The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-cell Acute Lymphoblastic Leukemia or Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma: A Report of the Children's Oncology Group Randomized Trial POG 9404

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Disciplines: Radiation Therapy, Pathology
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T-CELL #4 PROTOCOL
Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma

A Pediatric Oncology Group Phase III Study

PARTICIPANTS: All Pediatric Oncology Group Institutions

under refrigeration. The reconstituted dexrazoxane solution may be diluted with either 0.9% Sodium Chloride Injection, USP, or 5.0% Dextrose Injection, USP, to a concentration range of 1.3 to 5.0 mg/mL in intravenous infusion bags. The resultant solution is also stable for 6 hours.

3.115 **Supplier:** Dexrazoxane and its dilutent will be supplied by the NCI. Pharmacia Inc. (Columbus, Ohio) will provide the NCI with vials of dexrazoxane (500 mg) and dilutent (Sodium Lactate Injection M/6, 50 ml) from its commercial supply, for subsequent distribution. As soon as IRB approval is obtained, it is advisable to obtain a two day supply of drug to keep on hand at all times.

4.0 PATIENT ELIGIBILITY

4.1 T-Cell ALL

4.11 Age < 22.0 years and infants > 12 months.

4.12 Prior registration on the current ALL classification study (#9900 as of January 15, 2000) within 6 days (8 if the 6th day falls on a weekend or holiday). NOTE: The requirement for registration on a classification study is waived between November 15, 1999 and January 15, 2000.

4.121 In addition to the samples required for all patients registered on the POG Classification Study, those with T-ALL are required to submit samples for the following additional studies (failure to submit these samples results in the patient becoming ineligible for the POG 9404 treatment protocol, though still eligible for POG #9900):

4.1211 ~~PCR for detection of MRD in T-ALL with TAL-1(Southwestern) – (See POG #9400)~~ - Effective 11/25/98, no TAL samples for new patients should be sent to Dr. Bash. Samples should continue to be submitted for patients registered prior to 11/25/98.

4.1212 Drug Sensitivity profiles in T-ALL (Wayne State, MUSC)- (See POG #9900)

4.1213 Role of p53, p15, and p16 tumor suppressor genes in T-ALL (UCSD) - (See POG #9900)

4.122 Studies encouraged but not required for patient with T-ALL are:

~~**4.1221** Proliferation assays in lymphoblasts in T-ALL (Duke) – (See POG #9400)~~

4.13 DR-, T+: No prior therapy except for steroids or emergency XRT to the chest in patients with severe respiratory distress due to mediastinal disease.

Note: DR-, T- or DR+, T+ may be eligible if T-ALL is confirmed at the Johns Hopkins Reference Laboratory.

4.14 Previously untreated with the following exception:

4.141 Steroid treatment in the 48 hours prior to study entry will be allowed provided that a physical examination and CBC with differential were performed **immediately** prior to the beginning of steroids and results of both are known. For T-ALL patients, prior steroid use is governed by POG 9900.

4.142 Patients on chronic steroid treatment for another disease are NOT eligible for a POG New ALL protocol.

4.143 Emergency XRT to mediastinum in patients with severe respiratory distress due to mediastinal disease

4.15 Written informed consent according to institutional guidelines.

4.2 Lymphoblastic Lymphoma

4.21 Age < 22.0 years (infants < 12 months of age are eligible).

4.22 Biopsy-proven diffuse lymphoblastic lymphoma

4.221 Murphy Stage III or IV. (See Appendix VII.)

4.222 No prior therapy other than:

1) Emergency XRT to mediastinum in patients with severe respiratory distress due to mediastinal disease

2) Steroid treatment in the 48 hours prior to study entry will be allowed provided that a physical examination, CXR and CBC with differential were performed **immediately** prior to the beginning of steroids and results are known.

4.23 Pathology samples as per section 5.2.

4.24 Written informed consent according to institutional guidelines.

Year 1 **Required studies:** History, physical exam (incl. height, weight, and BP), CBC/diff/plts q month x 6 months then q 2 months x 6 months, BMA only if CBC is abnormal, LP/cytospin only if PE abnormal, functional status q 6 months. ***ECHO should be done at 3 years into the study.***

Elective studies: Protein, albumin, Ca, PO_4, lytes, Cr, Alk phos, LDH, AST, T. Bili, thyroid function studies, ALT q 2 months. If ALT is >2 x nl 6 months after completing therapy, obtain AST, bili, GGT, CMV, EBV titers, and hepatitis A, B, and C antibody panels.

Year 2 History, physical exam (incl. height, weight, BP), CBC/diff/plts q 3 months.

Year 3 History, physical exam (incl. height, weight, BP), CBC/diff/plts q 4 months.

Year 4 History, physical exam (incl. height, weight, BP), CBC/diff/plts q 6 months. ***ECHO should be done 6 years into the study.***

Year 5 History, physical exam (inc. height, weight, BP), CBC/diff plts. Obtain any other studies that remain abnormal and repeat until they are normal.

