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Addendum No. 2

Final Committee Draft	1/81
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Approved by CIB	7/22/81

CHILDRENS CANCER STUDY GROUP

PROTOCOL CCG-193 PILOT

TREATMENT OF PREVIOUSLY UNTREATED ACUTE LYMPHOBLASTIC LEUKEMIA FOR PEDIATRIC PATIENTS WITH UNFAVORABLE PROGNOSTIC FEATURES

NAV1.954221.003

INDUCTION

PREDNISONE (NSC-10023), VINCRISTINE (NSC-67574), DAUNOMYCIN (NSC-82151), L-ASPARAGINASE (NSC-109229), METHOTREXATE (NSC-740)

CNS / INTENSIFICATION

CYCLOPHOSPHAMIDE (NSC-26271), 6-MERCAPTOPURINE (NSC-755), CYTOSINE ARABINOSIDE (NSC-63878), METHOTREXATE, WHOLE X-RAY BRAIN

INTERIM MAINTENANCE

6-MERCAPTOPURINE, METHOTREXATE

REINDUCTION / REINTENSIFICATION

DEXAMETHASONE (NSC-34521), VINCRISTINE, ADRIAMYCIN (NSC-123127), L-ASPARAGINASE, CYCLOPHOSPHAMIDE, 6-THIOGUANINE (NSC-752), CYTOSINE ARABINOSIDE, METHOTREXATE

CONTINUATION

VINCRISTINE, PREDNISONE, METHOTREXATE, 6-MERCAPTOPURINE

CCSG STUDY COMMITTEE

Paul S. Gaynon, M.D.	Study Chairman
W. Archie Bleyer, M.D.	Study Co-Chairman
Peter G. Steinherz, M.D.	Study Co-Chairman
Jerry Finklestein, M.D.	Chemotherapy
Gregory Reaman, M.D.	Chemotherapy
Philip Littman, M.D.	Radiation Therapy
Denis Miller, M.D.	Morphology
Harland Sather, Ph.D.	Statistician
Denman Hammond, M.D.	Group Chairman

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4.0 TREATMENT

Seattle-New York-Chicago Modification of Berlin-Frankfort-Munster Protocol.

4.1 Phase I Induction (5 weeks)

During induction no dosage will be reduced or delayed because of myelosuppression. Induction will last 5 weeks (including 1 week rest).

4.11 Prednisone 60 mg/m^2/d p.o. - three divided doses/day x 28 d.

Taper as 30 mg/m^2/d x 4 d.
15 mg/m^2/d x 4 d.
7.5 mg/m^2/d x 3 d.
3.75 mg/m^2/d x 3 d.

4.12 Vincristine 1.5 mg/m^2/wk IV x 4 d 0, 7, 14, 21. (maximum dose 2.0 mg)

4.13 Daunomycin 25 mg/m^2/wk IV x 4 d 0, 7, 14, 21.

4.14 L'Asparaginase 6000u/m^2 p.o. tiw IM x 9 M W F. Start d 3.

4.15 Ara-C dose per age IT d 0 only, 20, 30, 50, 70 mg for age < 1, < 2, < 3, ≥ 3 years old respectively.

4.16 Methotrexate dose per age IT d 14,28.
6, 8, 10, 12 mg for < 1, < 2, < 3, ≥ 3 years old respectively.

4.17 A bone marrow will be performed on day 7 and 28. (Day 14 also if day 7 has > 25% blasts)

4.2 Phase II CNS/Intensification (5 weeks)

For patients in remission on day 28 of the study, CNS/Intensification will begin on day 35 or when peripheral counts recover with absolute neutrophil count greater than 500/mm^3 and platelet count greater than 100,000/mm^3. Therapy may be delayed at d 14 of the Phase for myelosuppression, but not on other days, i.e., once the Cyclophosphamide has been given the 6-MP, Ara-C, XRT, and IT MTX should not be modified or postponed, but the next Cyclophosphamide must be delayed until peripheral counts recover.

4.21 Cyclophosphamide 1 gm/m^2/q 2 wk IV d 0, 14.

4.22 6-MP, 60 mg/m^2/d p.o. x 28 d.

4.23 Ara-C 75 mg/m^2/d 4 days/wk IV or SC d 1-4, 8-11, 15-18, 22-25.

4.24 XRT-whole brain 180 rad/d x 10 d. Start d 0.

4.25 Methotrexate dose per age ITx4 d 4, 11, 18, 25.
6, 8, 10, 12 mg for < 1, < 2, < 3, ≥ 3 years old respectively.

4.26 A bone marrow will be performed three weeks following the final dose of Cyclophosphamide.

4.3 Phase III Interim Maintenance (8 weeks)

For all patients in remission upon completion of Phase II, Interim Maintenance will begin three weeks after the final dose of Cyclophosphamide in Phase II, or when peripheral counts recover with ANC ≥ 1000/m^3 and platelet count ≥ 100,000/mm^3, whichever occurs last. Therapy should be interrupted for ANC < 1000/mm^3 or platelets < 100,000/mm^3, and restarted at 3/4 dose when blood counts permit in order to maintain the ANC between 1000 and 2000/mm^3. Whether or not the scheduled therapy has been completed, a two week rest period will begin on day 42. Phase III will last no longer than 8 weeks.

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4.31 6MP 60 mg/m^2/d p.o. d 0-41.

4.32 Methotrexate 15 mg/m^2/wk p.o. d 0, 7, 14, 21, 28, 35.

4.33 A bone marrow aspiration, lumbar puncture and testicular biopsy (for boys) will be performed upon completion of this Phase.

4.4 Phase IV Reinduction/Reintensification (8 weeks)

Upon completion of Phase III, Interim Maintenance patients in remission will begin Phase IV Reinduction/Reintensification when absolute neutrophil count $\geq$ 1000/mm^3 and platelet count $\geq$ 100,000/mm^3. Once Reinduction is begun, therapy will not be interrupted or modified for myelosuppression. Reintensification will begin on day 35 of the Phase or when the counts recover - whichever occurs later. Drug doses in Reintensification will not be delayed or modified once it has begun.

