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ALLOGENEIC BONE MARROW TRANSPLANTATION
FOR PATIENTS WITH LEUKEMIA

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I. INTRODUCTION

The National Cancer Institute Cooperative Bone Marrow Transplant Group (BMTG) is a working group composed of investigators from the Medicine Branch, the Human Tumor Cell Biology Branch, and the Immunology Branch, NCI. It is the purpose of this group to foster basic and clinical research designed to obtain successful hematopoietic cell transplantation. The group will conduct trials of human bone marrow transplantation and act in consultation.

II. BACKGROUND

Patients with malignancy and other patients with bone marrow hypofunction have a high mortality primarily from infection secondary to granulocytopenia, and secondary from hemorrhage associated with thrombocytopenia. Supportive care of these patients with leukocyte and platelet transfusions has been employed to temporarily alleviate the primary hematologic defect. However, long-term hematologic support is not feasible because of difficulties in obtaining adequate quantities of leukocytes and because of alloimmunization to leukocyte and platelet antigens following multiple transfusions.

Marrow transplantation experiments with murine leukemia have demonstrated significant antileukemic activity (1,2). Temporary bone marrow engraftments have been observed in patients with acute leukemia receiving CML leukocyte transfusions at the NCI (3) and by Mathé, et al. in France (4). In these cases, remissions from the primary disease occurred during the period of graft survival. However, each of these patients eventually either rejected the graft or died with possible graft versus host disease (GVH or secondary disease). Attempts to transplant bone

marrow to patients with acute leukemia from an identical twin (isogenic) at the NCI and elsewhere have all resulted in eventual recurrence of leukemia within three to five months (longest remission of 50 weeks). Early experience with allogeneic bone marrow transplantation following total body irradiation (TBI) by Thomas, et al. (5) and Mathē co-workers (6) in unmatched donor-recipients has met with failure because of graft rejection or ensuing GVH, although three patients reported by Mathē had extended remissions lasting 8, 10, and 20 months. These remissions may have been the result of a specific (? immunologic) anti-leukemic effect of the graft.

Current experience with HL-A typing (histocompatibility testing) has shown that matching for these leukocyte antigens within families will greatly enhance the survival of tissue homografts in man, i.e., skin, kidney, liver, and heart. The use of HL-A typing in combination with the technique of mixed leukocyte cultures (MLC) may now permit prediction of graft acceptance and rejection in humans.

Recently, Santos, et al. (7) have reexamined interest in bone marrow transplantation by performing a marrow transplant to a patient with acute monocytic leukemia using a cytoxan (CYT) regimen for immunosuppression, which he had previously shown would induce specific tolerance to transplantation antigens in mice and rats. This patient who was probably mismatched for HL-A antigens (no MLC performed) developed moderately severe GVH and died 75 days following the transplant from pneumonia caused by A2 influenza virus. At postmortem examination, leukemia cells were not identified but characteristic changes of GVH were seen. Later, Gatti, et al. (8,9) and DeKoning, Et al. (10) transplanted HL-A

compatible marrow to a child with thymic aplasia using no immunosuppression. Bach and co-workers (11) transplanted marrow to a child with Wiskott-Aldrich syndrome using the "Santos Cytosan Regimen." This child has not recovered normal platelet counts post-transplant, but he has stopped hemorrhaging and is clinically and immunologically improved. Several additional patients have received marrow from histoincompatible donors following TBI or CYT. All of these patients have, subsequently, died presumably because of early graft rejection or fulminant GVH.

At the NCI since July, 1969, seven allogeneic bone marrow transplants were attempted in six patients with acute lymphocytic leukemia using their HL-A and MLC matched siblings as stem cell donors. All patients had become resistant to conventional chemotherapy prior to attempted marrow transplantation 7-55 months after diagnosis. All patients had received numerous random donor blood component transfusions (12-134 units) before transplantation. Cyclophosphamide (45 mg/kg/day x 4 days) was given to five of the recipients for immunosuppression, and total body x-ray (950 and 1,000 rads) to the others. All patients received methotrexate post-transplant in order to modify anticipated GVH reactions. Hematopoietic grafts were documented in five of the patients using a change in red blood cell type, cytogenetic and/or immunoglobulin typing markers. A single patient of blood group O Rh negative could not be engrafted on two occasions from an HL-A matched but red blood cell group A Rh positive mismatched donor. Remissions from leukemia were observed in three patients lasting 28, 91, and 149 days. GVH was documented by histologic criteria in two patients and suspected clinically in two others. One patient with a phenotypic HL-A match to his donor, succumbed to sepsis on day 31, two weeks after the onset of severe GVH. Both