6.0 TREATMENT PLAN AND MODIFICATIONS

6.1 Supportive Care Guidelines

Given the aggressive and highly immunosuppressive nature of this therapy, meticulous and intensive care is required in the management of patients entering this study. All patients should be well hydrated and alkalinized prior to initiation of therapy. Allopurinol must be given to prevent uric acid nephrotoxicity.

1. **Venous Access:** Placement of a percutaneous central venous catheter for administration of chemotherapy, nutrients, antibiotics, and blood products is strongly advised.

2. **Hydration and Alkalization:** The patient should be well hydrated, alkalinized and placed on allopurinol before initiation of therapy as follows:

   - ***Allopurinol***, 300 mg/m^2 orally, divided q 8 hrs
   - ***Hydration***, 2400-3000 ml/m^2/day IV, avoid potassium- containing solution
   - ***$NaHCO_3$***, 20-40 mEq/L of fluid to maintain urine pH $\geq$ 6.5

3. **Pneumocystis carinii prophylaxis**: At the end of induction week 4 of therapy TMP/SMZ (trimethoprim 150 mg/m^2/day and sulfamethoxazole 750 mg/m^2/day in 2 equally divided doses) should be given at 12-hour intervals on 3 sequential days per week. If the patient cannot tolerate TMP/SMZ due to hypersensitivity, consideration may also be given to the use of aerosolized pentamidine at a dose of 200mg/m^2 monthly or dapsone. (For children < 5 years old, IV pentamidine should

be used at a dose of 4 mg/kg monthly.) Continue until ≥ 6 months after completion of therapy.

4. **Nutrition:** The combination of chemotherapy-induced vomiting, infection and hemorrhage may result in significant weight loss. Progressive weight loss should be treated aggressively with supplemental enteral or parenteral nutrition.

5. **Infection:** Given the highly myelosuppressive nature of this therapy, infection may be a significant complication. Suspected infection should be treated aggressively following appropriate cultures, especially when patients are neutropenic. If defervescence does not occur within 4-6 days with a course of broad spectrum parenteral antibiotics, amphotericin B should be initiated.

6. **Transfusion Support:** Bleeding due to thrombocytopenia should be treated promptly with 5-6 U/m² of platelet concentrates. Packed red blood cell transfusions should be used to correct hypovolemia from blood loss or pre-existing anemia (Hgb <8.0 g/dl during induction).

7. **Mucositis:** Patients with severe mucositis (grades 3 or 4) who are unable to tolerate significant oral intake should be admitted to the hospital, placed NPO and started on hyperalimentation. Cimetidine 20-40 mg/kg/day or ranitidine 30 mg/m²/day may be given every 6 hours intravenously. Consideration should be given to use of antiherpetic or antifungal therapy as indicated. Please document mucositis very carefully as per Appendix II.

8. **Gammaglobulin Administration:** Quantitative immunoglobulins will be measured at diagnosis. IV IgG 400 mg/kg may be given to patients found to be IgG deficient at the investigator's discretion but should be noted clearly on the flow sheets. During therapy if patient becomes symptomatic with frequent infection, chronic diarrhea, repeated otitis, or pneumonia, quantitative immunoglobulins should be measured.

9. **Maximum Dosage Recommendations:**

Doxorubicin	60 mg/dose
Induction Methotrexate	80 mg/dose
Maintenance Methotrexate	80 mg/dose
High Dose Methotrexate	10 gms/24 hr infusion
Mercaptopurine	100 mg/day
Prednisone	80 mg/day (Induction)
	240 mg/day (Intensification)
Dexrazoxane	600 mg/dose

*Please note that the above recommendations all assume a maximum BSA of 2.0 m^2. Please use ideal body weight to calculate BSA. Regardless, if calculated BSA is > 2.0 m^2, it is strongly recommended not to give more than the above doses. This does not effect Vincristine (maximum dose = 2.0 mg) or intrathecal drug doses.

10. **G-CSF and Granulyte Transfusions:** Shall be considered individually for patients with granulocytopenia and severe infection after discussion with the study coordinator.

6.11 Patients also entering Sanofi Research Protocol No.: LTS 3257, an open label, multi-center compassionate use study of SR 29142 as a uriocolytic therapy for the prophylaxis and treatment of hyperuricemia in patients with leukemias or lymphomas will receive SR 29142, not allopurinol, and will follow the supportive care guidelines for hydratrion and alkalinization of that protocol. Patients with or at risk of acute hyperuricemia are eligible for SR 29142 therapy on the Sanofi Research Study LTS 3257 in lieu of allopurinol. POG institutions participating in the Sanofi Research Study of SR 29142 have been identified by the POG Operations Office and approved by Sanofi Research.

