T-Cell Lymphoblastic Leukemia Study

A Simulated Medical Research Protocol,
With Format After That Used by
The University of Rochester Medical Center
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I. PURPOSE OF THE STUDY AND BACKGROUND

A. Purpose of the Study: The objective of this study is to test the following hypothesis: If patients between the ages of two and five years of age (inclusive) with T-cell acute lymphoblastic leukemia are given standard regimens of continuation chemotherapy for three years, then their five-year survival rates will be statistically significantly greater than the five-year survival rates for similar patients given standard regimens of continuation chemotherapy for two years.

B. Background: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, representing nearly one-third of all pediatric cancers. The annual incidence of ALL is about thirty cases per million people, with a peak incidence in patients of two to five years of age. Although a small percentage of cases are associated with inherited genetic syndromes, the cause or causes of most cases of ALL are not known.

In cases of ALL, a lymphoid progenitor cell becomes genetically altered and then undergoes dysregulated proliferation and clonal expansion. In most cases, the pathophysiology of transformed lymphoid cells reflects the altered expression of genes whose products contribute to the normal development of B cells and T cells.

Historically, the prognosis of patients with T-cell ALL has been worse than that of patients with B-lineage ALL. With the use of intensive chemotherapy, however, the prognosis for patients with T-cell leukemia seems to improve. In particular, whereas patients with B-cell ALL typically require a two- to eight-month course of intensive chemotherapy, patients with T-cell or B-precursor ALL typically obtain an acceptable rate of cure only after a two- to two-and-a-half-year course of "continuation" therapy.

The improvement in survival for children with ALL over the past thirty-five years has been a remarkable achievement of the research community, particularly with the development of new chemotherapies tailored to the genetic identities of the leukemic cells. In the 1960s, less than 5% of children with ALL survived for more than five years. Today, about 85% of children with ALL live five years or more.

References: *Acute Lymphoblastic Leukemia*, by Jeffrey E Rubnitz (MD, PhD, Director of

Fellowship Training Program, Associate Professor, Departments of Pediatrics and Hematology-Oncology, University of Tennessee and St. Jude Children's Research Hospital), Last Updated February 25, 2005, and *Acute Lymphoblastic Leukemia in Children: Questions and Answers* from the National Cancer Institute, U.S. National Institutes of Health, Posted July 11, 2002.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

A. Number of Subjects: The total number of subjects expected to participate in this study is approximately one thousand, divided among ten research centers in the United States and other countries (see the List of Research Institutions & Subject Populations, attached), coordinated by the ALL Society, hereafter referred to as the "coordinating institution."

Please also see Method of Subject Identification and Recruitment, for the control population.

B. Gender of Subjects: The subjects shall be approximately 60% male and 40% female—that is, approximately six hundred males and four hundred females in total—given that ALL, and in particular T-cell ALL, is somewhat more prevalent among males than females in the general population.

C. Age of Subjects: The subjects shall range from two to five years of age inclusive—the age range of peak incidence of ALL—with an approximately equal number of subjects within each year-age group, as noted at the beginning of this study: that is, approximately two hundred and fifty (250) subjects who are two years of age; 250, three years of age; 250, four years of age; and 250, five years of age.

D. Racial and Ethnic Origin of Subjects: The subjects shall be approximately of the following racial/ethnic breakdown: five hundred Caucasians, two hundred and fifty African Americans and others of sub-Saharan African origin, and two hundred and fifty of other racial/ethnic origins (including non-Caucasian Hispanics, native Americans, and Asian Americans). This distribution reflects the fact that the annual incidence of ALL in Caucasian children younger than fifteen years of age in the United States is approximately twice that of African American children younger than fifteen years of age (thirty-three per million vs. fifteen per million).

E. Inclusion Criteria: Inclusion of subjects is based upon factors of gender, age, and race/ethnicity (as discussed above) as well as a positive diagnosis for T-cell ALL, involving a two-step procedure: a positive diagnosis for ALL, followed by a differential diagnosis of T-cell ALL (as opposed to B-cell or B-precursor ALL).