had identical HL-A haplotypes with two identified HL-A specificities at the first sublocus (HL-A 1,3) and two at the second sublocus (HL-A 7,8). Cells from this donor-recipient pair were mutually non-stimulatory in MLC. Two patients developed a cytomegalovirus infection post-transplant which in one patient persisted until death on day 131, 40 days after full return of ALL. It appears from these transplants that allogeneic bone marrow can be transplanted from HL-A, MLC, and ABO compatible donors to patients with ALL despite possible sensitization to histocompatibility antigens by prior transfusion exposure. GVH may occur despite matching in the HL-A system, but has been of a mild degree when a genotypic HL-A match can be documented between the donor and recipient. Further clinical trials of hematopoietic stem cell transplantation seem indicated at this time. Effective repopulation of the patient's marrow with compatible donor stem cells should: (1) provide self-perpetuating support of circulating formed elements in the blood, and (2) provide the opportunity to evaluate any antileukemic effect of allogeneic immunocytes.

III. PURPOSE

- A. To evaluate the possible antitumor effect of transplanted allogeneic bone marrow in patients with malignancy.
- B. To effectively repopulate bone marrow in patients with hypoplastic marrows secondary to disease and/or cytotoxic therapy.
- C. To define and evaluate the critical factors necessary for successful bone marrow transplantation, such as:
 1. The selection of a patient in relation to his previous

- therapy (cytotoxic drug, matched or random donor transfusion exposure, stage of disease, etc.).
2. Establishment of criteria for bone marrow donation using matching techniques available (ABO, HL-A, MLC, etc.)
 3. Evaluation of various pre-transplant immunosuppression regimens in terms of incidence and extent of marrow engraftment. (TBI, cytotoxans, or other cytotoxic drugs.)
 4. Evaluation of supportive care given to the patient during the transplant period (i.e., isolation procedure, bowel sterilization, platelet and leukocyte transfusion, etc.)
 5. Evaluation of various post-transplant immunosuppression regimens as related to the occurrence and treatment of GVH.
 6. Prevention of GVH through the use of marrow fractionation, immunosuppression, enhancing antibodies against recipient cells, etc., as these techniques are shown to be effective in the laboratory.

IV. SELECTION OF PATIENTS

- A. Each patient will be evaluated by the service referring the patient to the BMTG and will suggest the appropriate time for possible transplantation as outlined in the attached appendix for patients with acute leukemia. The patient and his entire family will have had HL-A typing and MLC if indicated (see Section VI) as soon as possible after admission to the NCI. Ultimately, the decision for transplantation rests with the attending physician and the Head of the Leukemia Service.

B. Pre-transplant status of the patient.

1. All evidence of infection must be cleared. (No temperature $>38^{\circ}\text{C}$ will be considered normal.)
2. Complications of primary disease must be under full therapeutic control, i.e., CNS leukemia.
3. The patient must be physiologically stable without evidence of metabolic, renal, hepatic, cardiac, dental, or hematologic complication of his primary disease. It is understood that a patient may potentially be quite ill and, consequently, each patient will be considered individually. However, the following basic guidelines will be used for evaluation:
 - a. Creatinine clearance $>50-60$ ml/min.
 - b. Overt hemorrhage should be well controlled with supportive platelet transfusion.
 - c. No evidence of clinically severe hepatic disease.
 - d. No evidence of clinically symptomatic cardiac disease, or abnormal EKG.
 - e. All patients must have had a recent thorough dental evaluation prior to isolation.