4.41 Reinduction:

4.411 Dexamethasone 10 mg/m^2/d p.o. x 28 d, 5 mg/m^2/d x 3 d, 2.5 mg/m^2/d x 3 d, 1.25 mg/m^2/d x 3 d.

4.412 Vincristine 1.5 mg/m^2/wk IV x 4 d 0, 7, 14, 21. (maximum dose 2.0 mg)

4.413 Adriamycin 25 mg/m^2/wk IV x 4 d 0, 7, 14, 21.

4.414 L'Asparaginase 6000 u/m^2 p.o. qod IM x 9 M W F. Start d 3.

4.42 Reintensification:

4.421 Cyclophosphamide 1 gm/m^2 IV d 35.

4.422 6TG 60 mg/m^2/d p.o. d 35-48.

4.423 Ara-C 75 mg/m^2/d IV or SC d 36-39, 43-46.

4.424 Methotrexate dose for age ITx2 d 39, 46.
6, 8, 10, 12 mg for $<$ 1, $<$ 2, $<$ 3, $\geq$ 3 years old respectively.

4.5 Phase V Continuation (96 weeks)

Phase V begins twenty-eight days after initiation of the Reintensification part of Phase IV, Reinduction/Reintensification, or following recovery of peripheral counts (ANC $\geq$ 1000/mm^3 and platelet count $\geq$ 100,000/mm^3) - whichever occurs last.

Phase V consists of 8 x 12 week cycles. The oral doses of 6-MP and Methotrexate may be adjusted for myelosuppression. Drug may be withheld for ANC $<$ 1000/mm^3 or platelets $<$ 100,000/mm^3 and restarted at 3/4 dose when counts recover, in order to maintain an ANC between 1000 and 2000/mm^3.

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If a patient who is scheduled to begin a new cycle has ANC < 1000/mm^3 or platelet < 100,000/mm^3, then the bone marrow aspirate, spinal tap with intrathecal methotrexate, and Vincristine and Prednisone for cycles 3, 4 and 5 will be postponed. If the period of myelosuppression lasts two weeks, a bone marrow will be performed. It need not be repeated when the counts recover.

4.51 Bone marrow aspirate d 0 of each 12 week cycle.

4.52 Methotrexate dose as per age IT d 0 of each 12 week cycle.
6, 8, 10, 12 mg for < 1, < 2, < 3, ≥ 3 years old respectively.

4.53 Vincristine 1.5 mg/m^2/wk IV x 2 d 0 and 7 cycles 3, 4, 5 only. (maximum dose 2.0 mg)

4.54 Prednisone 60 mg/m^2/day p.o. x 14 d 0-13 cycle 3, 4, 5 only.

4.55 6-MP 75 mg/m^2/day p.o. x 12 weeks d 0-83 of each cycle.

4.56 Methotrexate 20 mg/m^2/wk p.o q week x 11 wk 1-11 (not wk 0 of 12 wk cycle).

4.57 A bone marrow aspirate, LP and testicular biopsy (for boys) should be performed on d 84 of cycle 8. In all, therapy lasts 124 weeks.

5.0 STATISTICAL CONSIDERATIONS

Participating institutions will enter eligible patients alternately on CCG-193P and CCG-192P in order to detect unexpected problems in toxicity and compliance. This is done in preparation for the upcoming study, CCG-106.

6.0 PATIENT ELIGIBILITY

6.1 Diagnosis

6.11 Previously untreated acute lymphocytic or undifferentiated leukemia (peroxidase and Sudan black negative). Patients with Burkitt's tumor cell leukemia are not eligible and should be treated on the current CCG Non-Hodgkin's Lymphoma Study.

6.2 Age and Initial White Count

6.21 Less than 21 years of age but greater than one year of age. Age at diagnosis will be defined as age at date registered on study.

6.22 An initial white blood cell count greater than or equal to 50,000/mm^3, at the CCSG institution where treatment will be initiated. WBC counts from referring institutions should be recorded but will not be utilized to determine eligibility for assignment to study CCG-192P or CCG-193P. (For patients with WBC < 50,000 mm^3 who have the "lymphoma syndrome" - as defined in CCG-192P/193P Eligibility memo dated 3/26/82 - the institution may elect to have the patient entered on this study according to the investigator's discretion.)

6.3 Informed Consent

6.31 Informed consent in accordance with institutional policies approved by the Department of Health, Education and Welfare.

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7.0 REQUIRED OBSERVATIONS - Complete and submit End Phase/Cycle Report Forms after completion of induction, consolidation and each maintenance cycle.

7.1 Prior to Study

7.11 History and physical exam with measurement of hepatomegaly, splenomegaly, lymphadenopathy, height, weight, head circumference, and documentation of infection.

7.12 CBC with differential and platelet count - if patient was diagnosed at an outside institution, these results will be recorded in addition to the first CBC and platelet count done at the CCSG institution. Note the location at which each determination was made as well as all therapy (especially transfusions).

7.13 Chest x-ray: PA and lateral - in doubtful cases tomography and/or CT may be useful to determine the presence of a mediastinal mass.

7.14 Serum chemistries: creatinine, BUN, uric acid, SGPT, or 5' Nucleotidase, alkaline phosphatase, LDH, calcium, PO4, fibrinogen, PT, PTT, amylase

7.15 Serum Immunoglobulins – IgG, IgM, IgA.

7.16 Lumbar puncture - record cell count, cytology using cytocentrifuge, protein and glucose.

7.17 Bone marrow aspirate for:

7.171 Wright's stain - to assess morphology L_1, L_2, L_3 using FAB classification.

7.172 Histochemical analysis: PAS, ASD esterase with and without NAF, Sudan Black (and/or peroxidase), acid phosphatase.

7.173 Terminal transerase (TdT, optional)

7.174 One Wright or Wright-Giemsa stained and one non-stained slide (or cover slip preparations only if slides are not routine procedure at the investigator's institution) of the initial pretreatment diagnostic bone marrow aspirate should be send at: 1) diagnosis and 2) marrow relapse to:

Denis R. Miller, M.D.
New York, Cornell Medical Center
and Memorial Sloan-Kettering Cancer Center
Department of Pediatrics
1275 York Avenue
New York, NY 10021

7.175 Recommended but optional: glucorticosteroid receptors, lympho-

cyte function (suppressor and helper), cytofluorometry for cell cycle and DNA/RNA. Growth characteristics in semi-solid media (CFU-C, BFU-E, CEU-3).

