5.51 CNS leukemia at time of entry on study or prior to day 50 (during intensification):

Give one dose of 15 mg i.t. Mtx with Citrovorum factor 15 mg IV on day 1 at 24 & 48 hours. Begin Cranial RT (Section 5.9) on day 21 for patients with CNS leukemia at time of entry (or on day of CNS diagnosis for other patients). Give i.t. Mtx (but omit IV Mtx) on days 22, 29, and 36. (IV Mtx for others omitted also if it has not yet been completed.)

5.52 CNS leukemia developing during hematologic remission while receiving, or having completed, protocol therapy: continue protocol therapy for patients who experience CNS failure without hematologic relapse. Begin CNS RT (Sec 5.7). For patients who have completed protocol therapy, begin CNS RT (Section 5.7) and give 15 mg i.t. Mtx weekly until CNS is clear of leukemic cells and then monthly for 12 months.

5.6 Testicular Involvement

5.61 Biopsy Clinically Suspected Disease. Begin gonadal radiotherapy:

a. If testicular disease is present at the time of entry on study: Begin protocol treatment. If gonadal disease persists or worsens after week 22 (Intensification III), begin gonadal radiotherapy (Sec. 5.62).

b. If testicular disease develops during hematologic remission while patient is receiving or has completed protocol therapy: Begin radiotherapy (Sec. 5.62).

5.62 Testicular Irradiation: 2,600 cGy (1 cGy = 1 rad) in 13 sessions.

5.621 Equipment

Modality: Use external beam photon irradiation.

Energy: Use Radiation of megavoltage quality, i.e., Cobalt 60 or accelerator beams with nominal energy of 4 - 6 MeV. Appropriate bolus may be necessary to satisfy homogeneity criteria (Section 5.6262).

5.622 Treatment Volume: Include the entire scrotal contents, i.e. both testes, in the treatment fields. Use margins of at least 1/2 cm.

5.623 Treatment Dose
Prescription Point: the point along the central axis midway between the entrance and exit points of the testes) i.e., the midplane of the testes).

5.624 Total Dose

Describe absorbed dose in centigray-to-muscle tissue.

Deliver a total dose to the prescription point of 2,600 cGy in 13 treatments (200 cGy/fraction).

5.625 Time-Dose Considerations

Dose per Fraction: 200 cGy to the prescription point.
Deliver One Fraction per Day
Treat Five Days per Week
Total Elapsed Time: 17 days.
Time-Dose-Factor (TDF) to the prescription point for this treatment regimen is 43.

Account for any modification of the required dose fractionation or interruption of treatment by adjusting the daily or total dose to achieve a TDF of 43 to the prescription point. (See Orton and Ellis, BJR, 46:529-537, 1973).

5.626 Homogeneity and Reference Points

5.6261 Calculate the dose at two reference points located along the central axis at the following depths:

Point A: 0.5 cm from the anterior ("entrance") surface of the testes

Point B: 0.5 cm from the posterior ("exit") surface of the testes

5.6262 The doses at the homogeneity reference points (Point A and Point B) shall be within ±10% of the dose to the prescription point.

5.6263 For treatment with therapy accelerators it may be necessary to employ appropriate bolus to achieve the homogeneity criteria (Section 5.6262).

If bolus is used, record the folowing parameters and submit as part of the Quality Assurance Documentation:

a. Thickness, location, and composition of bolus material.

b. Mid-plane depth of testes without bolus

Note: Points "A" and "B" are defined with respect to the surface of the testis itself, and not the bolus material.

5.627 Treatment Technique

5.6271 Treat with a single, unopposed, anterior field each day.

Exception: it may be necessary to vary this technique to satisfy the homogeneity criterion (Section 5.6262) (i.e., ±10% of the prescription dose throughout the treatment volume). Thus, if testes >4 cm AP diameter, it may be necessary to treat with both AP and PA parallel-opposed portals or some alternative technique.

5.6272 Deliver Radiation with the patient supine (face up).

Support the testes posteriorly and, if possible, extend appropriately to minimize irradiation of the perineum.