V. DONOR SELECTION

- A. HL-A typing of a patient and his entire family must be performed as early in the course of his disease as possible and repeated until a final decision has been made concerning a possible match, within the family. For the present, no bone

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marrow transplant will be attempted unless there is evidence of identity between potential donor and recipient as determined by HL-A serotyping and haplotype analysis.

- B. MLC will be performed on all patients and siblings thought to be matched. A parent should also have an MLC performed simultaneously in order to have appropriate controls for interpretation of the test results.
- C. Complete ABO phenotyping of the patient and family will be performed on samples supplied to the NIH Clinical Center Blood Bank after the HL-A antigen matching is confirmed.
- D. All HLA typing studies will be performed by two different laboratories (Terasaki and NCI typing lab), and mixed leukocyte cultures between HL-A identical siblings will be performed at least twice.

VI. CURRENT METHOD OF MARROW TRANSPLANTATION (June, 1970 - Subject to modification by BMTG)

- A. Immunosuppression of the patient: The patient will be given either CYT or TBI in preparation for marrow transplantation. The ultimate and final decision will be made in consultation with BMTG.
 - 1. Cytosan (modified Santos Regimen): The current dose used is 45 mg/kg/day x 4 following a stimulatory dose of leukocytes from the donor (See Figure). Twenty-four hours following the last dose of CYT, the marrow will be transplanted.

2. Total body irradiation (TBI): Twenty-four hours prior to transplantation 950-1,000 rads midline dose will be delivered from a cobalt 60 source over a two to three-hour interval. No stimulatory dose of leukocytes is to be given.
- D. Marrow procurement: Bone marrow will be obtained from multiple aspirations sites on both anterior and posterior iliac crests, and the sternum with the donor under general anesthesia. The marrow will be aspirated in heparinized syringes and placed into sterile beakers containing a mixture of heparin and tissue culture media (TC-199), where it will be thoroughly mixed. After all marrow has been obtained, the marrow will be filtered with 300 and 200 micron mesh stainless steel screens to remove particulate matter. Samples will be obtained from this final mixture and compared to the peripheral blood total white blood cell count in order to obtain the corrected total number of nucleated bone marrow cells present. The marrow will then be directly infused intravenously without a filter.
- C. Supportive care of the patient during the transplant period:
1. Reverse isolation will be in an unmodified hospital room with gowns, gloves, hats, and masks for visiting family and hospital staff.
 2. Non-absorbable antibiotics will not be used initially to alter endogenous bacterial flora.
 3. Red blood cell support will be from random blood bank

donors using adequate planning to employ the freshest blood available from donors whose RBC type will not confuse any RBC "marker" being followed post-transplant in the recipient. Because of the refinement of red blood cell antigen grouping necessary, this intricate matching cannot be done on an emergency basis. All support for non-hemorrhagic anemia should be planned. All blood is to be irradiated with 1,500 R before transfusion.

4. Platelet support will be given from the matched marrow donor or family member if practical. Otherwise, the most suitable random donor will be employed. All platelets, even if from the matched donor, will be irradiated with 1,500 R before transfusion.
5. Granulocyte support for prophylaxis against infection will be given whenever a suitably matched donor is available. (See leukocyte transfusion protocol). Granulocytes will only be given on day 1, 3, 5 or 6, and 7 or 8 post-transplant to study the effect on incidence and severity of infection. All leukocytes will be irradiated with 1,500 R before transfusion. If a severe bacterial infection is documented in patients not scheduled to receive leukocyte transfusions, they will be instituted and continued until the infection has cleared. (See leukocyte transfusion protocol.)
6. Prevention of graft versus host disease (GVH): The

initial patients at the NCI received methotrexate post-transplantation in anticipation of graft versus host disease. The schedule was 10 mg/m² IV on day 1, 3, and 6 and 5 mg/m² IV weekly thereafter. Subsequent patients will receive this or other treatment only as determined on an individual basis, by the EMTG at the time of grafting. (Other regimens to be immediately used will include no post-graft immunosuppression and cytotoxans.)

