but one patient. This 3½-year-old girl displayed persistent malaise, nausea, vomiting, headache, and fever, necessitating abbreviation of this phase of therapy. She received all phases of therapy in maximum tolerated doses.

Therefore, of the 35 patients entering this study, 32 attained remission and 30 received all initial phases of therapy and entered the continuation chemotherapy phase.
Fig. 2.—Per cent of Patients remaining in hematological remission in the present study (Protocol V) compared to earlier studies. Hematological remission duration is the time from first remission marrow to first partial remission or relapse marrow. This corresponds to the definition of complete remission duration used by others (see text). The numbers in parentheses represent the patients in hematological remission as of June 30, 1970. The broken lines represent the current span of hematological remission durations in each protocol. A total of 126 previously untreated children with acute lymphocytic leukemia entered these studies and 114 (90%) attained remission. In Protocol IV, 42 of 45 who attained remission were randomized to receive half dosage or full dosage combination chemotherapy. (Central nervous system therapy given early in remission.)

Remission Duration and Survival (Figs. 1 to 3)

Twenty-one of 32 patients (64%) who attained remission and 20 of 30 (66%) receiving all phases of therapy are currently in continuous complete remission for 23 to 30 months (median 25 months). They enjoy normal childhood activities and attend school regularly.

Of the remaining ten children who received all phases of therapy, two died in remission of viral infections. A 9-year-old boy died of fulminating viral hepatitis after 13 months of continuous complete remission. Another boy died of disseminated cytomegalovirus infection after 14 months of continuous complete remission. In neither child was the onset of infection related to leukopenia, granulocytopenia, or physical signs of drug toxicity. Neither child had histological evidence of leukemia at autopsy.

Relapse of leukemia occurred in 8 of the 30 children receiving all phases of therapy. Hematological relapse ended complete remission status in five children after 12 to 27 months of continuous complete remission. Three of these developed nervous system leukemia 2, 5, and 7 months following hematological relapse. A fourth child died 4 months after hematological relapse and had no evidence of nervous system leukemia at autopsy. The fifth patient died 28 months from diagnosis, one month after hematological relapse, while under therapy for systemic histoplasmosis and encephalopathy of unknown etiology.
Nervous system leukemia ended complete remission status in the remaining three children. After 6 months of complete remission, one boy developed meningeal leukemia followed in 2 months by hematological relapse. Two children developed meningeal leukemia without hematological relapse after 14 and 24 months of continuous complete remission. They were treated with intrathecal methotrexate, which cleared the spinal fluid of leukemic cells and they remain in marrow remission for 27 and 29 months, respectively.

Twenty-three of the 32 children (72%) who attained remission (Fig. 2) and 22 of 30 (69%) receiving all phases of therapy have been in continuous hematological remission for 23 to 30 months. Twenty-five of the 32 children (78 per cent) who attained remission (Fig. 3) and 25 of 35 (71%) who entered the study have survived 2 years or longer from the date of diagnosis.

Infections

As noted above, one patient died of pseudomonas sepsis and peritonitis only 10 days after attaining complete remission and two died of viral infections after 13 and 14 months of continuous complete remission. Another patient developed systemic histoplasmosis after 26 months of continuous complete remission. Chemotherapy was discontinued and he subsequently experienced marrow relapse. Pneumocystis carinii pneumonia was diagnosed by pulmonary needle aspiration in three children while they were in complete remission. All were treated with pentamidine isethionate and recovered without sequelae. Also, during complete remission three children developed herpes zoster and two developed varicella. All recovered without direct sequelae; however, marrow
Fig. 4.—Comparison of the increase in height of patients after 1 and 2 years of therapy and the mean height increase for age in normal healthy children. The slopes are drawn to represent the ratio of the observed to the expected height increase for age. Only 8 of 30 patients attained 75 per cent or more of the expected height increase after 1 year on the study. After 2 years on the study, only 12 of 25 had attained 75 per cent of the expected height increase.

Relapse occurred in one child 5 weeks after his chemotherapy had been interrupted because of varicella.

Less serious infections included tonsillitis, pharyngitis, otitis media, segmental pneumonia, impetigo, cellulitis, blepharitis, gastroenteritis and urinary tract infection. The frequency of these infections was greater than expected in a general pediatric population, but most patients responded to therapy as well as children without serious underlying disease.

**Drug Toxicity**

Temporary reduction of drug dosages was frequently necessary because of toxicity. The 32 children who attained remission experienced a total of 240 leukopenic (less than 2000/cu. mm.) episodes during the 30 months of study. Two children who developed anemia with megaloblastic erythroid changes in the marrow recovered after reduction of methotrexate dosage. Thrombocytopenia prompted reduction of drug dosage in only one patient. Mucosal ulceration occurred infrequently and there was not a single episode of hemorrhagic cystitis.