5.628 Normal Tissue Sparing: Exclude the penis and urethra from the treatment field by fixing the penis over the symphysis pubis.

5.7 **Cranial Radiation Therapy:** If the patient fulfills criteria for CNS RT Section 5.51 and 5.52) give 2,400 cGy in 12 sessions. See Section 5.77 for quality assurance documentation.

5.71 Equipment

5.711 Modality: Use photon radiation.

5.712 Energy: Use radiation of megavoltage quality, i.e., Cobalt 60 or accelerator beams with a nominal energy of no less than 4 MeV, nor greater than 6 MeV.

5.713 Use Isocenter teletherapy units with a source to axis distance (SAD) ≥80 cm.

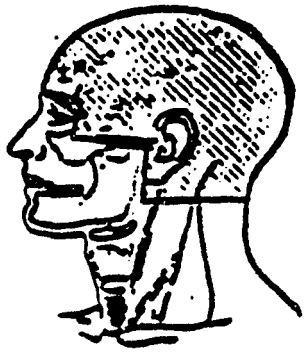
5.714 All radiation units used for protocol therapy must have their calibration verified and selected radiation beam parameters checked by the RPC or one of the regional CRP's.

5.72 Treatment Volume: Include the entire brain extending:

a. Anteriorly, to include the entire frontal lobe and the posterior half of the eyeball, including the optic disc and nerve superior to the vertex and posterior to the occiput.

b. Inferiorly, to a border of 0.5 cm below the skull base extending posteriorly to the C-2 vertebral level.

c. Superiorly, to a border of 0.5 cm beyond the periphery of the scalp. (See Figure).



5.73 Treatment Dose

5.731 Prescription Point: The point along the central axis of the lateral opposed beams midway between the two lateral entrance points (i.e., midplane).

If the cranium is treated with a "split beam" technique, i.e., with the central axes of the lateral beams passing through the orbits, the prescription point is defined as midway along the axis of maximum lateral skull separation. In this case, document the calculation of this point on the lower half of the RT-1 form under "Off-Axis Reference Points" as Reference point "A".

5.732 Total Dose

a. Describe absorbed dose in centigray (cGy) to muscle tissue: 1rad=1cGy
b. Do not correct for inhomogeneity secondary to bone absorption.
c. Deliver a total dose to the prescription point of 2,400 cGy in 12 treatments.

5.74 Time-Dose Considerations

5.741 Dose per Fraction: 200 cGy to the prescription point for 12 treatment fractions.

5.742 Deliver One Fraction per Day

5.743 Number of Fields per Fraction: Treat all fields during each treatment fraction.

5.744 Five Treatment Days per Week one fraction/day.

5.745 Total Elapse Time: 16 days.

122

5.746 Time-Dose-Factor (TDF): to the prescription point of 40.

Account for any modification of the required dose fractionation or interruption of treatment by adjusting the daily or total dose to achieve the originally prescribed TDF. (See Orton and Ellis, BJR, Vol. 46:529-537, 1973.)

5.75 Normal Tissue Sparing

5.751 Do NOT treat the spinal axis below the C-2 vertebrae.

5.752 Shield the anterior half of both eyes with customized individually cut shadow blocks of at least 5 HVL thickness. Take extreme care to avoid shielding the posterior orbits. Radio-opaque markers placed on the posterior orbital ridge to assist in the localization of the field and shadow blocks are recommended.

5.76 Treatment Technique

5.761 Treat with two lateral, equally-weighted, parallel opposed beams.

5.762 The source (target) to mid-plane distance shall be > 80 cm.

5.763 Deliver RT with the patient supine (face-up). (Truly parallel fields and shielding reproducibility are easier to obtain.) Immobilize the patient's head during treatment.

5.764 Treat both lateral radiation fields each day.

5.765 Shape fields with shadow blocks of ≥ five half-value layers thick.

5.766 Parallax problems in shielding the orbits can be minimized by using the "split beam" technique. With this technique,the central axis of the field passes through both orbits and the entire cranium is irradiated by one-half of the beam. If this technique is used:

a. Carefully insure that the dose is calculated midway along the axis passing through the maximum lateral separation of the skull, (not the central axis which passes through the patient's eyes).