Cytogenetics with Giemsa banding.

7.18 Electrocardiogram; echocardiogram or radioisotope Mugga study.

7.19 Wrist/hand x-ray for bone age, assessment of pubertal status by Tanner staging. Abdomen sonogram, CT, and/or IVP if testes are enlarged at diagnosis.

7.2 During Induction

7.21 Physical exam daily x 10 with recording of changes in organ and node size daily until normal, then day 14, 21, 28 and as clinically indicated.

7.22 CBC and platelet count including differential leukocyte count daily for 10 days then day 14, 21, 28 and as clinically indicated.

7.23 Bone marrow aspirate: day 7 and 28. If day 7 marrow has >25% blasts, repeat on day 14.

7.24 Lumbar puncture recording cell count, cytology, glucose and protein day 14, day 28. Culture if patient is febrile.

7.25 Chemistries: uric acid, SGPT, LDH, alkaline phosphatase, BUN, creatinine, calcium, phosphate, electrolytes daily x 3 then weekly or as required; glucose, amylase, fibrinogen, PT, PTT weekly.

7.26 Repeat chest x-ray if indicated.

7.3 During Phase II, III, and IV

7.31 Physical examination, Phase II and IV weekly, Phase III 2-4 weeks.

7.32 CBC including WBC differential and platelet count with each physical examination.

7.33 Bone marrow aspiration - day 63, 84, 140 (on entry to Phase II, III, IV)

If M_1 or M_2 intensification will continue and marrow will be repeated on day 63. If the day 49 marrow is M_3 the patient is off study.

7.34 Lumbar puncture, recording pressure cell count, and cytology protein and sugar on day 35, 42, 49, 56, 140, 147. The CSF must be cultured if the patient is febrile.

7.35 Chemistries: uric acid, SGPT or 5' nucleotidase, alkaline phosphatase, fibrinogen, amylase, glucose, LDH, calcium, phosphate, PT, PTT and urine analysis prior to L'Asparaginase, after 6 doses and at conclusion of consolidation.

7.36 Port films of radiation fields (Phase II).

7.4 During Continuation Maintenance (Phase V)

7.41 Physical examination - each visit (q4 weeks)

7.42 CBC including WBC, differential and platelet count each visit (q4 weeks)

7.43 Bone marrow aspiration - every three months (day 0 of each 12 weeks cycle). In the event of an M_2 marrow, repeat examinations will be performed every 2-4 weeks until M_1 or M_3 (off study).

7.44 Lumbar puncture - recording pressure cell count, cytology protein and glucose at the time of installation of I.T. MTX during each maintenance cycle q12 wk).

7.45 Chemistries: uric acid, BUN, SGPT, alkaline phosphatase, at the beginning of each maintenance cycle (q12 wk).

7.5 After Chemotherapy

7.51 CBC and platelet count each visit.

7.52 Physical exam monthly x 12, then q3 months x 4, then q4 months with detailed measurement of liver, spleen, lymphadenopathy, kidney size and pubertal studies.

7.53 Bone marrow examination q3 months x 8, then q4 months x 3, then q6 months x 2, then on clinical indication.

7.54 Chemistries: BUN, uric acid, SGPT or 5' nucleotidase, alkaline phosphatase q3 months.

7.55 Lumbar puncture q3 months x 4, q6 months x 2 (i.e. 2 yrs), then on clinical indication.

8.0 MODIFICATION FOR TOXICITY

8.1 During induction, Phase I

8.11 See 4.1.

8.12 Vincristine dosage should be decreased to 1.0 mg/m^2 in presence of severe jaw pain, paresis or obstipation. If symptoms do not recur resume full dosage. Vincristine should be withheld in presence of ileus and resumed at 30% lower dose after recovery.

8.13 L'Asparaginase should not be withheld for an asymptomatic coagulopathy. L'Asparaginase should be discontinued in the presence of pancreatitis (as documented by amylase studies), or severe liver dysfunction.

L'Asparaginase should not be held for hyperglycemia Patients should be treated with insulin if necessary. Ketoacidosis merits discontinuation of drug in Reinduction only. . . . If a patient develops a systemic hypersensitivity reaction to E. Coli L'Asparaginase it will be discontinued and Erwina Carrocovora L'Asparaginase will be used instead at the same dose schedule.

8.14 Prednisone dosage should be reduced by 30% if patient develops hypertension or diabetes. Diabetes should be controlled with insulin.

8.15 I.T. MTX may be replaced by Ara-C 50 mg/m^2 in cases of impaired (creatinine > 2.0 mg/dl) renal function. Platelet transfusions may

be necessary prior to lumbar puncture.

8.2 During CNS/Intensification and Reinduction/Reintensification, Phase II and IV.

8.21 See 4.2, 4.4

8.22 See 8.13

8.23 The dosage of I.T. MTX will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, citrovorum factor 12 mg p.o. will be administered 24-36 hours after the I.T. MTX injection. This recommendation is based on the demonstrated efficacy of this approach and on the relative concentration of MTX and 5-methyl-THF in CSF after systemic citrovorum therapy and I.T. MTX. See 8.15.

8.3 During Interim Maintenance and Continuation Maintenance, Phase II and IV.

8.31 See Section 4.3, 4.5.

8.32 When therapy results in ANC $<1000/mm^3$ or platelet count $<100,000/mm^3$ 6-MP and MTX should be withheld until ANC $>1000/mm^3$ and platelets $>$ 100,000, then resumed at 75% of dosage.