A tentative clinical diagnosis of ALL is typically associated with such signs of bone marrow failure as anemia, thrombocytopenia, or neutropenia, as evidenced by fatigue, pallor, petechiae, bleeding, or fever, as well as lymphadenopathy, hepatosplenomegaly, weight loss, bone pain, and/or dyspnea.

This tentative clinical diagnosis is then usually followed by appropriate laboratory studies of blood: CBC count, with possible low hemoglobin and platelet counts, and peripheral smear evaluated by a hematologist or hematopathologist for the presence and morphology of lymphoblasts. Such coagulation studies as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimers may also be undertaken.

A diagnosis of ALL shall be considered confirmed for the purposes of this study by standard morphologic, immunologic, and genetic examinations of bone marrow aspirate (see the references cited in the Background, above, for specific diagnostic procedures).

Furthermore, a clinical diagnosis of T-cell ALL is typically associated with high blood leukocyte counts; central nervous system (CNS) involvement; and in about one-half of all cases, a mediastinal mass, as revealed by chest radiography.

A diagnosis of T-cell ALL shall be confirmed for the purposes of this study by the expression of T-cell—associated surface antigens on lymphoblasts, of which cytoplasmic CD3 is specific.

F. Exclusion Criteria: Any potential subjects not meeting all of the above-mentioned inclusion criteria, including a confirmed diagnosis of T-cell ALL, shall be excluded from this study.

G. Vulnerable Subjects: Children have been selected as the exclusive subjects for this study because leukemia is the most common type of childhood cancer, representing approximately one-third of all cancers in children under fifteen years of age; and some 80% of childhood leukemias are ALLs.

III. METHODS AND PROCEDURES

A. Methods and Procedures: Please see the Inclusion Criteria (above) for a discussion of the basic labs, immunophenotyping, and cytogenetic and molecular diagnostic tests required for making the initial diagnosis of T-cell ALL. In addition, if the physical examination of any male patient reveals enlarged testes, ultrasonography should be performed to evaluate for testicular infiltration.

Depending on the clinical circumstances, a patient newly diagnosed with ALL should obtain a number of consultations, as with the following specialists: a pediatric oncologist (who refers the patient to the appropriate subspecialists), a pediatric surgeon (to place a central venous catheter, used for administering chemotherapy, blood products, and antibiotics as well as for drawing blood samples), a psychosocial team (of psychologists and social workers, who help guide the patients and their families through the various issues posed by ALL and its treatment), a radiation oncologist (if craniospinal radiation is required), and other subspecialists as required (such as a nephrologist or an infectious disease expert).

Frequent clinic visits will be required to administer outpatient chemotherapy, to monitor blood counts, and to evaluate new symptoms.

The treatment of childhood T-cell ALL (like that of other forms of ALL except B-cell ALL) has four components: remission induction, consolidation, continuation, and treatment of subclinical CNS leukemia.

Remission induction therapy (or simply "induction therapy") typically consists of three or four drugs, which may include a glucocorticoid, a vincristine, an asparaginase, and an anthracycline. This type of therapy induces complete remission in more than 95% of patients.

Consolidation (or "intensification") therapy is given shortly after remission has been achieved, in an attempt to further reduce the leukemic cell burden before the emergence of drug resistance. In this phase of therapy, the drugs are used at higher doses than during induction or different drugs are used, such as high-dose methotrexate and 6-mercaptopurine, epipodophyllotoxins with cytarabine, or multiagent combination therapy (note, however, that the improvements in relapse-free survival gained by intensification with anthracyclines or epipodophyllotoxins must be weighed against the late sequelae of these agents, which include cardiotoxicity and treatment-related acute myeloid leukemia). Consolidation therapy was first used successfully in the treatment of patients with "high risk" disease (see Potential Risks & Their Prevention, below) but also appears to improve the long-term survival of patients with "standard risk" disease, such as T-cell ALL. The addition of intensive re-induction therapy, administered soon after remission has been achieved, benefits patients in both risk groups.