The height of each child was measured at every clinic visit. The increase in height after 1 and 2 years on the study is compared in Fig. 4 to the mean height increase expected for age. After 1 year on therapy, only 8 of 30 children had attained 75 per cent or more of their expected height increase. Eleven of 30 had grown less than 50 per cent of the expected height increase.
After two years of study only 12 of 25 had attained 75 per cent of the height increase expected for age.

**DISCUSSION**

The present study concerns itself with one of the major impediments to cure of acute leukemia: proliferation of leukemic cells in anatomical sites not exposed to therapeutic concentrations of drugs, primarily in the central nervous system. Sequestration of leukemic cells in the nervous system serving as a potential nidus for systemic relapse was suggested by Johnson from studies with L1210 murine leukemia.

The importance of nervous system leukemia as a potential source of systemic relapse as well as a clinical complication is underscored by the current results of earlier combination chemotherapy studies. In Protocols I–III, irradiation of the central nervous system early in remission was used for the purpose of eradicating clinically undetectable leukemic cells, thus preventing subsequent development of meningeal leukemia and termination of complete remission. Of 37 patients who attained remission, 30 have relapsed and 29 have developed nervous system leukemia. In 16 of the 30 (53%), the nervous system was the initial site of relapse in a median time of 11 months (range: 2 to 28 months).

In Protocol IV, nervous system therapy was not given during remission. Thirty-nine of 42 patients who attained remission have relapsed and 35 have had nervous system leukemia. In 25 of the 39 (64%), the nervous system was the initial site of relapse in a median time of 10 months (range: 1 to 39 months). Therefore, nervous system leukemia terminated complete remission at the same time and frequency whether or not patients had received 500 to 1200 R of “prophylactic” craniospinal radiotherapy early in remission.

After 23 to 30 months in the present study, only three of the 30 patients who attained remission and received nervous system therapy have developed nervous system leukemia as the initial site of relapse. As seen in Fig. 1, 66 per cent of patients were in complete remission for 4 to 12 months in Protocols I–IV, a striking contrast to the present study (Protocol V) in which 66 per cent of patients currently enjoy continuous complete remission for 23 to 30 months. The greater intensity of central nervous system therapy in the current study may be responsible for this difference.

The duration of initial complete remission in this study is superior to the duration of initial hematological remission reported for other treatment regimens. The prednisone, vincristine, methotrexate, 6-mercaptopurine regimen of Henderson ("POMP") gave a 13.5-month median duration of hematological remission. The prednisone, vincristine, intermittent methotrexate schedule of Acute Leukemia Study Group B resulted in a 10.4-month median duration of hematological remission. A cyclic regimen using prednisone, 6-mercaptopurine, methotrexate, and cyclophosphamide led to a 14-month median duration of hematological remission. Another cyclic regimen using prednisone, methotrexate, and 6-mercaptopurine yielded an 11-month median duration of hematological remission.

Intensive combination chemotherapy programs used previously at this cen-
ter have resulted in prolonged disease-free survival in 15 to 20 per cent of patients (Fig. 1). The complete remission duration curves have leveled off after 2 years. In other words, the majority of children who have remained in continuous complete remission for two years have tended to maintain this status, at least until the present time.

Although not the primary goal of these studies, survival duration is plotted in Fig. 3 for comparison. In the present study, 78 per cent of children who attained remission have survived two years or longer. Recently a 75 per cent 2-year survival was reported for a chemotherapy program employing prednisone, vincristine, and methotrexate and a 25 per cent 5-year survival was predicted. However, no information was provided concerning the remission status of the patients, and the results were criticized for retrospective selection of chemotherapeutically responsive patients. If we consider survival duration of all patients who entered the present study, without selection, whether or not they attained remission or received all phases of therapy, 25 of 35, or 71 per cent, have survived 2 years or longer.

Serious infection during remission resulted primarily from nonbacterial microorganisms. This is consistent with our general experience. Unfortunately, granulocytopenia, leukopenia and physical drug toxicity did not precede these infections. Better predictive indices of toxicity are needed to help avoid these complications and are currently under study. Another index of the toxicity of the therapeutic regimen reported here was the growth retardation seen in most of the patients. This result differs from a study showing no change in the growth rate of children under therapy for leukemia, but the chemotherapy in that study was less intensive.

The successful administration of maximally tolerated combination therapy requires frequent observation and a readiness to adjust therapy. Although toxicity of radiotherapy and intrathecal methotrexate necessitated dosage reduction in only one patient, combination chemotherapy dosage was reduced on one or more occasions in every patient.

We conclude from the results of this study that continuous complete remission of childhood acute lymphocytic leukemia is significantly prolonged by intensive nervous system therapy and combination chemotherapy. The toxicity and infections encountered are significant, but certainly not prohibitive, in view of the results obtained.

REFERENCES

6. Acute Leukemia Group B: New treatment schedule with improved survival in
THERAPY OF CHILDHOOD LYMPHOCYTIC LEUKEMIA

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