9.0 MANAGEMENT OF CNS and EXTRAMEDULLARY LEUKEMIA

9.1 CNS Leukemia (22, 23, 24, 25)

9.11 Diagnosis of CNS leukemia

The presence of more than 5 WBC/mm^3 cerebrospinal fluid (CSF) and the confirmation that these cells are leukemic by examination of a cytocentrifuge are both required to make the diagnosis of meningeal leukemia. If the centrifuge is positive but the WBC $\leq 5/mm^3$, or if the WBC $>5/mm^3$ but the cytocentrifuge is negative, spinal taps should be repeated until both criteria are satisfied. Patients who develop hypothalmic syndrome or cranial nerve palsies and who do not have

other evidence of Prednisone or Vincristine toxicity without positive CSF cytology probably have early CNS leukemia and should be treated accordingly.

9.12 Treatment of CNS leukemia at diagnosis.

9.121 No modification of systemic induction therapy will be made if CNS disease is present at diagnosis.

9.122 IT MTX will be given qwk until the CSF WBC is less than $5/mm^3$. Following this, I.T. MTX will be given as per protocol (day 14, 28, 39,46,53 and 60). At the beginning of intensification therapy, these patients will receive 1200r spinal radiation (200r/day x 6) in addition to 1800r cranial RT. These patients will then receive I.T. MTX during maintenance as per protocol (q12 wk).

9.13 Treatment of CNS leukemia during BM remission

(On chemotherapy or in the observation phase)

9.131 I.T. MTX qwk until two consecutive CSF examinations are clear of blasts. This is to be followed by 2400r WB XRT and 1200r XRT to the spinal cord with two further doses of IT Methotrexate at one week intervals and maintenance IT MTX as per protocol (q12 wk).

9.132 Systemic reinduction therapy start back on day 0 of Induction regimen.

9.133 One month following completion of spinal radiation placement of an Ommaya reservoir may facilitate intraventricular chemotherapy.[26]

9.134 Chemotherapy will continue 36 months past reinitiation of maintenance.

9.2 Testicular leukemia.[27,28]

9.21 Diagnosis is made by open wedge biopsy. Symptomatic and occult diseases are treated similarly. Bilateral treatment should be delivered even when the biopsy on one side is negative, CAT to delineate the status of the retroperitoneal nodes is recommended. See appendix for surgical guidelines.

9.22 At diagnosis

9.221 Systemic therapy will not be altered.

9.222 Both testes will be irradiated as soon after the biopsy as possible: 2400r in 200r fractions. (Retroperitoneal disease should receive 2000r in 200r fractions (18.441).

9.23 Testicular disease during maintenance or off-therapy.

9.231 Testicular radiation as in 9.222.

9.232 Systemic reinduction as in 9.132. No additional cranial radiation will be given, but IT MTX be added.

9.233 Continue therapy for 36 months past day of reinitiation of maintenance.

9.3 Other extramedullary diseases

9.31 Biopsy proven extramedullary disease (bone, skin, soft tissue, anterior chamber of the eye) during BM and CNS remission will be treated by local radiation and systemic reinduction as in 9.232 and 9.233.

10.0 ELIGIBILITY FOR PROGRESSION TO SUBSEQUENT PHASES OF STUDY

10.1 Induction

10.11 Previously untreated patients with ALL/AUL under 21 years of age who meet the criteria under eligibility. Informed consent according to institutional policies.

10.2 CNS/Intensification

10.21 M_1 ($\leq$ 5% blasts) or M_2 (6 to 25% blasts) marrow on completion of Induction.

10.3 Interim Maintenance

10.31 M_1 or M_2 marrow on completion of CNS/Intensification.

10.32 CSF examination

10.33 ANC $\geq$ 1000/mm^3 and platelet count $\geq$ 100,000/mm^3.

10.4 Reinduction/Reintensification

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10.41 M_1 or M_2 bone marrow.

10.42 CSF examination

10.43 Bilateral testicular wedge biopsies.

10.5 Continuation maintenance

10.51 M_1 or M_2 marrow at the end of each 12 week cycles of maintenance with continuous complete remission.

10.52 CSF examination.

10.6 Observation

10.61 No evidence of leukemia in marrow, testes, etc.

11.0 OFF STUDY CRITERIA

11.1 M_3 ($\geq$ 25% blasts) marrow on day 28 of induction or anytime thereafter.

11.2 Death.

11.3 Lost to follow-up.

12.0 EXPERIMENTAL DESIGN - See schema 12.1, 12.2, 12.3, 12.4 and 12.5.

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PREVIOUSLY UNTREATED ACUTE LYMPHOBLASTIC LEUKEMIA WITH POOR PROGNOSTIC FEATURES (REVISED 02/09/82)

PHASE I INDUCTION (5 WEEKS)

DAYS ON PHASE	0	7	14	21	28	35
VINCRISTINE 1.5MG/SQ M - MAX 2.0MG	V	V	V	V		
DAUNOMYCIN 25MG/SQ M	D	D	D	D		
L-ASPARAGINASE 6000U/SQ M - START D3	L L L	L L L	L L L			
PREDNISONE 60MG/SQ M [illegible], TAPER OVER 14 DAYS	[illegible]					
ARA-C IT DOSE 20,30,50,70MG FOR AGE <1,<2,<3, AND >3	A					
METHOTREXATE IT DOSE 6,8,10,12MG FOR AGE <1,<2,<3, AND >3			M		M	
BONE MARROW	B	B	?B?		B	

E II CNS/INTENSIFICATION (5 WEEKS)

PHASE	0	7	14	21	28	35
CYCLOPHOSPHAMIDE 1.0GM/SQ M	C		C			
6-MERCAPTOPURINE 60MG/SQ M	6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6					
ARA-C 75MG/SQ M	A A A A	A A A A	A A A A	A A A A		
WHOLE BRAIN IRT 180 RADS/FX X 10 FX	X X X X X	X X X X X				
METHOTREXATE IT DOSE 6,8,10,12MG FOR AGE <1,<2,<3 AND >3	M	M	M	M		
BONE MARROW						B

PHASE III INTERIM MAINTENANCE (8 WEEKS)

DAYS ON PHASE	0	14	28	42	56
6-MERCAPTOPURINE 60MG/SQ M	6666666666666666666666666666666666666666				
METHOTREXATE PO 15MG/SQ M	M M M M M M				
BONE MARROW					B
DIAGNOSTIC LP					L
TESTICULAR BIOPSY					T