VII. OUTLINE OF RECORDS TO BE KEPT AND LABORATORY STUDIES TO BE PERFORMED DURING AND AFTER THE TRANSPLANT

This schedule of laboratory studies has been prepared to evaluate the toxicity associated with immunosuppression for bone marrow transplantation and to define the limitations and complications of bone marrow transplantation in the treatment of leukemia. This outline lists the minimum studies that should be obtained on potential bone marrow donor candidates and recipients.

A. General comments (See attached figure for timetable.)

1. Hospitalization.

- a. Donor must be hospitalized for 24 hours preceding the procedure.
- b. Recipients will be placed in an unmodified hospital room with reverse isolation precautions (gown, mask, hat, and gloves) on the day preceding immunosuppression.

2. Consent forms

- a. Donor: Operative consent for "multiple bone

marrow aspirations under general anesthesia from bilateral iliac crests and sternum."

- b. Recipient: Informed consent for "Bone Marrow Transplantation."
 3. In order to maintain complete NIH records, it is essential that a daily physical examination, daily weights, and all laboratory data be recorded in the leukemia flow sheets.
 4. Allopurinol should be administered to all recipients during the initial transplant period.
 5. When cytoxan is used for immunosuppression, large quantities (3,000 ml/m²) of intravenous fluids must be administered each day of and for 48 hours following the course of therapy.
- B. Pre-transplant evaluation of the donor
1. Complete history and physical examination
 2. Chest x-ray
 3. EKG
 4. BUN, glucose, SGOT, bilirubin, prothrombin time, PTT, fibrinogen, protein electrophoresis, routine urinalysis
 5. Serologic tests: Australia antigen, toxoplasmosis titer, CMV-CF titer, candida titer, aspergillus ppt. titer
 6. HL-A typing x 2 (NCI lab and Terasaki)
 7. HLC x 2
 8. In vitro "cellular cytotoxicity" assay between donor and recipient.
 9. CBC, reticulocyte count

10. Bone marrow aspirate with cytogenetics
11. Red blood cell phenotyping
12. Skin testing (requires at least three weeks for completion of studies). Antigens to be used: PPD, mumps, trichophyton, brucella, SKSD, histo (cocci). Donors will be sensitized to DNCB and brucella. This requires at least three weeks and should be done when the confirmatory HL-A and MLC are performed.
13. Anesthesia Department clearance for surgery.
14. Storage of blood products
 - a. Platelets from the donor will be frozen for use during the post-transplant period for support of the patient.
 - b. One unit of whole blood will be obtained in the plasmapheresis lab and stored in the Clinical Center Blood Bank for reinfusion to the donor after marrow donation.
 - c. Peripheral blood lymphocytes will be obtained by plasmapheresis and frozen for future studies.
 - d. Leukocytes will be obtained from the donor one day prior to immunosuppression (Tx day-5) for infusion to patient as the stimulatory dose of HL-A antigens.
 - e. 20 ml of serum for storage.
15. Urine and saliva are to be cultured for CMV.
16. Cross match two units of blood to "hold for surgery" several days before surgery.

17. Obtain permission from the Chief, Surgery Branch, NCI, to have the donor go to the recovery room following surgery.

C. Pre-transplant evaluation of recipient

1. HL-A typing x 2 (NCI and Terasaki)
2. MLC x 2
3. In vitro cellular cytotoxicity assay
4. Serum for serum bank (20 ml) may be obtained over a period of several days
5. Peripheral blood lymphocyte response to PHA
6. Skin testing (see donor section for antigens)
7. Skin punch biopsy (at least two weeks before Tx)
8. Baseline cultures when patient placed in isolation room (Tx day -5)
 - a. Blood, stool, urine, perineal skin, and throat, for aerobic bacteria and fungus
 - b. Urine, throat washings and saliva for CMV
9. Stool for occult blood
10. Serologic tests: Australia antigen, toxo. titer, candida titer, aspergillus ppt. test, CMV-CF titer
11. Bone marrow with cytogenetics (In vitro culture of bone marrow aspirate should be attempted.)
12. EKG within the week preceding cytoxan or TBI.
13. Chest x-ray within the week preceding cytoxan or TBI.
14. Complete RBC phenotyping and isohemagglutinin titers (if to be used as transplant marker; transfuse patient with blood products containing none of the donor marker antigens).

