Treatment of Acute Lymphoblastic Leukaemia

LUCIUS F. SINKS

From the Department of Pediatrics, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

When a child with acute lymphoblastic leukaemia is first diagnosed he may be severely anaemic, granulocytopenic, and thrombocytopenic; therefore, the immediate concern is to decide whether replacement therapy in the form of selected blood components is required, i.e. red cells, granulocytes, or platelets. This supportive therapy is obviously of prime importance as induction chemotherapy requires approximately 4 weeks to achieve a remission and during that period the child’s life is threatened by either severe anaemia, infection, or haemorrhage.

It has been amply shown that platelet-rich plasma can decrease severe haemorrhage in these children when threatened by thrombocytopenia (Han et al., 1966). Repeated packed cell transfusions, rather than whole blood, are often necessary in the early stages. Though there has been a suggestion that normal granulocytes harvested in sufficient quantities may be of aid in combating infection problems when there is granulocytopenia, this has not been widely accepted and presents, at this time, serious problems in supply.

The child should be investigated as to the extent of the disease; that is, whether the central nervous system (CNS) is involved as well as other structures such as bone, kidneys, and testicles. Involvement of these areas determines to some degree the type of therapy indicated. It is now appreciated that approximately 50% of such children will eventually develop CNS leukaemia, and efforts must be directed to forestall and hopefully to prevent its development.

**Specific Therapy**

Acute leukaemia is a disease of unknown aetiology and is rarely curable; however, we have been able to achieve a steady improvement in our results, so that at present 20% of leukaemic children can expect to live 5 years without evidence of disease.

The specific therapy for this disease has developed in an empirical fashion over the last 25 years. Its rarity has made it difficult for any one physician, or any one centre, to make decided progress in therapy, and has persuaded physicians and paediatricians to form co-operative groups. One such group is Acute Leukemia Group B (ALGB), founded in 1956 and now an international organization. During its short existence, many schemes of therapy have been tried under controlled conditions, and gradually improvements have been achieved. I will describe briefly some of the ‘preliminary results of our most recent study (Sinks, 1971), and thereby illustrate the principles governing our approach when comparing different treatment schemes.

Our prime object is to make the initial remission as prolonged as possible. We now know that the development of CNS leukaemia during a phase of haematological remission almost invariably presages a haematological relapse within a few months at least. Therefore, we now accept that some form of treatment directed to the CNS must be included in any scheme aimed at achieving maximal prolongation of remission. Whether this should consist of radiotherapy or intrathecal chemotherapy, or a combination of the two, remains at the moment a crucial question demanding an urgent answer.

In Fig. 1 the study design is set out (Study No. 6801). 514 children with acute lymphoblastic leukaemia were randomized to two different induction regimens,* with and without an initial course of L-asparaginase, followed by either (a) vincristine (VCR) and prednisone, or (b) vincristine, prednisone, and daunorubicin (DNR). This completed their induction phase.

During induction, 50% of the children received ‘prophylactic’ intrathecal methotrexate and the others received none.

*In the Personal Practice series of articles an author is invited to give his own views on some current practical problems.

When remission was achieved, one of four

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*For details of dosages, etc. see Appendix.
maintenance schedules was assigned to the patient by drawing a randomization card. It consisted of either (c) and (d) twice-weekly methotrexate, with 'pulse doses' of either VCR and prednisone, or VCR, DNR, and prednisone. The other alternatives were (e) and (f) 6-mercaptopurine daily with once-weekly methotrexate, and the same two alternative types of pulse dose described.

The preliminary results shown in Fig. 2 show that prophylactic intrathecal methotrexate protects approximately 85% of the patients from developing CNS leukaemia over a 30-month period; whereas 50% of those children who did not receive this method of therapy developed CNS involvement. The other thought-provoking result of this study is that children pretreated with L-asparaginase (Fig. 3) followed by maintenance schedule of 6-MP, once-weekly methotrexate, and VCR plus predni-

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*Our results with long-term use of daunorubicin suggest that cardiotoxicity is a real danger. The drug should not be given for longer than 12 months, or in a total dose exceeding 500 mg/m². (See also article by R. N. Matthews and J. H. Colebatch, Archives, 1972, 47, 272--Editor.)

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**Fig. 1.**—Design for a therapy trial in which 514 children with acute lymphoblastic leukaemia were placed.

**Fig. 2.**—Effect of intrathecal methotrexate, given in inductions and as part of maintenance therapy.

**Fig. 3.**—This group of children all received initially L-asparaginase, followed by induction of remission with vincristine + prednisone. Four different maintenance schedules were then randomized. Cases in Group C did best, with 75% still in remission after 2 years.
sone pulse doses, are doing exceptionally well with approximately 75% still in remission more than 2 years after diagnosis.

Radiotherapy

Recently radiotherapy has been used as an adjunct in treatment. In an effort to prevent CNS leukaemia, children have been exposed to cranial radiation of 2400 rads, together with intrathecal methotrexate. The use of these combined methods has led to claims that as many as 95% of the children could be protected from developing CNS leukaemia (Pinkel et al., 1971).

Outpatient Therapy

These children receive this intensive therapy as outpatients, they attend school, and enjoy the usual activities. Therefore, these statistics also mean that the quality of the life of these children approaches normal.

In order to maintain intensive therapy as an outpatient, one must organize personnel and facilities in such a way that bone marrow aspirates, intrathecal methotrexate, intravenous chemotherapy, and supportive transfusions are all available on an outpatient basis. Usually the facilities and manpower to maintain these activities and the supportive care are only available at centres designed to provide such. It is, therefore, strongly recommended that all children with acute lymphoblastic leukaemia be referred initially to such a centre that they may benefit from the most up-to-date therapy and thus have the greatest likelihood of achieving a prolonged remission.

REFERENCES


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Appendix

Though the optimum method of employing the existing cytotoxic drugs available for treating lymphoblastic leukaemia and the dosage of these drugs are of course far from proven, it may be useful to set out a typical current treatment schedule which incorporates some of the lessons learned from trials such as those described in this paper.

1. Induction phase.* Vincristine 2 mg/m² i.v. weekly together with prednisone 40 mg/m² daily, both given for a minimum of 3 weeks, or if remission has not occurred, for up to 6 weeks.

2. Postremission phase. (a) 6-mercaptopurine 90 mg/m² daily, orally. (b) Methotrexate 15 mg/m², once weekly, orally. During this phase 'inducer' drugs are given as follows. (c) Once a month for 6 months, vincristine 2 mg/m² i.v., and prednisone 40 mg/m² for 7 days.

At the 6th month, and again at the 9th month, 2 weekly doses of vincristine along with a 2-week course of prednisone are given.

At the 12th month 3 weekly doses of vincristine, plus a 2-week course of prednisone are given, and thereafter this is repeated every 6 months.

3. Prophylactic treatment to CNS. Uncertainty about how this should be carried out and the possible use of radiotherapy have already been voiced in the foregoing text. It is probably wise to give intrathecal methotrexate 12 mg/m² once a week during the initial vincristine induction phase, and to continue thereafter at monthly intervals.

Correspondence to Dr. L. F. Sinks, Department of Pediatrics, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14203, U.S.A.

*Note added in proof: At one time L-asparaginase was given daily for 5 days followed by prednisone and vincristine, but subsequent analysis failed to confirm that it extended the period of remission when compared with induction with vincristine and prednisone alone.*