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PREVIOUSLY UNTREATED ACUTE LYMPHOBLASTIC LEUKEMIA WITH POOR PROGNOSTIC FEATURES (REVISED 10/19/81)

PHASE IV REINDUCTION/REINTENSIFICATION (8 WEEKS)

WEEK ON PHASE	0	1	2	3	4	5	6	7	8
VINCRISTINE	V	V	V	V					
1.5MG/SQ M - MAX 2.0MG									
ADRIAMYCIN	A	A	A	A					
25MG/SQ M									
L-ASPARAGINASE	LLL	LLL	LLL						
6000U/SQ M - START D3									
DEXAMETHASONE	[illegible]								
10MG/SQ M X 28, TAPER OVER 9 DAYS									
CYCLOPHOSPHAMIDE						C			
1.0GM/SQ M									
ARA-C						AAAA	AAAA		
75MG/SQ M									
6-THIOGUANINE						6666666666666			
60MG/SQ M									
METHOTREXATE IT						M	M		
DOSE 6,8,10,12MG FOR AGE <1,<2,<3, AND >3									
MARROW	B								

PHASE V CONTINUATION MAINTAINANCE (8*12 WEEK CYCLES)

WEEK OF CYCLE	0	1	2	3	4	5	6	7	8	9	10	11	12/0
VINCRISTINE	V	V		CYCLES 3, 4, AND 5 ONLY!									
1.5MG/SQ M - MAX 2.0MG													
PREDNISONE	[illegible]			CYCLES 3, 4, AND 5 ONLY!									
60MG/SQ M X14 DAYS													
METHOTREXATE IT	M												
DOSE 6,8,10,12MG FOR AGE <1,<2,<3, AND >3													
METHOTREXATE PO		M	M	M	M	M	M	M	M	M	M	M	
20MG/SQ M													
6-MERCAPTOPURINE	666666666666666666666666666666666666666666666666666666666666666666666666666666666666												
75MG/SQ M													
BONE MARROW	B												

A BONE MARROW ASPIRATE, LUMBAR PUNCTURE AND TESTICULAR BIOPSY WILL BE OBTAINED UPON COMPLETION OF THE FINAL CYCLE

15.0 STUDY COMMITTEE

Member	Responsibility
Paul S. Gaynon, M.D.	Study Chairman Division of Hematology/Oncology Children's Memorial Hospital Chicago, IL 60614 (312) 880-4587
W. Archie Bleyer, M.D.	Study Co-Chairman Division of Oncology Childrens Orthopedic Hospital P.O. Box C-5371 Seattle, WA 98105 (206) 634-5427
Peter Steinherz, M.D.	Study Co-Chairman Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021 (212) 794-7951
Jerry Finklestein, M.D.	Chemotherapy
Gregory Reaman, M.D.	Chemotherapy
Philip Littman, M.D.	Radiation Therapy
Denis Miller, M.D.	Morphology
Harland Sather, Ph.D.	Statistician
Denman Hammond, M.D.	Group Chairman

18.0

APPENDIX

RADIATION THERAPY GUIDELINES

18.1 Introduction

In the present section, the guidelines for administration of radiotherapy to children with ALL enrolled in studies 106 are detailed.

18.11 CCG-106

All patients on these studies will receive 1800 rad tumor dose calculated at the mid plane to the entire cranial meninges in conjunction with I.T. MTX during the intensification phase of therapy. If CNS leukemia is present at diagnosis, see Section 18.13.

18.111 Infants under one year of age will have their cranial radiotherapy delayed until they have reached their first birthday, at which time they will receive the 1800 rads in 10 doses without interruption of their systemic chemotherapy.

18.12 Persistent Masses

Patients who have masses 3 cm or greater at diagnosis will receive 2000 rad tumor dose to the involved area during the induction phase of therapy in 200 rad fractions. Multiple fields in sequence may be used if large volume needs to be mediated.

18.13 CNS Leukemia at Diagnosis

All patients who present with CNS leukemia at diagnosis will have their induction-intensification therapy modified as detailed in Section 9.12. I.T. MTX will be given q 3-4 days during induction therapy till CSF clears. On day 28 if the bone marrow is M_1 or M_2, 1800 rad tumor dose will be given to the cranial meninges and 1200 rad tumor dose will be given to the spinal axis during the intensification phase. These patients will all receive I.T. MTX every 84 days at the beginning of each of the maintenance cycles. Maintenance therapy will otherwise be randomized.

18.14 CNS Leukemia During Marrow Remission

All patients who develop CNS leukemia during the maintenance phase of the study will be treated as outlined in Section 9.13. These patients will be treated with 2400 rads whole brain and 1200 rads spinal radiation, weekly I.T. methotrexate for six weeks and will receive Reinduction 2, as detailed in Section 9.132.

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18.15 Other Extramedullary Relapse During Marrow Remission

Details of treatment for extramedullary relapse outside the CNS during marrow remission are given in Section 9.23 and 9.3. The sites of extramedullary relapse will be given 2000 rad tumor dose except the kidney which will receive 1200 rad tumor dose.

18.16 The radiation therapy check list is to be submitted to the Operations Office at the conclusion of each course of radiation therapy.

18.2 Definitions

18.21 Cranial - lateral treatment portals include the entire cranial meninges to the level of C2.

18.22 Cranio-spinal axis - cranial irradiation as in 18.21 plus irradiation portals which encompass the entire spinal axis to include the sacral roots down to the tip of the coccyx.

18.23 Bulky disease - lymph node or soft tissue mass $\geq$3cm in greatest diameter, mediastinal mass (any size).

18.24 Extramedullary relapse as first event - recurrence of disease during ne marrow remission in organs or soft tissue, i.e., CNS, testes, kidney, kin, bone, etc.

