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Recent Results from Total Therapy Study X for Standard and High Risk Acute Lymphoblastic Leukemia in Children: Recognition of New Clinical and Biologic Risk Features*

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A. Introduction

The initiation of Total Therapy Study X in 1979 marked important new directions for leukemia studies at St. Jude, since for the first time treatment for standard and high risk forms of lymphoblastic leukemia differed radically. Furthermore, recognizing the heterogeneity of childhood ALL, the blast cell characteristics of each new patient were prospectively investigated by standard methods [1–3], and the independent impact of various clinical and biologic features on the outcome of therapy was thoroughly investigated. This report will present highlights of our recent results.

B. Total Therapy X: Study Design

For purposes of protocol assignment, children with ALL were defined as high risk if they possessed any of the following features at diagnosis: white blood cell count greater than 100 000/mm^3, a mediastinal mass, lymphoblasts forming spontaneous rosettes with sheep erythrocytes (E+), and/or central nervous system disease. Children lacking these features were standard risk. Using these criteria, approximately 20% of our childhood ALL population is classified as high risk, and the remaining 80% are standard risk.

The background and rationale, specific drug schedules and dosages, and preliminary results of Total Therapy Study X for standard risk (X-S) and high risk patients (X-H) have been presented in detail elsewhere [4, 5]. Briefly, Total Therapy X-S asked the following questions: (a) can the hematologic relapse rate in standard risk ALL be reduced by periodic intravenous (i.v.) infusions of methotrexate or by a sequence of drug pairs during continuation therapy; and (b) can central nervous system relapse be adequately prevented by alternative treatments, rather than the standard 2400 rad cranial irradiation and intrathecal (i.t.) methotrexate early in remission? After remission induction with prednisone, vincristine, and asparaginase, standard risk patients were randomized into two groups: (a) IVIT, i.e., methotrexate (1000 mg/m^2) in 24-h i.v. infusions, plus i.t. methotrexate, weekly ×3, followed by a standard backbone of oral daily mercaptopurine and weekly methotrexate maintenance for 120 weeks, interrupted every 6 weeks for the first year for an i.v. MTX infusion with coordinated intermittent i.t. MTX treatments; and (b) RTSC, i.e., cranial irradiation (1800 rad) plus i.t. methotrexate, followed by rotational sequential combination drug pairs for the first year of maintenance, with methotrexate plus mercaptopurine (weeks 1–36), cyclophosphamide and adriamycin (weeks 36–54), VM-26 and Ara-C (weeks 54–72), followed by an additional standard year of oral mercaptopurine and methotrexate (weeks 72–120).

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Study X-H examines the efficacy of early and intermittent treatment with a new drug pair, VM-26 and Ara-C, questioning whether or not the high risk for relapse could be reduced by use of this drug combination, superimposed on an otherwise standard antileukemia regimen. Treatment begins with VM-26 (165 mg/m^2) plus Ara-C (300 mg/m^2) twice weekly for 2 weeks, followed by prednisone, vincristine, and asparaginase at standard doses for 4 weeks. Following this early therapy, an additional 2-week consolidation phase of VM-26 and Ara-C at the same dosages and on the same schedule preceded continuation therapy with daily mercaptopurine and weekly methotrexate, both administered orally for 30 months. In addition, 2-week reinforcement pulses of VM-26 and Ara-C are given every 8 weeks for the first 12 months. Central nervous system prophylaxis is by means of intermittent intrathecal methotrexate during the first year of therapy, following which patients in remission receive cranial irradiation (2400 rad).

C. Results

From June 1979 until the end of 1983, 330 children with standard risk ALL entered Total X-S, and 94% achieved a complete remission in 4 weeks. Subsequently, 154 were randomized to the IVIT methotrexate arm of continuation therapy, and 155 were randomized to receive the rotational combination drug treatment, RTSC. During the same period, 101 children with high risk presentations of ALL entered Total X-H, and 84% achieved remission.