15. Saliva should be sent to the Blood Bank to determine secretor status. (Saliva must be sent within one hour of collection to be valid. Make arrangements with M. McGinniss.)
 16. Transfuse to hemoglobin 12-14 gm%
 17. Place patient in reverse isolation room and initiate daily Phisohex baths
 18. Peripheral blood lymphocytes are to be obtained by plasmapheresis and frozen. It is best that this be initiated several weeks before the date of transplant.
- D. Serial laboratory tests to be obtained on recipient during the transplant period (see attached figure).

Day 0 - day of transplant

Day -1 - day before Tx

Day -5 - day before 4-day immunosuppression regimen

1. Blood studies:

a. Hematology

(1) Hgt, WBC, diff., platelet count, retic., daily by platelet lab

(2) Sedimentation rate EIW (or whenever violet top tube can be drawn) by platelet lab

(3) Serum specimen for serum bank: at least 5 cc clotted blood to platelet lab each time venous blood is drawn (minimum TIW)

b. Renal and liver function tests - Immediately prior to and daily during immunosuppressive regimen, every other day for 10 days, then EIW.

SGOT, SGPT, alkaline phosphatase, creatinine phosphokinase, bilirubin, LDH, EUN, creatinine, glucose, urinalysis

- c. Clotting studies: Immediately prior to and daily during immunosuppressive regimen, every other day x 2, then weekly
 - (1) Prothrombin time (PT)
 - (2) Partial thromboplastin time (PPT)
 - (3) Fibrinogen
 - (4) Factor analysis as indicated
- d. Stool for occult blood: Day -5, -3, -1, +1, +3, +6, and twice weekly
- e. Other blood tests: Immediately prior to immunosuppression and weekly thereafter until patient discharged from the hospital
 - (1) Protein electrophoresis
 - (2) Immuno-electrophoresis
 - (3) Serologic tests: Candida titer, aspergillus ppt., toxoplasmosis titer, CMV-CF
 - (4) Ischemagglutinin titers, antibody screen, and Coomb's test
 - (5) If RBC marker used, RBC phenotype weekly
 - (6) If secretor difference found between donor and recipient, fresh saliva specimen should be sent weekly to the Blood Bank.
 - (7) Creatinine clearance

2. Bone marrow examinations: Day -5, 0, +5, +10, +15, and weekly thereafter if marrow function is returning
 - a. Routine marrow aspirate
 - b. Needle biopsy
 - c. Cytogenetics each time if chromosome marker exists or aneuploid cell line has previously been identified
 - d. In vitro culture of bone marrow aspirate
3. Miscellaneous studies
 - a. Cultures: Day -5, -1, +3, +7, +11, +15, +20, and weekly if bone marrow function has returned
 - (1) Aerobic bacterial and fungal cultures of blood, stool, urine, throat, and perineal skin
 - (2) Urine, throat, and saliva for CMVIf patient is febrile, obtain daily blood cultures.
 - b. Radiology: Chest x-ray day -5, 0, +1
 - c. EKG: Day -5, -4, -3, -2, -1, 0, +2, +4, +6
 - d. Pathology specimens
 - (1) Skin biopsy to be taken 48 hours after the appearance of any rash or desquamation. (Serum samples should be stored daily during any period of skin rash.)
 - (2) Liver biopsies should be obtained from all patients having evidence of GVH with liver involvement.
 - e. Evaluation of immunologic capacity
 - (1) Skin tests: Repeat same pre-transplant battery

of skin test antigens including antigens that the bone marrow donor had positive, i.e., DNCC, brucella, on day 0, +14, +30, and monthly thereafter.

- (2) Immunization: At three weeks post-transplant immunize the patient with Vi antigen. Obtain 5 ml serum 10 days later to measure humoral response. Do not immunize patient with A or E substance.
- (3) Response of peripheral blood lymphocytes in vitro to PHA, MLC, and other antigens should be measured on day -5, daily x 7 days, then weekly thereafter. Send 10 cc heparinized blood (10 U/ml) to Room 2B45. Cytogenetic analysis can be performed on this same peripheral blood sample.