6.2 Outline of Therapy

6.21 Treatment 1 (*Closed to accrual as of 9/27/2000*)

6.211 **Induction (Weeks 1 - 6 from diagnosis)**
Vincristine 1.5 mg/m^2 IVP days 1, 8, 15 (max 2.0 mg)
Vincristine 2 mg/m^2 IVP day 22 (max 2.0 mg)
Prednisone 40 mg/m^2/day (in 3 divided doses) PO x 21 (days 1-21)
Doxorubicin 30 mg/m^2 IVP days 1, 2, 22
Methotrexate 40 mg/m^2 IVP day 2 *(Give at least 8 hrs. after DOX dose)*
6-MP 50 mg/m^2/day PO x 14 days: Weeks 4 & 5 (days 22-35)

IT Ara-C-Weeks 1, 2*, 3 Dose by age - See section 6.522

IT MTX/Ara-C Week 4 Dose by age – See section 6.524

Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)

6.212 **Consolidation Weeks 7 - 33**
Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2/day (in 3 divided doses)PO x 5 days q 3 weeks
Doxorubicin 30 mg/m^2 IVP q 3 weeks (to total dose of 360 mg/m^2)
6-MP 50 mg/m^2/day PO x 14 days q 3 weeks
L-Asp 25,000 IU/m^2 IM q week x 20 doses (Weeks 7-26)

IT MTX/Ara-C weeks 7, 10, 16*, 22 Dose by age - see section 6.524

* ***Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)***

XRT 1800 cGy to cranium - Begin week 22 (see Appendix IV)

6.213 **Continuation Weeks 34 - 108 (Until 24 months CCR)**

Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2/day (in 3 divided doses)PO x 5 days q 3 weeks

Methotrexate 30 mg/m^2 weekly IVP or IM ***Omit wks 40, 58, 76, 94 when IT MTX/Ara-C is given. If blood count stable with nadir ANC > 1,000 escalate MTX dose to 40 mg/m^2 (maximum 80 mg/dose).***
6-MP 50 mg/m^2/day PO x 14 days q 3 weeks
IT MTX/Ara-C weeks 40, 58, 76, 94. See section 6.524 for doses.

6.22 Treatment 2 (*Closed to accrual as of 9/27/2000*)

6.221 Induction (Weeks 1 - 6 from diagnosis)

Vincristine 1.5 mg/m^2 IVP days 1, 8, 15 (max 2.0 mg)
Vincristine 2 mg/m^2 IVP day 22 (max 2.0 mg)
Prednisone 40 mg/m^2/day (in 3 divided doses) PO x 21 (day 1-21)
Doxorubicin 30 mg/m^2 IVP days 1, 2, 22
Methotrexate 40 mg/m^2 IVP day 2 *(Give at least 8 hrs. after DOX dose)*
6-MP 50 mg/m^2/day PO x 14 days: Week 4 & 5 (days 22-35)
Zinecard (DZR) 300 mg/m^2 IVP **pre-DOX (days 1, 2, 22)**

IT Ara-C-Weeks 1, 2*, 3 Dose by age - See section 6.522

IT MTX/Ara-C Week 4 Dose by age – See section 6.524

Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)

6.222 Consolidation Weeks 7 - 33

Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2 /day (in 3 divided doses)PO x 5 days q 3 weeks
Doxorubicin 30 mg/m^2 IVP q 3 weeks (to total dose of 360 mg/m^2)
6-MP 50 mg/m^2/day PO x 14 days q 3 weeks
L-Asp 25,000 IU/m^2 IM q week x 20 doses (Weeks 7-26)
Zinecard (DZR) 300 mg/m^2 IVP **pre-DOX**

IT MTX/Ara-C weeks 7, 10, 16*, 22 Dose by age - see section 6.524

* ***Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)***

XRT 1800 cGy to cranium - Begin week 22 (see Appendix IV)

6.223 Continuation Weeks 34 - 108 (Until 24 months CCR)

Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2/day (in 3 divided doses) PO x 5 days q 3 weeks
Methotrexate 30 mg/m^2 weekly IVP or IM ***Omit wks 40, 58, 76, 94 when IT MTX/ARA-C is given. If blood count stable with nadir ANC > 1,000 escalate MTX dose to 40 mg/m^2 (maximum 80 mg/dose).***
6-MP 50 mg/m^2/day PO x 14 days q 3 weeks

IT MTX/Ara-C weeks 40, 58, 76, 94. See section 6.524 for doses.

6.23 Treatment 3

6.231 Induction (Weeks 1 - 6 from diagnosis)

Vincristine 1.5 mg/m^2 IVP days 1, 8, 15 (max 2.0 mg)
Vincristine 2 mg/m^2 IVP day 22 (max 2.0 mg)
Prednisone 40 mg/m^2/day (in 3 divided doses) PO x 21 (day 1-21)
Doxorubicin 30 mg/m^2 IVP days 1, 2, 22
Methotrexate 40 mg/m^2 IVP day 2 *(Give at least 8 hrs. after DOX dose)*
6-MP 50 mg/m^2/day PO x 14 days: Week 4 & 5 (days 22-35)
HD MTX 5 gm/m^2 IV week 4 (See section 6.39 for administration)
LCV Starting 36 hours from the beginning of HD MTX: 75 mg/m^2 IV followed by 6 doses 15 mg/m^2 IV or PO q 6 hours. (See Section 6.39)