The results to date, as of May 1984, with a median follow-up of 2 years, are statistically superior to our institutional historical experience with comparable standard and high risk patients treated on Total Therapy Studies VIII and IX. The added benefit of the addition of VM-26 and Ara-C to the antileukemic management of high risk ALL patients is particularly apparent, as approximately 50% of patients continue in their first complete remission for 2–3 years following diagnosis. Protection against central nervous system relapse in the group of children on X-S receiving 1800 rad cranial irradiation, plus intrathecal methotrexate (RTSC group) has been adequate and better than the IVIT group, though there is at present a slight superiority in the proportion of patients in continuous complete remission on the IVIT arm of X-S. Whether IVIT methotrexate therapy prevents or merely delays relapse and/or whether it is an acceptable alternative for CNS prevention for children with good prognostic features (for example WBC less than 10 000) will require longer follow-up. Faster rates of systemic methotrexate clearance following i.v. MTX treatment have also been identified as a factor associated with a higher probability of early relapse [6], underscoring a need for further study of interindividual variability in pharmacodynamics as a critical determinant of end results of leukemia trials.

D. Risk Analysis: Recognition of New Factors

In addition to the clinical features of well-established prognostic importance in childhood ALL, such as age and initial circulating white cell count, our studies have revealed new biologic features which have independent prognostic impact on the outcome of therapy in Total X. We have found the most important biologic variables determining the outcome of therapy for ALL to be related to the genetic characteristics of the leukemic clone, as revealed both by the study of the karyotype and by determination of the degree of aneuploidy as measured by the flow cytometric determination of the DNA index ([1, 2, 7] and Williams et al. in preparation). The DNA index (DI), i.e., the ratio of the DNA content of leukemic versus normal G_0/G_1 cells, ranges from 1.06 to 2.0, median 1.2. In our experience, children with a DI > 1.16 have significantly better responses to treatment on Total X-S than do those with either a diploid or pseudodiploid DNA content (DI = 1) or those in the intermediate range, DI = 1.01–1.15. Such cases with DI > 1.16 correspond to those with > 53 chromosomes in the leukemic stem line, a correlation which accounts for the good prognosis associated with this ploidy group,

Table 1. Pretreatment risk assessment for ALL cases assigned to Total Therapy study XI

Risk factor[a]	Unfavorable characteristics
DNA index	$\leqq 1.15$
Cytogenetics	Pseudodiploid or translocation present
Race	Nonwhite
White blood cell count	$\geqq 25\,000/mm^3$
Age	<2 or >10 years

[a] Better risk patients are defined as possessing either none or only one unfavorable characteristic at diagnosis. Worse risk cases are defined as having two or more unfavorable features

as previously reported by us and noted by the Third International Workshop of Chromosomes in Leukemia [8]. Cases with hyperdiploid cellular DNA content (DI > 1.16) are also associated with the favorable age range of 2–9 years and with blast cell surface expression of the common ALL antigen. Though flow cytometry has definite advantages over conventional karyotyping for the detection of hyperdiploid ALL cases, cases with 44–48 chromosomes can not reliably be distinguished from diploid; and, of course, flow cytometric analysis does not detect the presence of structural chromosome abnormalities such as balanced translocations, since the net DNA content is unaffected. Karyotypic translocations are an important and unfavorable prognostic feature with an independent adverse impact on outcome, even after adjustment for white blood cell count, age, and other features of conventional prognostic significance. Translocations have not been observed in our experience in ALL cases with more than 50 chromosomes. The techniques of flow cytometry for analysis of cellular DNA content and karyotype analysis for detection of structural chromosome abnormalities in leukemic cell populations are thus complementary techniques, desirable in the study of every newly diagnosed case of ALL, and helpful for risk assessment in treatment stratification. Indeed, in our new front-line treatment protocol for children with ALL (Total Therapy Study XI), we have incorporated both the cytogenetic analysis and the DNA index, along with initial white blood cell count, age and race, into a newly devised pretreatment risk assignment (Table 1) based on the multivariate analysis of our experience in Total Therapy Study X.

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