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T-Cell Acute Lymphoblastic Leukemia in Children

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Newer chemotherapeutic and support programs have resulted in survival of approximately 40%–50% of children with acute lymphoblastic leukemia (ALL) (Sallan et al. 1980; George et al. 1979; Haghbin 1977). It is likely that children who fail conventional therapy programs represent subsets of patients whose disease is biologically distinct, and, as such, require different therapeutic strategies. Approximately 15%–20% of children with ALL have lymphoblasts with surface receptors for sheep erythrocytes or T-cell antigens. In a treatment program at our institution patients with T-cell disease had a median disease-free survival of 12 months compared to 47 months for those with non-T-cell disease ($P=0.0004$) (Fig. 1) (Sallan et al. 1980). The majority of relapses in the T-cell population occurred at extramedullary sites, whereas nearly all of the non-T-cell patients relapsed in the bone marrow. When it became apparent that patients with T-cell disease enjoyed a less than 20% disease-free survival, a new treatment strategy was designed.

A. The Rationale for T-cell ALL Therapy

The treatment program reported herein entails three major differences from conventional ALL regimens: (1) the inclusion of chemotherapeutic agents that are more selective for T-cells; (2) special attention to extramedullary sites; and (3) thymectomy.

Frei and his co-workers (1974) have demonstrated that the most commonly used antileukemic agents, methotrexate and 6-mercaptopurine, are less cytotoxic in experimental murine T-cell leukemias, such as AKR leukemia, than are drugs such as cyclophosphamide and cytosine arabinoside (Ara-C). Extrapolations from these experimental systems suggested that the treatment of human T-cell leukemia might be facilitated by the incorporation of drugs active in the AKR system. Therefore, we chose to treat with cyclophosphamide, Ara-C, and adriamycin as well as vincristine and prednisone (see schema, Fig. 2).

Because the majority of relapses in patients with T-cell ALL occurred in extramedullary sites (Sallan 1980), our T-cell ALL treatment program attempted to intensify therapy to the testes and central nervous system (CNS). Other investigators have demonstrated that prophylactic testicular irradiation can prevent the occurrence of testicular relapse (Nesbit et al. 1980). Thus, we irradiate both testes of all male T-cell ALL patients to 2400 rad. Although cranial irradiation and intrathecal methotrexate provide relatively good CNS "prophylaxis" (Green et al. 1980), at our institution the majority of failures of this mode of therapy have been T-cell patients. To strengthen CNS therapy we added intermittent high-dose, systemic Ara-C given in a 120 h continuous infusions. Pharmacokinetic studies of continuous infusion of Ara-C suggest that cytotoxic levels of drug can be attained in the cerebrospinal fluid shortly after the institution of the infusion and remain at therapeutic doses throughout the duration of the infusion (Weinstein et al. 1978).

The rationale for thymectomy is based primarily on experimental evidence from AKR systems. It has been shown that the addition of thymectomy to cytotoxic therapy with cyclophosphamide prolonged survival in AKR mice when compared to treatment with cyclophosphamide alone (Athanasiou et al. 1978). In addition, we hypothesized that