IT Ara-C-Weeks 1, 2*, 3 Dose by age - See section 6.522

IT MTX/Ara-C Week 4 Dose by age – See section 6.524

Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)

6.232 Consolidation Weeks 7 - 33

Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2/day (in 3 divided doses)PO x 5 days q 3 weeks
Doxorubicin 30 mg/m^2 IVPq 3 weeks (to total dose of 360 mg/m^2)
6-MP 50 mg/m^2/day PO x 14 days q 3 weeks
L-Asp 25,000 IU/m^2 IM q week x 20 doses (Weeks 7-26)
HD MTX 5 gm/m^2 IV wks 7, 10, 13 (see section 6.39 for administration)
LCV Start 36 hours from the beginning of HD MTX: 75:mg/m^2 IV followed by 6 doses 15 mg/m^2 IV or PO q 6 hours. (See Section 6.39)

IT MTX/Ara-C weeks 7, 10, 16*, 22 Dose by age - see section 6.524

* ***Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)***

XRT 1800 cGy to cranium - Begin week 22 (see Appendix IV)

6.233 Continuation Weeks 34 - 108 (Until 24 months CCR)

Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2/day (in 3 divided doses)PO x 5 days q 3 weeks
Methotrexate 30 mg/m^2 weekly IVP or IM ***Omit wks 40, 58, 76, 94 when IT MTX/Ara-C is given. If blood count stable with nadir ANC > 1,000 escalate MTX dose to 40 mg/m^2 (maximum 80 mg/dose).***

6-MP 50 mg/m^2/day PO x 14 days q 3 weeks

IT MTX/Ara-C weeks 40, 58, 76, 94. See section 6.524 for doses.

6.24 Treatment 4

6.241 Induction (Weeks 1 - 6 from diagnosis)

Vincristine 1.5 mg/m^2 IVP days 1, 8, 15 (max 2.0 mg)
Vincristine 2 mg/m^2 IVP day 22 (max 2.0 mg)
Prednisone 40 mg/m^2/day (in 3 divided doses) PO x 21 (day 1-21)
Doxorubicin 30 mg/m^2 IVP days 1, 2, 22
Methotrexate 40 mg/m^2 IVP day 2 *(Give at least 8 hrs. after DOX dose)*
6-MP 50 mg/m^2/day PO x 14 days. Weeks 4 & 5 (days 22-35)
Zinecard (DZR) 300 mg/m^2 IVP **pre-DOX (days 1, 2, 22)**
HD MTX 5 gm/m^2 IV week 4 (See section 6.39 for administration)
LCV Start 36 hours from beginning of HD MTX: 75 mg/m^2 IV followed by 6 doses 15 mg/m^2 IV or PO q 6 hours. (See Section 6.39)

IT Ara-C-Weeks 1, 2*, 3 Dose by age - See section 6.522

IT MTX/Ara-C Week 4 Dose by age – See section 6.524

****Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)***

6.242 Consolidation Weeks 7 - 33

Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2/day (in 3 divided doses)PO x 5 days q 3 weeks
Doxorubicin 30 mg/m^2 IVPq 3 weeks (to total dose of 360 mg/m^2)
6-MP 50 mg/m^2/day PO x 14 days q 3 weeks
L-Asp 25,000 IU/m^2 IM q week x 20 doses (Weeks 7-26)
Zinecard (DZR) 300 mg/m^2 IVP **pre-DOX**
HD MTX 5 gm/m^2 IV wks 7, 10, 13 (See section 6.39 for administration)
LCV Start at hour 36 from the beginning of HD MTX: 75 mg/m^2 IV followed by 6 doses 15 mg/m^2 IV or PO q 6 hours. (See Section 6.39)

IT MTX/Ara-C weeks 7, 10, 16*, 22 Dose by age - see section 6.524

* ***Only for patients with CNS 2 or 3 disease. (See section 6.51 for POG definition of CNS disease)***

XRT 1800 cGy to cranium - Begin week 22 (see Appendix IV)

6.243 Continuation Weeks 34 - 108 (Until 24 months CCR)

Vincristine 2 mg/m^2 IVP q 3 weeks (max 2.0 mg)
Prednisone 120 mg/m^2/day (in 3 divided doses)PO x 5 days q 3 weeks
Methotrexate 30 mg/m^2 weekly IVP or IM ***Omit wks 40, 58, 76, 94 when IT MTX/Ara-C is given. If blood count stable with nadir ANC > 1,000 escalate MTX dose to 40 mg/m^2 (maximum 80 mg/dose).***
6-MP 50 mg/m^2/day PO x 14 days q 3 weeks
IT MTX/Ara-C 58, 76, 94. See section 6.524 for doses.

6.3 Drug Administration

6.31 **Vincristine** is administered by IV push (2 mg max).

6.32 **Prednisone** is given orally, divided into 3 doses per day (240 mg/day max).

6.33 **L-asparaginase**: 25,000 IU/m^2 IM for 20 doses in consolidation.