Continuation therapy is the focus of this particular study. Whereas B-cell ALL is treated with a two- to eight-month course of intensive therapy, obtaining conventionally acceptable cure rates for patients with B-precursor and T-cell ALL requires approximately two- to two-and-a-half years of continuation therapy: shorter durations of therapy typically produce high relapse rates. The purpose of this study is to ascertain whether increasing the duration of a "standard regimen" of continuation therapy from two years to three years will significantly increase cure rates.

For the purposes of this study, the "standard regimen" of continuation therapy shall involve weekly parenterally administered methotrexate given with daily, orally administered 6-mercaptopurine, interrupted by monthly pulses of vincristine and a glucocorticoid (note, however, that although these pulses have improved outcome, they are associated with avascular necrosis of the bone).

Finally, treatment of subclinical CNS leukemia is another essential component of ALL therapy. Although cranial irradiation effectively prevents overt CNS relapse, concern about subsequent neurotoxicity and brain tumors has led many investigators to replace irradiation with intensive intrathecal and systemic chemotherapy for most patients: this strategy

has produced excellent results, with CNS relapse rates of less than 2% in some studies.

B. Data Analysis and Data Monitoring: The mean and median five-year survival rates of the study population will be compared with those of the control population (see Method of Subject Identification and Recruitment) and any statistically significant differences will be noted. A similar (three-year vs. two-year continuation therapy) analysis will be made for each initial-year-age group (two-year-olds, three-year-olds, et al.), for each gender group, and for each racial/ethnic group.

Each research institution will before the commencement of the study appoint a Data Monitoring Committee, approved by the coordinating institution and not composed of persons otherwise involved with the study, whose responsibilities will include reviewing the methods and procedures employed during the study on a regular basis (not less frequently than once a month), monitoring the data collected (not less frequently than once a month), and stopping the study at their institution at any point at their own discretion—with as much prior notice to the coordinating institution as is practicable and medically advisable—based upon (but not limited to) such factors as the safety or welfare of the subjects or the efficacy of the study.

C. Data Storage and Confidentiality: Each research institution and the coordinating institution will designate one or other minimum number of data collection agents who will be responsible for the efficient, secure, and confidential collection, maintenance, and retrieval of research data, in electronic form as well as hard-copy. The identity of each research subject will be kept confidential by means of a coding system, whose encryption will be known only to the data collection agent(s) at each institution and a minimum number of others at that institution and at the coordinating institution. The coordinating institution shall establish procedures and forms required by every institution for the sharing of confidential research data or subject identifiers.

IV. RISK/BENEFIT ASSESSMENT

A. Risk Category: The subjects in this study will be unavoidably presented with Greater than Minimal Risk (that is, risk greater than that ordinarily encountered in daily life or during the performance of a routine physical examination or test).

B. Potential Risks & Their Prevention: ALL is a life-threatening disease: anything that delays proper diagnosis and treatment can lead to death. In general, ALL patients should be initially transferred to a facility in which they can be in the care of a pediatric oncologist, preferably a center that participates in multi-institutional clinical trails, such as the study described in this protocol.

Among ALL patients, those with T-cell ALL are placed by convention into a "standard risk" group (as compared to those patients with certain forms of B-lineage ALL who are placed in a "low risk" or "high risk" group). The following

discussion of risks for ALL patients in general thus applies to T-cell ALL patients in particular.

Among the risks associated with leukemia and its therapy in general (see Methods and Procedures, above) are Tumor Lysis Syndrome (see below), renal failure, sepsis, bleeding, thrombosis, typhlitis, neuropathy, encephalopathy, seizures, secondary malignancy, short stature (if there is craniospinal radiation), growth hormone deficiency, and cognitive defects.

It must be ensured that the parents or legal guardians of the minor subjects have a reasonable understanding of the expected adverse effects of each medication used in the treatment for ALL. In addition, it is essential that parents or guardians understand signs and symptoms that require medical attention, such as signs and symptoms of anemia, thrombocytopenia, and especially infection. Parents must know how to quickly access medical help from the oncology team.