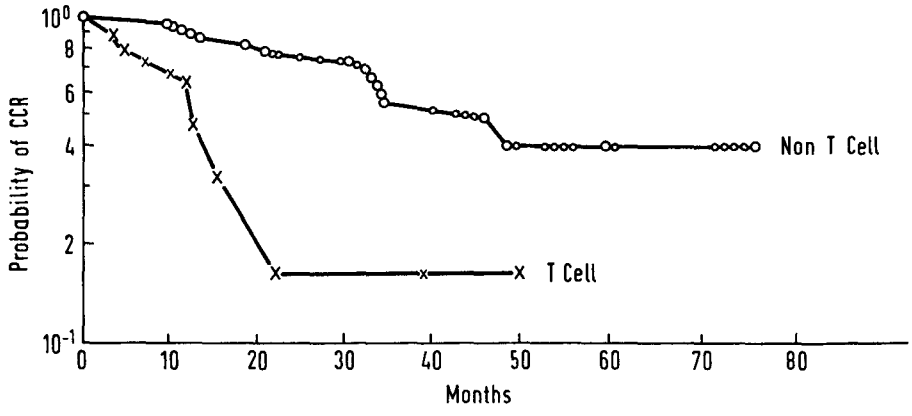

Fig. 1. T-cell and Non-T-cell leukemia disease free survival

lymphocytes may be continuously transformed in the thymus by hormonal factors secreted by thymic epithelial cells. Although high dose radiation therapy could ablate the thymic epithelial cells, it would do so at the cost of added toxicity to both the esophagus and heart when it was used concurrently with adriamycin. Therefore, we chose to ablate the thymus by total thymectomy.

B. Preliminary Results

Since March 1977 17 patients with immunologically proven T-cell ALL have been entered onto the T-cell protocol, 12 from our institution and 5 from Yale-New Haven Medical Center. Two patients died during induction of sepsis and pneumonitis. Of the 15 patients who entered complete remission, 3 have relapsed.