6.34 **Methotrexate:** During induction, MTX is given Day 2 for all treatment arms at a dose of 40 mg/m^2 (maximum 80 mg/dose). During maintenance, MTX is given to all patients at a dose of 30 mg/m^2. MTX can be given IM or for patients with an indwelling venous access by IV push.*

*If blood count stable with nadir ANC > 1,000 escalate MTX dose to 40 mg/m^2 (maximum 80 mg/dose).

Patients on treatment arms 3 and 4 receive HDMTX at weeks 4, 7, 10, and 13 according to guidelines in Section 6.39.

6.35 **Oral 6-mercaptopurine** (6-MP) 50 mg/m^2 is given as one dose per day, at bedtime. Do not give with milk. Give on an empty stomach (100 mg/day max).

6.36 **Leucovorin** is given IV at 75 mg/m^2 36 hours after the start of IV HDMTX. This is followed by 6 doses at 15 mg/m^2 IV or PO every 6 hours.

6.37 **Zinecard** (DZR) should be given by slow IV push or rapid IV infusion. After completing the infusion of Zinecard, and prior to a total elapsed time of 30 minutes (from beginning of the Zinecard infusion), the intravenous Doxorubicin should be given (Zinecard - 600 mg/dose max).

6.38 **Doxorubicin** should be diluted in normal saline and given IV push over 15 minutes through a central venous line or a fresh, freely-flowing peripheral venous line (60 mg/dose max).

6.39 **High Dose Methotrexate Infusion (HDMTX):**

HDMTX max dose 10 gm/24 hrs

****To be started at least 8 hours but not more than 24 hours following the dose of doxorubicin.**

****Hold Bactrim on the day of HDMTX infusion and for at least 72 hours after the start of the HDMTX infusion and until the MTX level is less than 0.1 uM.**

****Hold any nonsteroidal anti-inflammatory medications or aspirin-containing medications on the day of HDMTX infusion and for at least 72 hours after the start of the HDMTX infusion and until the MTX level is less than 0.1 uM.**

Prehydrate with D_5 0.25 NS + 60 mEq $NaHCO_3$/L at 125mL/m^2/hour for ≥ 6 hours and until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. HDMTX should be mixed in 2400 mL/m^2 of D_5 0.25 NS + 60 mEq $NaHCO_3$/L to run at 100 mL/m^2/hour. Adjust fluid volume and sodium bicarb to maintain urine sg and pH at above parameters. Additional fluids may be given piggyback if required to maintain the sg < 1.010. If urine pH drops below 7.0 give bicarb at 25 mEq/m^2 over 15 minutes. Continue hydration and alkalinization throughout HDMTX infusion, and until the MTX level is less than 0.18 uM at a minimum.

Hour 0: MTX 0.5 gm/m^2 IV over 30 minutes followed by MTX 4.5 gm/m^2 continuous IV infusion over 23.5 hours. Be certain that the HDMTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours is **not** encouraged but is acceptable.

Hour 24: **MTX level, BUN, creatinine** (immediately at end of infusion). Blood samples can be drawn from intravenous access devices. If MTX level ≥ 100 uM: increase hydration to 200 mL/m^2/hour, start leucovorin at 100 mg/m^2 every 3 hours, monitor MTX level, BUN, creatinine every 12 hours and call study coordinator.

Hour 36: **Leucovorin 75 mg/m^2** as a single IV dose should be given exactly 36 hours after the START of HDMTX infusion.

Hour 42, 48, 54, 60, 66, 72: **Leucovorin 15mg/m^2** IV or PO as tolerated x 6 doses and until MTX level < 0.1 uM. Discontinue leucovorin only when MTX level < 0.1 uM.

Hour 48: **MTX level, BUN, creatinine.** May discharge after hour 48 if MTX level ≤ 0.18 uM and patient able to hydrate orally and take remaining doses of leucovorin. If level > 0.18 but < 5 uM; increase hydration to 200 mL/m^2/hour with alkalinization, and continue leucovorin. If level > 5 uM; increase hydration fluids to 200 mL/m^2/hour, increase leucovorin to 15 mg/m^2 every 3 hours, and repeat MTX level, BUN, creatinine every 12 hours and call study coordinator.

Hour 72: **MTX level.** Discontinue leucovorin if MTX level < 0.1 uM. If level > 0.1 but < 0.18 uM then give leucovorin 15 mg/m^2 every 6 hours x 4 doses, until 96 hour level available and < 0.1 uM. If level > 0.18 but < 0.5 uM; continue increased hydration and leucovorin 15 mg/m^2 every 6 hours until level < 0.1 uM. If level > 0.5 uM, then continue increased hydration; give leucovorin 15 mg/m^2 every 3 hours, repeat MTX level, BUN, creatinine every 12 hours, and call the study coordinator.

6.391 Management of the patient with delayed MTX clearance:

As above increase hydration, alkalinization, and leucovorin based on MTX levels obtained at 24, 48, 72 hours from the START of HDMTX infusion.