18.3 Procedure

Radiation treatment is to be given with supervoltage only, i.e., Co-60, four and six MeV Linacs or higher photon energies. Photon energies above 10 MeV are not recommended. Tumor dose are midplane doses for brain, kidney and masses. The tumor dose to the cervical and thoracic spinal cord will be calculated at four centimeters depth and the tumor dose to the lumbar and sacral region will be calculated at five centimeters. Treatments will be given five days a week at 180 rad per day for CNS prophylaxis and 200 rad tumor dose per day for overt CNS leukemia. Opposed, parallel equally weighted portals will be used for the treatment with other techniques as indicated. Treatment to the spinal axis, testes and skin will be given through single unopposed ports.

All treatment portals should be treated at each radiotherapy session for prophylaxtic CNS. Treatment will be given in 180 rad tumor dose per treatment, five days per week until 1800 rad tumor dose has been achieved. The time lapse should not exceed 15 calendar days. Patients receiving treatment for overt CNS leukemia will receive 200 rad fractions for a total of 1800 rads. Patients will begin treatment at day 28 unless the absolute granulocyte count is less than 500 cells/mm^3, platelet count is less than 50,000/mm^3 or there is evidence of sepsis. When treatment is delayed because of a low granulocyte count or low platelet count, radiotherapy should start as soon as the granulocyte count is recovering and has exceeded 1000 cells/mm^3 or the platelet count is recovering and has exceeded 75,000/mm^3. Patients who have had their radiotherapy delayed because of sepsis or suspected sepsis may start treatment as soon as they have

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18.15 Other Extramedullary Relapse During Marrow Remission

Details of treatment for extramedullary relapse outside the CNS during marrow remission are given in Section 9.23 and 9.3. The sites of extramedullary relapse will be given 2000 r tumor dose except the kidney which will receive 1200 r tumor dose.

18.16 The Radiation Therapy Reporting Forms (postcard, RT-1, RT-2) are to be submitted to the QARC in Rhode Island.

18.2 Definitions

18.21 Cranial - lateral treatment portals include the entire cranial meninges to the level of C2.

18.22 Cranio-spinal axis - cranial irradiation as in 18.21 plus irradiation portals which encompass the entire spinal axis to include the sacral roots down to the tip of the coccyx.

18.23 Bulky disease - lymph node or soft tissue mass $\geq$ 3 cm in greatest diameter, mediastinal mass (any size).

18.24 Extramedullary relapse as first relapse - recurrence of disease during bone marrow remission in organs or soft tissue, i.e., CNS, testes, kidney, skin, bone, etc.

18.3 Procedure

Radiation treatment is to be given with supervoltage only, i.e., Co-60, four and six MeV Linacs or higher photon energies. Photon energies above 10 MeV are not recommended. Tumor dose are midplane doses for brain, kidney and masses. The tumor dose to the cervical and thoracic spinal cord will be calculated at four centimeters depth and the tumor dose to the lumbar and acral region will be calculated at five centimeters. Treatments will be given five days a week at 180 r per day for CNS prophylaxis and 200 r tumor dose per day for overt CNS leukemia. Opposed, parallel equally weighted portals will be used for the treatment with other techniques as indicated. Treatment to the spinal axis, testes and skin will be given through single unopposed ports.

All treatment portals should be treated at each radiotherapy session for prophylactic CNS. Treatment will be given in 180 r tumor dose per treatment, five days per week until 1800 r tumor dose has been achieved. The time lapse should not exceed 15 calendar days. Patients receiving treatment for overt CNS leukemia will receive 200 r fractions for a total of 1800 r. Patients will begin treatment at day 28 unless the absolute granulocyte count is less than 500 cells/mm^3, platelet count is less than 50,000/mm^3, or there is evidence of sepsis. When treatment is delayed because of a low granulocyte count or low platelet count, radiotherapy should start as soon as the granulocyte count is recovering and has exceeded 1000 cells/mm^3 or the platelet count is recovering and has exceeded 75,000/mm^3. Patients who have had their radiotherapy delayed because of sepsis or suspected sepsis may start treatment as soon as they have

been afebrile for 72 hours and/or asymptomatic. Patients who develop sepsis during radiotherapy should have the radiotherapy stopped. Radiotherapy should be interrupted if the absolute neutrophil count falls below 500/mm^3 or if the platelet count falls below 50,000/mm^3.

18.4 Technique

18.41 Cranial - Use lateral opposed portals for the treatment to the brain. These portals should extend from the anterior, superior and posterior "fall-off" down to the level of C_2. The entire sub-arachnoid space and optic nerve should be included in the portals. The eyes are blocked; however, the block should not extend posterior to the lateral canthus or superior into the anterior fossa (see Figure 1 or Figure 2).

18.42 Cranio-spinal Axis - Patients who receive craniospinal radiotherapy for overt CNS leukemia will have the head treated as in cranial technique above. The spinal axis should be treated with only posterior portals. The width of the spinal field should be four to five centimeters in the cervical and thoracic cord area and not less than five centimeters in the lumbar area. The sacral area should be expanded at the lower margin of L_4 to six or eight centimeters so that the sacral roots are encompassed. The inferior margin of the portal should be extended down to the coccyx (see Figure 3). The divergent edge of the spinal portal should parallel the divergent edge of the inferior margin of the cranial portal. Appropriate portal separation between the cranial and spinal portals should be used. Portal junctions should be shifted at least once during therapy. This separation will be determined by the appropriate physics of each individual machine. Should it be necessary to divide the spinal cord into two or more fields on appropriate field separation should be used and margin shifted once during treatment.

If the cranial spinal irradiation is to be given after previous cranial irradiation, the junction between fields should be at C_{3-4}.

18.43 Bulky Disease - Patients, who present an diagnosis, with bulky disease as defined in 18.23 will be given 2000 rad tumor dose in ten treatments of 200 rad each to the involved areas. This treatment should be given during induction. The mass should be given a two to three centimeter margin. Electron beam or appropriate superficial x-ray may be used for superficial masses. The tumor dose will be calculated at the estimated depth of the tumor.

18.44 Extramedullary Relapse other than CNS - Extramedullary relapse other than CNS should be treated concurrently with reinduction.