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BONE MARROW TRANSPLANT PLAN (Modified Santos Regimen)

BONE MARROW INFUSION
From matched
HL-A DONOR

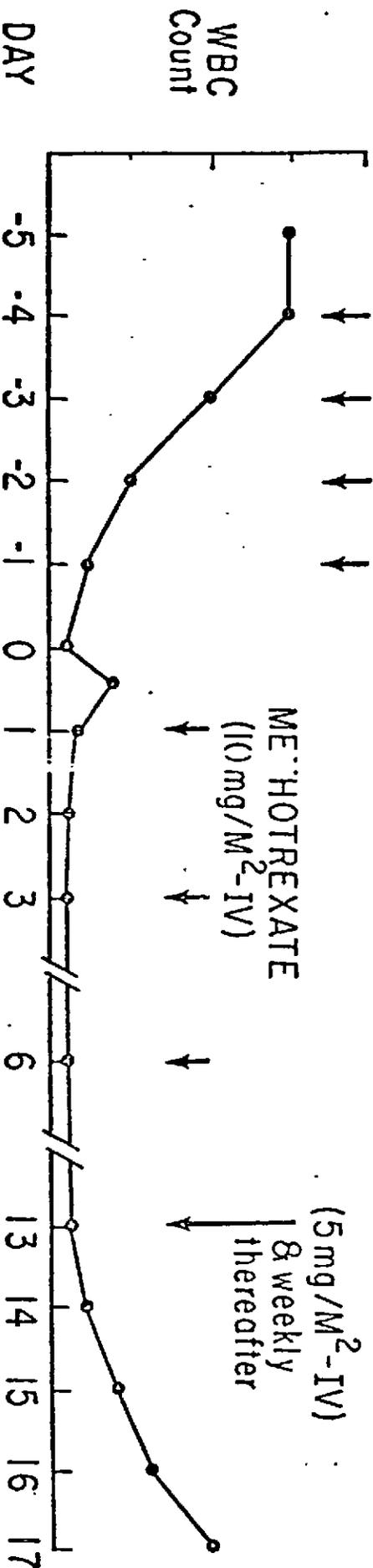
Antigenic Stimulus
(WBC's or whole blood)

CYTOXAN
(45mg/kg/day, IV)

METHOTREXATE
(10 mg/M²-IV)

(5 mg/M²-IV)
8 weekly
thereafter

Period of intensive Hematologic support
with irradiated RBC's, WBC's, and platelets



PRE-TRANSPLANT CHECK LIST

NAME OF PATIENT

UNIT NUMBER

ITEM	DONOR	RECIPIENT
1. Complete H & P		
2. Consent forms		
3. Baseline CBC		
4. EKG		
5. Chest X-ray		
6. Renal, liver function tests and clotting studies (creatinine clearance on recipient)		
7. Cultures: Bacteria (aerobic and anaerobic) Fungi		
8. Urine and saliva for CMV		
9. Serologys: CMV, Toxoplasmosis titer Australia antigen Candida and Aspergillus		
10. HL-A typing (confirmatory)		
11. MLC		
12. in vitro cellular cytotoxicity assay		
13. Skin tests (PPD, DNCB, etc.)		
14. Bone marrow with cytogenetics		
15. Red cell phenotyping and saliva for secretor		
16. Peripheral blood lymphocytes frozen		
17. Serum for serum bank		
18. Blood products stored		
19. Anesthesia clearance		
20. Operating room schedule posted		
21. Cross match 2 units of blood		
22. Recovery room scheduled		
23. Lymphocyte response to PHA & MLC		
24. Skin punch biopsy		
25. Stool occult blood		
26. Transfuse to 14 gm% hgb		
27. Arrange for isolation room		
28.		
29.		
30.		
31.		

ALLOGENEIC BONE MARROW TRANSPLANTATION
FOR PATIENTS WITH LEUKEMIA

Selection of Patients for Bone Marrow Transplantation
Acute Leukemia Service

Acute Lymphocytic Leukemia: All patients will be treated with standard acute leukemia