Include the entire cranium within the area of the split beam in which the variation from central axis dose (at 10 cm depth in a uniform water phantom) is less than ± 5%.

b. Calculate an isodose map and submit as part of the Quality Assurance documentation. Clearly label the isodose lines with the total dose received to demonstrate that the homogeneity requirement (± 5%) is met throughout the treatment volume.

5.77 Quality Assurance and Documentation:

5.771 Submit the following (or copies) within three days of beginning RT to:

Arvin S. Glicksman, M.D., Director
Quality Assurance Review Center
Rhode Island Hospital
593 Eddy Street
Providence, Rhode Island 02902
401-277-5215

1. **Localization films:** right (R) & left (L) lateral, for CNS or AP for gonadal.

2. **Verification (portal) films** R & L lateral for CNS or AP for gonadal.

3. **Polaroid pictures of the patient in treatment position** (with fields appropriately marked). Whenever possible the **"double exposure"** port film technique which reveals the adjacent structures is preferred.

4. **Radiotherapy Initial Report Form (RT-1).**

5. **Daily Dose Calculation:** Check for gonadal RT calculation of daily dose to reference point A & B (the AP separation of the testes (without bolus) should be clearly indicated.

5.772 Forward copies of the following upon completion of treatment:

1. **Radiotherapy Total Dose Record (RT-2).**

2. **Treatment record** (show daily doses and all dose calculations).

3. **Any dose calculation worksheets** for central axis calculations.

4. **Appropriate isodose maps** and reference point calculations if "split beam" technique is used. (See 5.731 & 5.732).

12

8.0 REQUIRED DATA

8.1 Tests and Observations	Day On Study	Day 1 of Course	Post Treatment Follow-up*
Signed informed consent	X		
History & Progress Notes	X	X	X
Physical Examination	X	X	X
Pulse, Blood Pressure, Temp	X	X	X
Surface Area	X	X	X
Performance Status	X	X	X
Tumor Measurements	A	A	A
Neurological Exam and fundoscopy	X	X	X
Staging			
Chest x-ray	X	X	X
CBC, differential & platelet count	X	B	X
Reticulocytes	X	PRN	PRN
Cytochemistry, Surface antigens (8364)**	X		
Bone marrow Asp & Bx	X	day 22, day 50, then q 6 wk	X
CSF glucose, protein, cells, cytocentrifuge	X	when i.t. Mtx is given	C
Laboratory			
PT/Ptt	X	X	
Glucose, amylase and fibrinogen during i-asp	X	X	
Creatinine	X	X	X
Electrolytes	X	X	
SGOT/SGPT/Alk. Phos./Bili/LDH	X	X	X
Uric Acid, Ca^{++}, PO_4, Glucose,	X	X	X
Total Protein, Albumin	X	X	X
Urinalysis	X	X	X
EKG	X	PRN	PRN
Gated cardiac radionuclide scan	X	D	D

*Following completion of intensification IV, at least every 2 months for 1 year, then every 3 months x 5 years

**Must be repeated in patients at relapse.

A Note specifically Liver, Spleen, Lymph Node size & mediastinal mass

B Day 1 of each course and prior to Mtx dose

C q 6 mo up to 2 years of follow-up, then as indicated

D Repeat if clinically indicated. Also note that a repeat test is required at week 22 - 24

RN When clinically appropriate

8.2 **Modifications of this protocol:** It is recognized that this protocol stipulates an ideal clinical design which, for a number of reasons, may not be approached perfectly. Patient compliance, physician preference, test availability, holidays, and other factors may necessitate minor changes in scheduling, dosing, and other aspects of the protocol which do not substantially change the experimental design. The conduct of the study is under the direction of the patient's physician, and it is the obligation of the Study Chair and the Committee Chair to ascertain whether cases have been treated in accordance with the intent of this protocol.

122

9.0 CRITERIA FOR RESPONSE

The June 1974 modification of the CALGB criteria for evaluating acute leukemia will be used.