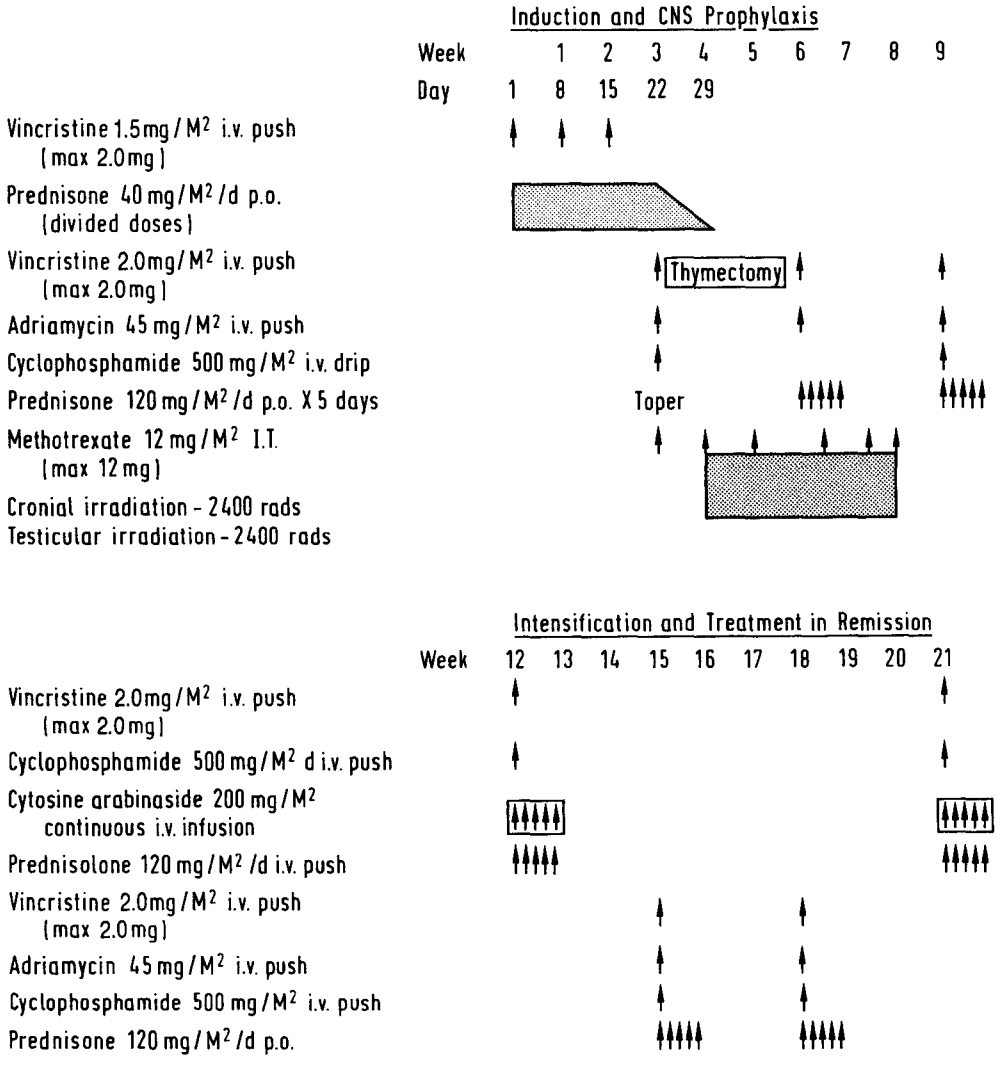

Fig. 2. Schema for treatment of T-cell leukemia

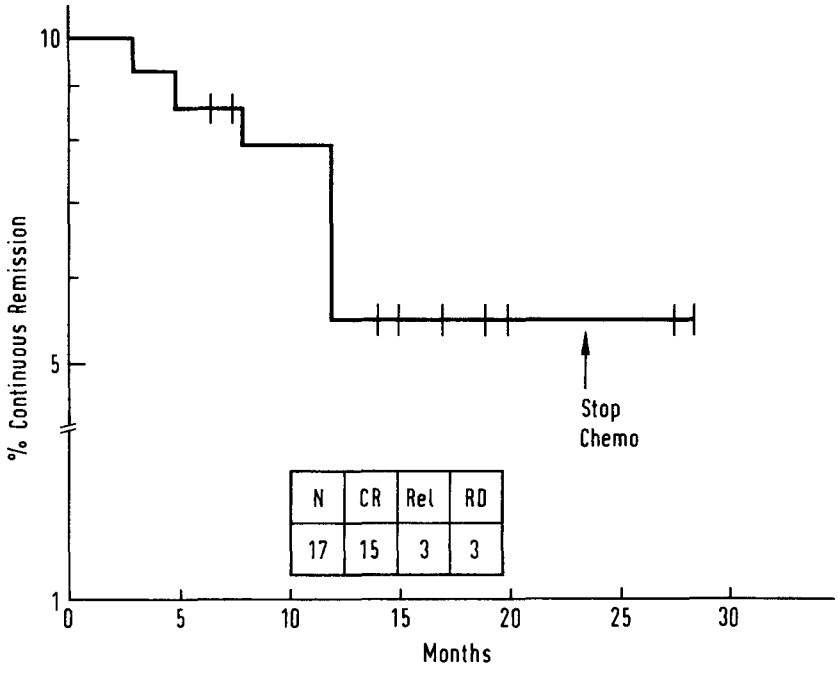

Fig. 3. Childhood T-cell ALL

The relapses occurred at 5, 12, and 12 months and were in the bone marrow in the first two patients and the CNS in the third patient. There have also been three remission deaths at 3, 8, and 12 months. The first two deaths were from sepsis (one episode in the only patient who did not have a thymectomy) and the third death resulted from adriamycin-induced cardiomyopathy. Eleven patients remain in continuous remission from 7+ to 28+ months. The median follow-up for the program has been 15 months. Two patients have electively discontinued therapy and remain disease-free for 28 months. The disease-free survival curve for this group is shown in Fig. 3.

C. Summary

Children with T-cell ALL have a biologically distinct subset of disease and require special treatment. This T-cell protocol suggests that the selection of chemotherapeutic agents, the emphasis on extramedullary prophylaxis, and thymectomy may be one rational approach to the treatment of these patients. The therapy program is highly immunosuppressive and requires expertise in pediatric supportive care. Future considerations must recognize the importance of T-cell subsets (Reinherz et al. 1979) as well as the use of antileukemic monoclonal antibodies and other innovative approaches to therapy.

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