Frequent hospitalizations may be required to deal with complications of therapy, including the need for antibiotics or for blood or platelet transfusions. Any patient who is neutropenic and who develops chills or fever must be admitted immediately for intravenous broad-spectrum antibiotics.

Please see the attached chart listing the names, doses, contraindications, interactions, and precautions associated with the various drugs to be used in remission induction therapy, consolidation therapy, and intensification or continuation therapy; and see Methods and Procedures (above) for duration of therapy with each drug and timing of administration within each treatment cycle.

In particular, prior to the administration of anthracyclines, obtain an echocardiogram and ECG; and because of the use of methotrexate, avoid dietary folate supplementation.

Tumor Lysis Syndrome is a risk for ALL patients before and during the initial, induction phase of chemotherapy (see Methods and Procedures, above). In this syndrome, metabolic disturbances are caused by the rapid, systemic release of the intracellular contents of leukemic blasts that are destroyed by chemotherapy or that have died before therapy has even begun. The primary signs and symptoms of Tumor Lysis Syndrome include hyperuicemia, hyperphosphatemia, hypocalcemia, and hyperkalemia. Because hyperuricemia (resulting from metabolism of purines) can lead to crystal formation with tubular obstruction and possible acute renal failure, requiring dialysis, electrolytes and uric acid should be closely monitored throughout initial chemotherapy. Allopurinol should be administered to prevent or correct hyperuricemia. To prevent complications of Tumor Lysis Syndrome, all patients should initially receive IV fluids at twice maintenance rates, usually without potassium. Sodium bicarbonate is added to the IV fluid to achieve moderate alkalinization of the urine (pH 7.5–8), in order to enhance the excretion of phosphate and uric acid. However, a higher urine pH should be avoided, to prevent crystallization of hypoxanthine or calcium

phosphate. Some physicians evaluate for leukemic kidney involvement by means of renal ultrasound to assess the risk of Tumor Lysis Syndrome.

To prevent *Pneumocystis carinii* pneumonia (PCP) infection, all patients should be on trimethoprim and sulfisoxazole.

To prevent candidiasis, patients should be on oral nystatin or Mycelex troches; and patients with a high risk of relapse should also be on daily itraconazole.

To prevent microbial infections in the mouth, patients need to swish and spit such antimicrobials as Peridex or Biotene four times daily.

C. Potential Benefits to the Subjects: Potentially significantly greater chance of five-year survival with the three-year regimen of continuation therapy compared to the two-year regimen.

D. Alternatives to Participation: There is no obligation for any parent or legal guardian to give consent for his or her minor to become a subject in this study nor any limitation in his or her seeking any treatments for their minor elsewhere. Any parent or legal guardian contacted by any research institution or the coordinating institution about this study who does not wish to participate shall be encouraged to seek treatment for their minor patient elsewhere.

V. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT/ASSENT

A. Method of Subject Identification and Recruitment: The subjects in this study shall be identified and recruited only by physicians, administrators, or others within the research institutions or within the coordinating institution who have legal access to the private medical records of the subjects. In order to minimize the potential for actual or perceived coercion, the parents or legal guardians of each potential subject will be encouraged to seek a medical opinion concerning the potential risks and benefits to the subject for participating in this study from a physician not associated with the research or coordinating institution.

The control population shall consist of those subjects who would have met the inclusion criteria of this study (above) but who have yielded existing data from previous controlled studies of subjects given a standard two-year regimen of continuation therapy (see the attached list of Historic Research Data).

The identity, health status, and all other matters of privacy concerning each of the subjects in this study as well as all members of the control population shall be protected to the fullest extent possible and always within the limits established by law. Only authorized members of the research study, at the participating institutions or within the coordinating institution, shall have access to such information; and the number of these authorized members shall be kept to a practical minimum.

