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Bethesda 14, Maryland

Protocol #1

PROTOCOL FOR A

COOPERATIVE STUDY IN THE CHEMOTHERAPY

OF ACUTE LEUKEMIA

PARTICIPATING HOSPITAL AND RESPONSIBLE INVESTIGATORS

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CRITERIA FOR EVALUATION OF RESPONSE TO THERAPY OF ACUTE LEUKEMIA

A. Marrow (per 200 cells counted)

1. Absence of cells that can be individually identified as leukemic and reduction in the number of blasts to less than 10%.

2. Definite improvement in the marrow as evidenced by a marked or sustained reduction in the number of leukemic cells and blasts with increase in normal myelopoiesis (either leukopoiesis, erythropoiesis or both).

3. No improvement, or improvement less than that sufficient to qualify for A 2.

B. Peripheral blood.

1. Return to and maintenance of a) hemoglobin at values greater than 11 gm/100 cc; b) platelets at normal levels for your laboratory; c) granulocytes to near normal levels. Factors other than leukemia that may alter this (e.g. drug toxicity) do not invalidate the remission if after correction the above obtains. Leukemic cells must be absent from the peripheral blood.

2. Significant improvement in the peripheral blood.

3. No change, or less than B 2.

C. Physical findings.

1. Subsidence of all evidence of leukemic infiltrations (liver, spleen, lymph nodes and others, if present).

2. Significant reduction in leukemic infiltration.

3. No change, or less than C2.

D. Clinical.

1. No symptoms ascribable to leukemia.

2. Definite improvement though still symptomatic.

3. No improvement, or less than D 2.

Complete Remission.

A1, B1, C1, D1.

Partial Remission.	Clinical Remission.
A1 or 2, B1 or 2, C1 or 2, D1 or 2.	D1 or 2

This study is being undertaken to evaluate the following:

1. The efficacy of combined 6-mercaptopurine and methotrexate therapy in acute leukemia.

2. The relative efficacy and toxicity of intermittent and continuous methotrexate therapy during the administration of 6-mercaptopurine in acute leukemia.

Selection of Patients.

The following criteria must be met before a patient can be admitted to the study:

a) An unequivocal diagnosis of acute leukemia must depend on morphologic changes in the bone marrow which must show one of the following:

   1. Invasion and at least partial replacement of the marrow by a single cell type of immature leukocyte (myeloblasts, promyelocytes, monoblasts or lymphoblasts).

   2. Invasion of the marrow by leukemic cells which can be individually identified (cells with Auer bodies or abnormal lymphoblasts corresponding to the lympho-leukosarcoma cell of Doan) without regard to their number.

b) Patients with acute leukemia in remission, either spontaneous or induced, or those in whom improvement is patently occurring, will not be admitted to the study. They may subsequently be admitted should relapse occur and the criteria outlined in (a) above obtain. Previous antimetabolite or steroid therapy, regardless of duration or prior toxicity are not excluding factors.

   To exclude factors of selection all patients admitted to the service of the responsible investigators in the participating hospital units who fulfill the above criteria must be admitted to the study.

Data to be obtained on admission.

Laboratory:

- Red blood cell count
- hematocrit
- hemoglobin
- reticulocyte count
- platelet count
- white blood cell count
- differential
- erythrocyte sedimentation rate
- urinalysis
- blood urea nitrogen
- uric acid

Admission Laboratory Data (cont'd)

serum albumin and globulin
calcium
phosphorus
alkaline phosphatase
bilirubin
sodium
potassium
chlorides
BSP
cephalin flocculation
thymol turbidity

X-ray

Chest film
Skeletal survey to include:
PA and lateral of skull
PA and lateral of entire spine
PA of pelvis
upper and lower extremities
hands and feet

Bone marrow examination to include smear, cut sections, and if possible, supravital preparations.

Serial Observations

Node Size Spleen Size Liver Size	In cm. In cm. below the costal margin	2 times weekly.
Hemoglobin White blood cell count Differential count Platelet count		2 times weekly.
Reticulocyte count Uric acid		1 time weekly.
Calcium Phosphorus Alkaline Phosphatase Blood Urea Nitrogen	In the presence of osseous lesions.	1 time every 2 weeks

Bone marrow aspiration should be performed:

(1) to establish the diagnosis
(2) to establish the presence of remission
(3) to ascertain whether pancytopenia during the course of treatment is attributable to drug toxicity
(4) to follow the duration of remission.

There should be a weekly review of each patient concerning the advisability of a bone marrow aspiration.

Pairing of Patients

The patients will be paired for factors of known or probable influence on response to therapy. These include the following:

A. Type of acute leukemia.
   1. Lymphocytic
   2. Myelocytic or monocytic

B. Age
   1. Under 15 years of age
   2. Over 15 years of age (i.e. beyond the 15th birthday).

C. History of previous methotrexate therapy
   1. Present
   2. Absent

D. History of previous 6-mercaptopurine therapy
   1. Present
   2. Absent

E. Total duration of previous antifolic or 6-mercaptopurine therapy.
   1. Greater than 21 days
   2. Less than 21 days

This results in a total of 29 categories as depicted in the attached graph.