For subsequent courses:

- DO NOT EXTEND leucovorin or modify subsequent courses if patient did not experience > Grade II mucositis or > 1 week delay in administration of chemotherapy. However, if patient again has delayed clearance, treat as in section 6.39.

- If patient experienced Grade II clinical toxicity and 48 hour MTX level was > 0.18 but <5 uM then increase hydration to a rate of 200 mL/m^2/hour prior to, during, and for at least 24 hours immediately following HDMTX for next course.

- If patient experienced Grade III or IV clinical toxicity and 48 hour MTX level was > 0.18 but < 5 uM then reduce dose of MTX by 25% of the original dose (i.e. 3.75 gm/m^2/dose; with 10% dose as bolus and 90% dose as infusion) for next course maintaining hydration at 200 mL/m^2/hour and following leucovorin rescue schedule as above. Reduce dose by another 25% (of the original dose) if patient still has delayed clearance and Grade III or IV toxicity. If patient has adequate clearance or ≤ Grade II toxicity escalate dose in 25% increments back to the original doses as able with subsequent courses.

6.392 Management of the patient with markedly delayed MTX clearance:

If 24 hour MTX level > 100 uM OR 48 hour level > 5 uM OR 72 hour level > 0.5 uM increase hydration, increase leucovorin, monitor BUN, Cr and call study coordinator, as above. For subsequent courses:

- If patient experienced Grade II clinical toxicity then increase hydration to a rate of 200 mL/m^2/hour prior to, during, and for 24 hours immediately following HDMTX for next course and dose reduce HDMTX by 25% of the original dose (i.e. 3.75 gm/m^2/dose; with 10% dose as bolus and 90% dose as infusion) with leucovorin as above. If tolerated without delayed excretion, increase MTX dose by 25% for each course until full dose achieved.

- If patient experienced Grade III or IV clinical toxicity then reduce dose of MTX by 50% of the original dose (i.e. 2.5 gm/m^2/dose; with 10% dose as bolus and 90% dose as infusion) for next course maintaining hydration at 200 mL/m^2/hour and following original leucovorin rescue schedule as above. Call study coordinator if patient still has delayed clearance or Grade III or IV toxicity. If patient has adequate clearance and ≤ Grade II toxicity with the reduced dose course then escalate dose by 25% (of the original dose) for each course until administration of full dose MTX achieved.

- **For patients with MTX level > 10 uM more than 42 hours after beginning MTX or with a creatinine > 1.5x normal or with a calculated creatinine clearance < 60 mL/m^2/min and delayed MTX excretion, notify study coordinator ASAP and consider use of Carboxypeptidase G2 rescue. Call 301-496-5725 to order Carboxypeptidase-G2.**

6.393 Management of the patient with clinical toxicity despite appropriate MTX clearance:

- If mucositis ≥ Grade III develops despite an appropriate fall in MTX level begin leucovorin rescue at hour 36 from the START of HDMTX infusion at a dose of 75 mg/m^2 IV x 1, then 15 mg/m^2 every 3 hours x 4, then every 6 hours until MTX level < 0.08 uM. Also increase hydration to a rate of 200 mL/m^2/hour with alkalinization as above.

- If mucositis occurs despite increased leucovorin rescue, decrease MTX dose by 25% (of the original dose) and resume standard dose leucovorin as above.

- If subsequent course is not associated with mucositis resume original leucovorin rescue and attempt to increase to full dose MTX during next course.

6.310 Intrathecal Therapy (IT Ara-C and IT MTX/Ara-C) doses and volumes are age-dependent (see Sections 6.522 and 6.524). For IT MTX/Ara-C, each drug should be made up in 1/2 of the final total volume, using preservative-free saline. The drugs are then pooled in one syringe prior to administration. The final concentration should be 1.5 mg/ml for MTX and 3 mg/ml for Ara-C. The volume of CSF removed should be equal to the volume of medication delivered. Following administration, the patient should be flat for 30 minutes to enhance drug delivery to the head.

6.311 Craniocervical XRT: 1800 cGy to brain and meninges (see Appendix IV for detailed dosing and administration guidelines). For all patients to start with a dose of tit meds on day 1 of the cycle which begins week 22 or later chronologically. For patients whose chemotherapy cycles have been delayed during consolidation then cranial XRT may be started simultaneously with week 19 cycle as long as this is chronologically $\geq$ 22 weeks and $\leq$ 25 weeks from start of treatment and $\geq$ 9 weeks from last dose of HDMTX.

6.312 Testicular Radiation Therapy Guidelines: For patients with evidence of testicular involvement radiation is recommended according to dosing and administration guidelines in Appendix IV. Testicular involvement should be assumed if testicular enlargements exists at presentation. Biopsy is not required for documentation.

6.4 Dose Modifications

6.41 Specific agents and reasons for modification:

6.411 **Vincristine:** ≥gr. 3 peripheral neuropathy or severe constipation - stop until clear and resume at 1/2 dose; bilirubin >2 mg/dl - give 1/2 dose.