18.441 Testes - Both testes will be treated to a dose of 2000 rad tumor dose in 10 treatments of 200 rad each. However, if either testes measures greater than five centimeters in diameter, the dose will be 3000 rad tumor dose in 15 treatments of 200 rad each. Both testes will be included in the single anterior field which should exclude the penis. The dose should be delivered to the exit surface of the mass. If a megavoltage source is employed, a 0.5 cm bolus is recommended.

18.442 Kidneys - Kidneys will be treated with parallel opposed portals to 1200 rad tumor dose midplane in six treatments of 200 rad each. The midline structures should be blocked if not involved.

FIGURE I: CRANIAL PO: L (INFERIOR BORDER PARALL TO REID'S BASELINE)

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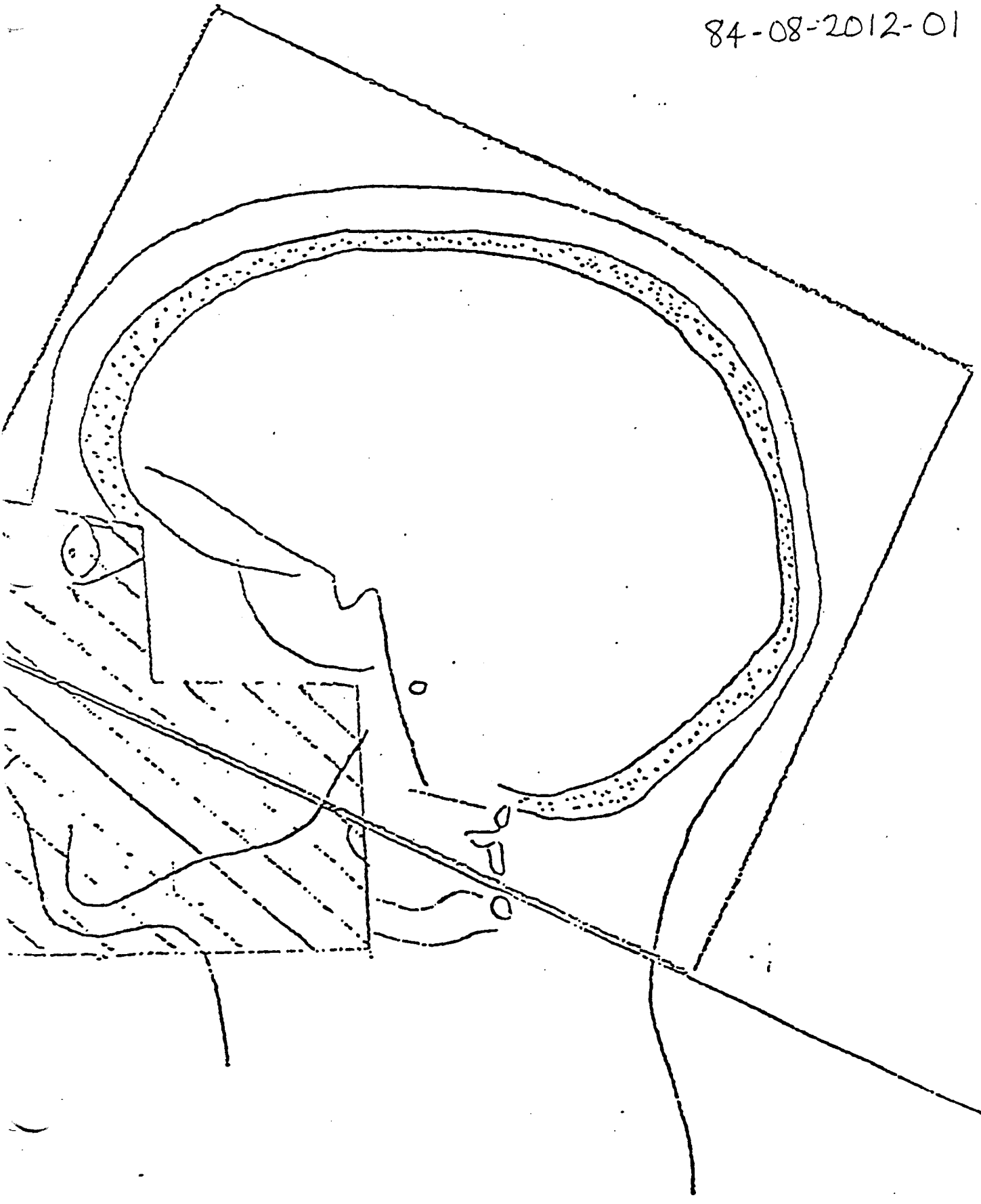

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FIGURE II: CRANIAL PORTAL (INTERIOR BORDER PERPENDICULAR TO LONG AXIS OF THE BODY)