B. Process of Consent: Informed consent from each subject's parent(s) or legal guardian(s), as well as assent from each minor subject, shall be obtained in a process conducted by a specially designated agent at each research institution. Before consent is obtained, the agent shall make an appointment with the subject and his/her parent(s) or legal guardian(s) and schedule sufficient time to explain to them the research study and to answer any of their questions (as needed, the research institution will in any such contacts with the agent supply a language translator at its own expense). During this meeting, the agent shall present a detailed summary of this research protocol, including all potential risks and benefits to the subject, as well as standard Informed Consent and Assent forms (see attached examples) to the parent(s) or legal guardian(s), who shall be told to take the forms home with them. The agent shall encourage the parent(s) or legal guardian(s) to consider the research study carefully among themselves and with any outside parties—such as family members, friends, clergy, or medical professionals—before returning to sign the forms, in a second meeting with the agent. The consent and assent forms shall be signed in the presence of at least two witnesses who are not employed by the research institution and who shall also sign both forms. In addition, in any meeting with the agent, the subject's parent(s) or legal guardian(s) may bring with them legal counsel or any other advisor(s) of their own choosing, such additional persons being of a reasonable number. If the subject or his/her parent(s) or legal guardian(s) have additional questions to be answered before signing the forms, the agent shall do so to the best of his or her ability, within the time constraints of this study. No subject or his/her parent(s) or legal guardian(s) shall be at any time required or coerced to sign the consent or assent forms; the agent shall make clear that the only penalty for not signing these forms will be omission from the research study—any treatments otherwise agreed upon for the subject by the research institution or any of its member physicians shall not be in any way compromised by failure of the subject or his/her parent(s) or legal guardian(s) to sign the consent or assent forms.

C. Subject Capacity: Each minor subject shall be given a short standardized test (see attached example) to establish the minimum level of mental capacity required to understand the assent form and the instructions to be given in the study; successful completion of this test shall be attested to in writing as part of the declaration of each witness. The capacity of the subject's parent(s) or legal guardian(s) to sign the consent form shall be attested to in writing as part of the declaration of each witness.

D. Subject/Representative Comprehension: In the second meeting with the consent agent (see above), the agent in the presence of the witnesses shall ask certain questions concerning significant particulars of the study and of the consent and assent agreements (see attached list) in order to test the comprehension of the subject and his/her parent(s) or legal guardian(s). This comprehension shall be attested to in writing as part of the declaration of each witness.

E. Debriefing Procedures: Unless specified elsewhere, there shall be no psychological or physical information gathered by the research study that will be purposefully withheld at any time from the subject's parent(s) or legal guardian(s)—who may, however, at their discretion, as in writing, request that certain information be withheld at any time before, during, or after the study from the minor subject.

F. Consent Forms: Please see the attached copies of the standard Informed Consent Form for Studies Involving Human Subjects and the standard Assent Form for Minor Subjects, each modified in accordance with the particulars of this Research Protocol. The first page of each consent or assent form shall be printed on the letterhead of the coordinating or appropriate research institution.

G. Documentation of Consent: The consent agent at each research institution shall be responsible for obtaining (as above) and maintaining in a secure location all consent and assent agreements for this study at that institution and all of their copies. The agent shall provide in a timely fashion at least three copies of each signed agreement to the coordinating institution, which shall designate an agent for maintaining these forms in a secure location at the coordinating institution. Each agent, at each institution, shall also be responsible for the timely retrieval of any agreement, in accordance with each institution's policies; and each institution shall make reasonable provisions for the maintenance and retrieval of all agreements and other records concerning this study in the event of any incapacitation of the consent agent or of any other person or device or procedure required.

H. Costs to the Subject: Neither the subjects nor their parents or legal guardians nor any of their insurance companies shall be charged for any of the diagnostic, treatment, or other procedures performed in this study, whose costs are covered by the grants listed on List of Research Grants (attached).

I. Payment for Participation: There are no reimbursements or payments to the subjects or their parents or legal guardians for participation in this study; however, see Potential Benefits to the Subjects as well as Costs to Subjects (above).