6.412 **Prednisone:** Uncontrolled hypertension - stop until controlled and resume at 1/2 dose. Use insulin for hyperglycemia. Severe steroid withdrawal symptomatology (myalgias, arthralgias, etc.) should be treated by use of a 4 day course of full dose, followed by a 2-4 day rapid taper. Persistent withdrawal symptomatology can be subsequently treated using a 50% dose after consultation with the study coordinator. For aseptic necrosis, permanently stop. For bone fractures, hold prednisone until fractures are healed then resume as per schedule. For patients who experience severe behavioral or mood changes the dose can be decreased by 50% after consultation with the study coordinator.

6.413 **Doxorubicin:** ANC > 750/µl, APC >1000/µl, Plt > 100,000/µl to start DOX. ANC and platelet criteria do not apply for week 1 or 4 therapy since they are part of induction. Should mucositis (≥ gr. 3) occur hold dose till recovered then decrease dose by 20%. Bilirubin >2 mg/dl - 1/2 dose; >3.5 mg/dl - hold dose. If patient develops signs and symptoms of congestive heart failure (i.e. pulmonary or peripheral edema, dyspnea on exertion, poor feeding, increased liver size, and deterioration in exercise tolerance or grade IV cardiac toxicity) which are not attributable to other known causes such as sepsis or renal failure, **STOP DOX**, perform ECG and echocardiogram, and call study coordinator. **No dose modifications should be made purely on the basis of subclinical changes in ECG or ECHO without first consulting the study coordinator or Dr. Steven E. Lipshultz (Cardiology).** In general, this will apply to patients with shortening fractions below 28% or if cumulative dose (360 mg/m^2) not reached in 1 years elapsed time and/or ejection fractions below 50%. There will be no drug substitution for DOX if discontinued. If DOX is discontinued do not administer DZR. If DOX is reduced, DZR should be dose reduced to keep the ratio of DZR:DOX at 10:1. If there is a dose cut made for DOX then the patient should continue DOX for > planned 12 cycles in order to reach a cumulative dose of 360 mg/m^2 but not > 360 mg/m^2. The last dose of DOX may need to be adjusted to avoid going over the 360 target. ***Do NOT stop DOX at < 345 mg/m^2!***

6.414 **L-asparaginase:** Pancreatitis - stop; diabetes - use insulin; gr. 1 allergic reaction - premedicate with Benadryl 1 mg/kg PO q 6 hrs beginning 30 min. prior to L-asp dose and continuing until 18 hrs after the L-Asp dose. If gr. 2, 3 or 4 allergic reaction occurs or if E.coli asparaginase is unavailable - switch to PEG-L-asparaginase 2,500 U/m^2 IM weekly. Allergic reaction to PEG-L-asparaginase, or if PEG is unavailable - switch to Erwinia 25,000 IU/m^2 IM weekly. For CNS events (bleed, thrombosis, infarction), hold asparaginase and resume when all clinical symptoms have resolved (and evidence of recanalization in case of thrombus as evidenced by CT/MRI). For deep vein thrombosis, hold asparaginase and begin treatment with anticoagulant medication. Check antithrombin III level, if low consider replacement therapy. Resume asparaginase after coagulation status stabilized, usually 3-4 weeks. Continue until a total of 20 doses asparaginase given. Symptomatic hypoalbuminemia or anasarca should be treated with albumin infusion. Do not discontinue asparaginase for severe hypoalbuminemia without contacting the study coordinator. If bleeding without thrombocytopenia occurs check PT, PTT, fibrinogen. Give FFP if coagulation studies are severely abnormal and ≥ gr.2 hemorrhage occurs or if coagulation studies are severely abnormal and patient is to have LP performed this cycle.

6.415 **Methotrexate:** To start MTX ANC > 750/µl, APC > 1000/µl, Plt >100,000/µl. During continuation if ANC < 750 etc., hold MTX for 1 week. If an ANC < 750 results in "missed" MTX doses for 2 or more cycles then reduce both MTX and 6-MP doses by 20% at the start of the next cycle. Re-escalate MTX then 6-MP as follows: increase in 20% increments according to patient tolerance to maintain an ANC nadir of > 750-1,000 and platelet count > 75,000-100,00. Liver transaminases >20 x normal value, or ≥gr. 3 mucositis, or intracavitary fluid accumulation such as pleural or pericardial effusion - delay cycle pending recovery to normal levels. If abnormal values of ALT=3-20x occur see Section 6.418. If > grade 2 renal toxicity occurs, hold HDMTX and consult coordinator. **DO NOT reduce dose of HDMTX course without consulting the study coordinator.**

If a dose of MTX is held or "missed" secondary to low counts (or any other reason) do not make it up. Continue through the three week cycle and as long as parameters are met starting the next cycle.