When the diagnosis has been made and the appropriate pairing category selected, the top envelope should be opened for instructions as to therapy. The pairs have been randomized (Fisher & Yates). Following this, postcards should be sent to the other participating units indicating the pair category so that they also can eliminate that envelope from their file..

There will be occasions when the type of leukemia, as judged by bone marrow examination will be equivocal. The bone marrow smears in such cases should be sent to Dr. George Brecher of NIH, Bethesda, Md., who is serving as Morphologic Consultant for this study. If, after being reviewed by Dr. Brecher, the morphologic type remains equivocal, the investigator may do one of the following:

a) Certain clinical data (age, location of infiltration, etc.) may make a certain type of leukemia quite probable. The investigator may then select the category on that basis. If the course of the disease proves him wrong, the case can be transferred to its proper category when the ultimate evaluation is made.

b) If, after consideration of all hematological and clinical data, the investigator feels that there is no significant probability for either type, the patient should be placed in category 29.

All of the above will serve to avoid selection, to centralize the study, and to keep the participating investigators abreast with the patient volume and distribution.

Therapeutic Programs

The following therapeutic programs will be compared:

A Methotrexate 2.5 mg. daily
6-mercaptopurine 3 mg/Kg daily

A' Methotrexate 7.5 mg. every 3 days
6-mercaptopurine 3 mg/Kg daily

B Methotrexate 5.0 mg. daily
6-mercaptopurine 6 mg/Kg daily

B' Methotrexate 15.0 mg. every 3 days
6-mercaptopurine 6 mg/Kg daily

C Methotrexate 1.25 mg. daily
6-mercaptopurine 1.5 mg/Kg daily

C' Methotrexate 3.75 mg every 3 days
6-mercaptopurine 1.5 mg/Kg daily

Procedure of Chemotherapy

I. Combined therapy, either continuous or intermittent, should be continued according to schedule A or A' for 35 days. At this time the doses of each should be shifted to schedule B or B' unless:

a) A dynamic beneficial alteration of the leukemic process is in progress.

b) Thrombocytopenia and agranulocytosis are sufficient in the judgement of the investigator to preclude increasing antimetabolite dosage.

If the dosage has not been shifted to B or BI at 35 days because of the above factors, it should subsequently be shifted to B or B' when these factors no longer obtain.

Therapy under schedule B or B' should continue until toxicity develops (criteria for toxicity below).

Further Procedure

II. After toxicity has occurred, either at the A or A' or B or B' doses, therapy should be withheld until toxicity is no longer manifest as demonstrated by appropriate clinical and hematological (including bone marrow) studies. This should be a minimum of 10 days. Then:

1. If toxicity occurred at B or B'.
   a) and there has been no response to antimetabolite therapy (at least a partial remission) the study is terminated for that patient.
   b) and there has been a definite hematological response (at least a partial remission) combined antimetabolite therapy should be reinstituted at the A or A' schedule and continued until:

(1) Relapse occurs. At this time schedule B or B' should be followed, and procedure II-1 again executed. (It is assumed that schedule B or B' will invariably produce toxicity).
(2) Toxicity recurs.
Further antileukemic therapy should be withheld until relapse occurs at which time schedule A or A' should be reinstituted and executed as in I & II.

2. If toxicity occurred during schedule A or A':

a) and there has been no response (at least a partial remission) combined therapy should be reinstated at schedule C or C' and continued
(1) for 35 days at which time schedule A or A' should be reemployed and executed as in I.
(2) If toxicity develops within 35 days or schedule C or C' the study is terminated for that patient.

b) and there has been hematological response (at least a partial remission) therapy should be reinstituted at C or C' and continued until
(1) Toxicity recurs. Further therapy should be withheld until relapse occurs at which time combined therapy should be reinstituted at C or C' and executed as in II-2.
(2) Relapse occurs. At this time the dose should be shifted to A or A' and executed as in I with the exception that should toxicity recur without hematological response on schedule A or A' the study is terminated for that patient.

Toxicity

Toxicity which warrants cessation of drug therapy at any dosage schedule should include one of the following:

A. Significant myelosuppression as evidenced by:
a) Hypocellularity of the marrow confirmed by section with or without thrombocytopenia or neutropenia.
b) Significant progressive decrease in platelet or absolute neutrophile levels, after an initial rise has occurred, not associated with marrow infiltration by leukemic cells.
c) In the presence of a leukemic marrow patter progressive thrombocytopenia or neutropenia to the point of appreciable hazard to the patient.
B. Progressive oral ulceration not demonstrably due to other causes.
C. Gastrointestinal symptoms, progressing in severity and not demonstrably due to other causes.