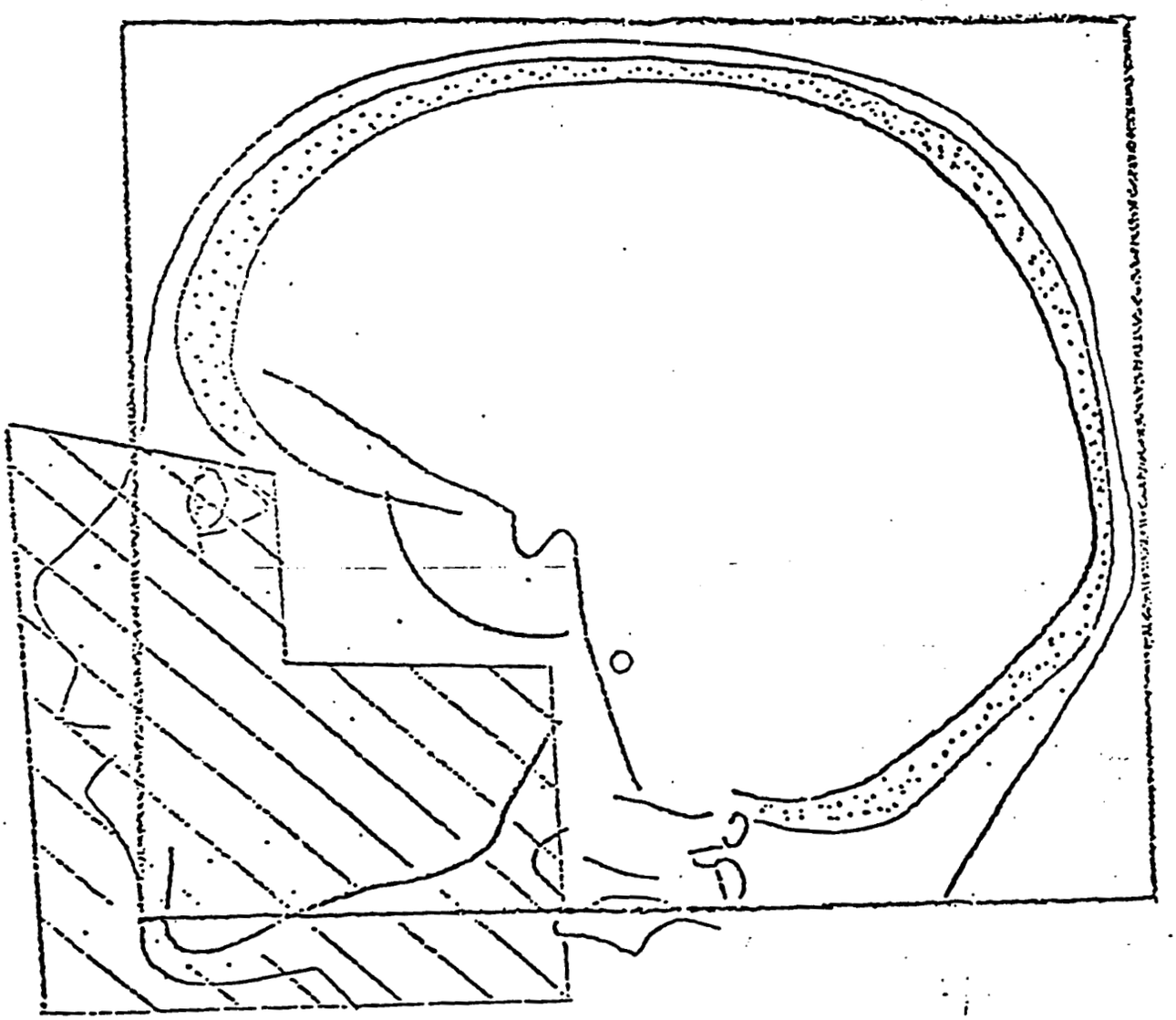

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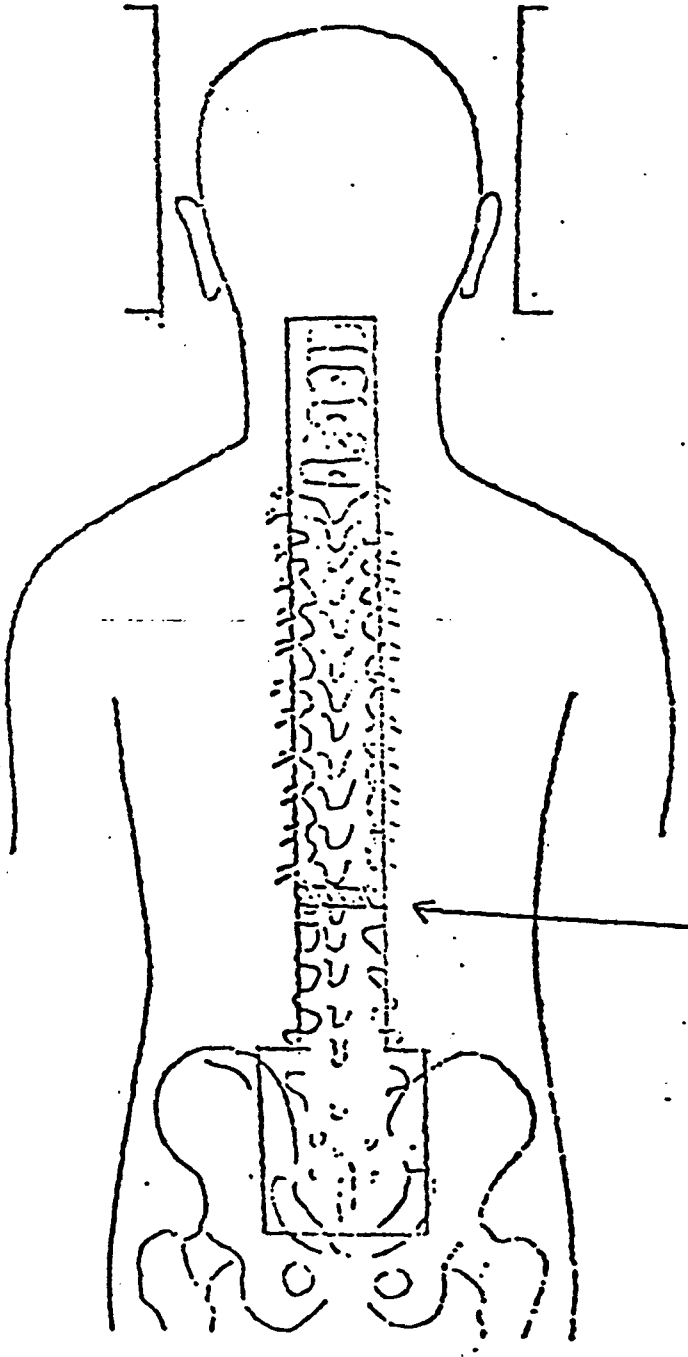
FIGURE III: SPINAL PORTALS



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18.443 Bone lesions - Bone lesions will receive 2000 rad tumor dose in 10 treatments of 200 rad each. A margin of normal bone should not exceed two to three centimeters. Bone lesions should be treated parallel opposed with the tumor dose delivered to midplane. The growth plate should be excluded from the field portal if possible.

18.444 Skin lesions - Skin lesions will receive 2400 rad tumor dose in 12 treatments of 200 rad each. A margin of two centimeters of normal skin should be treated. Electron beam or appropriate superficial x-ray may be used. The dose delivered should be calculated at the estimated depth, or thickness of the lesion.