9.1 **Bone Marrow:** See Appendix IA

9.2 **Peripheral Blood:** See Appendix IB

10.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

10.1 **Duration of Treatment**

10.11 **M_0, or M_1:** Continue treatment or follow-up as specified in the protocol and observe for relapse. See Section 10.14.

10.12 **Failure to achieve M_1 by day 50 or relapse:** Remove from protocol therapy. Observe for survival. Treat as deemed appropriate by the patient's physician.

10.13 **Extramedullary Leukemia**

Keep Patients with extramedullary relapse on study if the recurrence can be treated locally e.g., radiotherapy for gonadal (see Section 5.6) or CNS leukemia (see Section 5.7). Record the following on flowsheets:

1. Relapse site
2. Diagnosis method (histological wherever possible)
3. Therapeutic measures taken to control recurrence
4. Bone marrow differential at diagnosis of extramedullary relapse

10.14 **Relapse**

Patients who achieve complete remission (M_0, M_1) will continue on protocol until the appearance of hematologic relapse as defined by:

1. One bone marrow aspirate with 50% or more lymphoblasts and leukemic cells present.

2. Two or more marrow aspirates which show progressive repopulation with lymphoblasts and leukemic cells in excess of 5% culminating in 25% or more.

3. One marrow aspirate which shows 25% or more lymphoblasts and leukemia cells in the presence of 2% or more circulating lymphoblasts.

10.15 **Extramedullary Relapse**

CNS Relapse - See Section 5.72.

10.16 **Gonadal Relapse Involvement** - See Section 5.6.

10.2 **Extraordinary Medical Circumstances:** If, at any time, the constraints of this protocol are detrimental to the patient's health, the patient shall be withdrawn from protocol therapy. In this event:

10.21 Notify the Study Chair.
10.22 Document the reason(s) for withdrawal on flow sheets.
10.23 Follow the patient for survival and relapse if a response has been observed.

10.3 Unexpected or Life-Threatening Toxicity

10.31 Direct questions regarding drug therapy to the Study Chair.

10.32 In the event of unusual, life-threatening, or lethal toxicity, that is caused by the treatment, call:

The Study Chair
The Central Office (617) 732-3676, and
Call the IDB 24-hour hot line (301-496-1196) within 24 hours, as required by law.

See NCI, CDT Investigational Agent Adverse Drug Reaction Reporting Chart.

Send Form FDA 1639 (Drug Experience Report) to the IDB, within 10 days, with a copy to the Central Office.

The Chairman's Office will notify the other investigators at the Study Chair's request. Reporting of marrow hypoplasia or aplasia in leukemic patients is not required.

11.0 ANCILLARY THERAPY

11.1 Patients should receive **full supportive care,** including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.

11.2 Treatment with **hormones or other chemotherapeutic agents** will result in the patient's removal from the study, except for steroids administered for documented CNS metastases, adrenal failure, septic shock, or hormones administered for non-disease-related conditions, e.g., insulin for diabetes. **Glucocorticoids may not be used as antiemetics.**

11.3 **Palliative radiation therapy** may not be administered while the patient is on study.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design: The purpose of this Phase III trial is to compare the results of a daunorubicin-based induction and consolidation regimen to a regimen alternating mitoxantrone and daunorubicin. Patients will be grouped into two defined strata based on their age at time of entry onto the study and will then be randomized with equal probability to one of two treatment regimens, defined as follows: Regimen I - daunorubicin-based, Regimen II - alternating mitoxantrone and daunorubicin.

12.2 Endpoints: The primary endpoints are the frequency of complete remissions observed, length of remission duration, and overall survival. Remission duration is defined as time from response (date of CR) to date of death, relapse, or last follow-up contact. Survival is defined to be time from entry to date of death or last follow-up contact. Observed toxicities (CALGB ratings) will also be evaluated.

12.3 Number of patients to be studied: 300 patients will be randomized to treatment and allowing for approximately 5% ineligibility, 286 eligible patients are expected for comparison; 143 on each treatment arm. Accrual will continue for 5 years, assuming an accrual rate of 5 patients per month (as in Study 8011). One year of follow-up from the closing date of this study will be required; at this time, approximately half of the patients will have failed (median survival on 8011 was 2.5 years).