Other Therapy during the study:

1. Steroid and ACTH:
Because these compounds have rapid antileukemic action and/or they can, at time, control bleeding in the absence of a platelet rise, their use during the study will be inevitable.

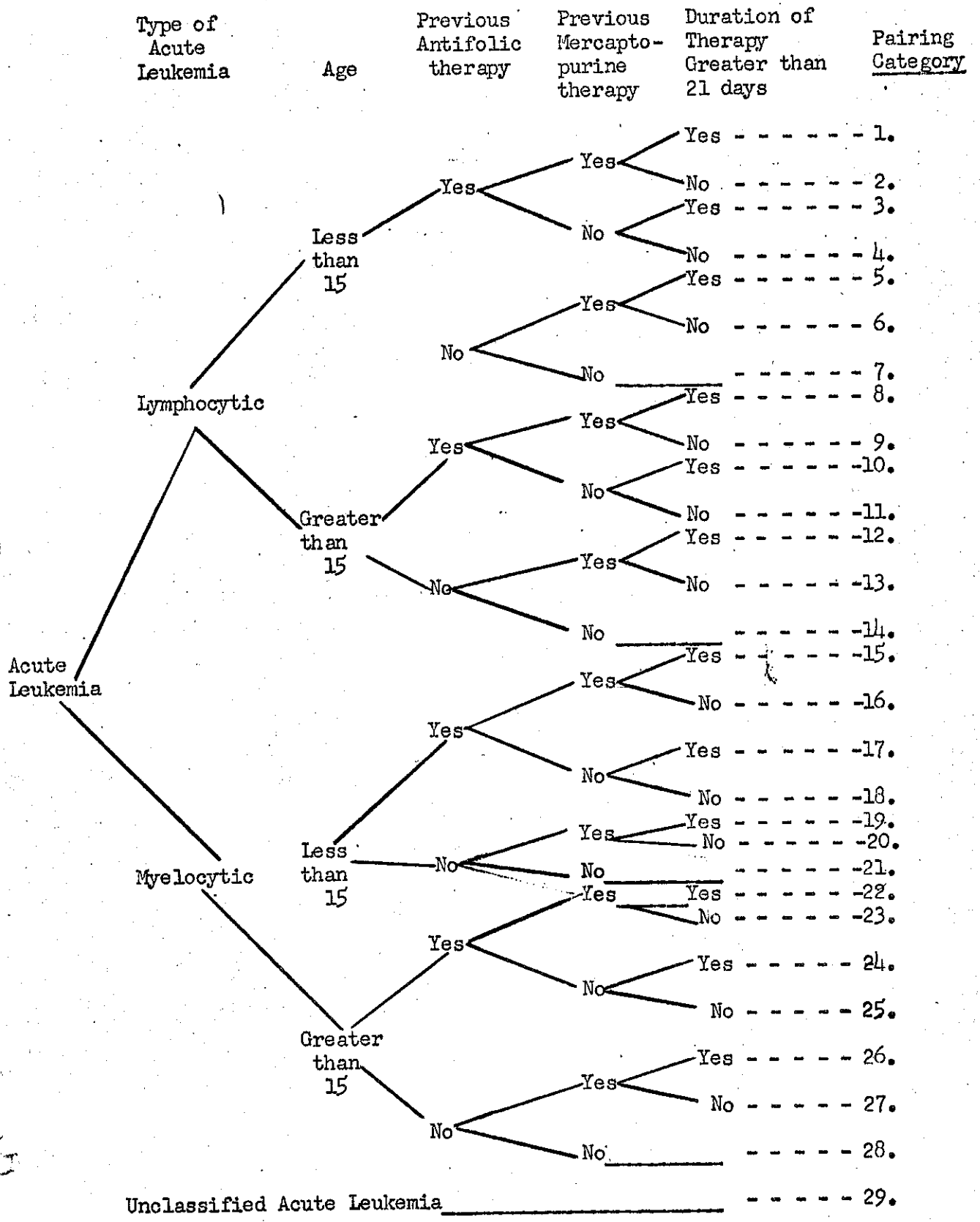
Investigators are urged never to use them electively during the study as response to combined antimetabolite therapy will be difficult to interpret. Should their use be mandatory they should be tapered and discontinued as soon as possible.

If the clinical situation on admission necessitates the use of steriods, the dosage should be tapered as soon as the clinical situation permits and antimetabolite therapy should not be instituted until the bone marrow criteria under "Selection of Patients" obtain.

2. Other antileukemic therapy:

Antimetabolites and other drugs that might influence the course of the disease should not be used during the study.

3. Transfusions and antibiotics should be used optimally.


Type of Acute Leukemia
Age
Previous Antifolic therapy
Previous Mercapto-purine therapy
Duration of Therapy Greater than 21 days
Pairing Category
Acute Leukemia
Lymphocytic
Myelocytic
Less than 15
Greater than 15
Yes
No
1.
2.
3.
4.
5.
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28.
Unclassified Acute Leukemia
29.