6.416 **6-Mercaptopurine:** To start 6-MP ANC > 750/µl, APC >1000/µl, Plt > 100,000/µl. During continuation if ANC < 750 etc., hold MTX for 1 week. If an ANC > 750 results in "missed" MTX doses for 2 or more cycles then reduce both MTX and 6-MP doses by 20% at the start of the next cycle. Re-escalate MTX then 6-MP as follows: increase in 20% increments according to patient tolerance to maintain

an ANC nadir of > 750-1,000 and platelet count > 75,000-100,00. Liver transaminases >20 x normal value, mucositis, - delay cycle pending recovery. If abnormal values > 3-20x normal occur, see Section 6.418. Do not stop in middle of 14 day course unless patient develops febrile neutropenia or elevation of liver transaminases (>20 x normal value). If severe mucositis occurs (≥ gr. 3), decrease dose by 20%.

6.417 **Intrathecal Therapy:** Delay IT and contact study coordinator, if bilirubin >3 mg/dl, ALT >20 x normal, serum creatinine >1.5 mg/dl, or for any CNS toxicity. Intrathecal therapy should be given at the start of a cycle. IT will be delayed if cycle is delayed.

6.418 **Transaminase elevations:** Samples for the determination of ALT and/or AST values must be drawn immediately prior to a course of MTX/6-MP. It is unacceptable to draw blood samples for these tests immediately following the MTX/6-MP infusions as 100% of patients are expected to have significant elevations at this time. ALT and/or AST elevations up to 10X normal are not uncommon. Therapy should not be decreased or delayed, even if elevations persist at this level. ALT values of 10 to 20X normal should be observed for one course of MTX/6-MP without a decrease in dose or a delay in therapy. Discontinue TMP/SMZ if the ALT elevation persists or increases until the ALT is ≤ 10X normal, then resume full dose. An ALT value of 20X normal mandates holding therapy until the level returns to < 10X normal. Should therapy be withheld for elevated transaminases during a cycle (i.e. week 2 or 3), do not "make up" that week. Resume therapy at the correct point chronologically with the start of the next cycle. Persistence of ALT above 20X normal for >2 weeks requires an evaluation including: AST, Bili, Alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C CMV and EBV serologies. A liver biopsy should be considered before additional therapy is given. Under such circumstances, please CONTACT STUDY COORDINATOR.

6.42 Drug Combinations for Consolidation and Maintenance

6.421 **VCR/DOX/PRED/6-MP:** To start a cycle the following criteria must be met, ANC > 750, APC > 1000 and platelets > 100,000. ANC and platelet criteria do not apply for week 1 or 4 therapy since they are part of induction. If any one of these parameters are less than this, delay all chemotherapy x 1 week (except L-asparaginase - **do not hold L-asparaginase for myelosuppression**) and/or recovery of counts. If ≥ 2 cycles are delayed by ≥ 1 week, AND the patient is not receiving or has discontinued TMP/SMZ, decrease DOX and 6-MP by 20% or during continuation decrease MTX and 6-MP by 20%. Re-escalate dosage of both agents to 90% after two cycles without delay and ≤ grade 1

toxicities then increase to 100% dosage after an additional 2 cycles without delay and ≤ grade 1 toxicities.

If neutropenia or thrombocytopenia results in ≥ 7 day delay in chemotherapy on 2 occasions or if ≥ 14 day delay even once, discontinue Bactrim as PCP prophylaxis. Pentamidine or dapsone should be used instead. If neutropenia or thrombocytopenia again results in chemotherapy delays ≥ 7 days the doses of DOX and 6-MP or the MTX and 6-MP should be decreased by 20%.

6.5 Treatment of CNS Leukemia

In the event that the initial spinal tap is contaminated by peripheral blood, an attempt should be made to repeat the tap to obtain a diagnostic sample prior to the instillation of intrathecal chemotherapy. If it is still not diagnostic, the CNS should be stratified as CNS 2 and the extra spinal taps given. If the determination of CNS status is still questionable, please contact the study coordinator. IT will be delayed if cycle is delayed. IT meds should be given at the start of a cycle.

6.51 Definitions

CNS negative patients = CNS 1.

Patients with < 5 WBC/μl and positive cytomorphology = CNS 2.

CNS with ≥ 5 WBC/μl and positive cytomorphology = CNS 3.

6.52 Treatment

6.521 If patients are CNS 2 or 3 at diagnosis (see section 6.51 for definitions of CNS 1, 2, and 3), administer an additional dose of IT Ara-C during week 2 of therapy and an additional dose of IT MTX/Ara-C during week 16 of therapy.

6.522 Intrathecal Ara-C (IT Ara-C)

Age	Ara-C	Volume	Alternate Volumes
1 - 1.99 yr	20 mg	8 ml	5ml
2 - 2.99 yr	30	10	6
3 - 8.99 yr	40	12	8
≥ 9 yr	40	15	10

6.523 **Intrathecal Ara-C (IT Ara-C)** doses and volumes are age-dependent (see section 6.522). The volume of CSF removed should be equal to the volume of medication delivered.

Following administration, the patient should lie prone or in Trendelenberg position for 30 minutes to enhance drug delivery to the head.

6.524 Intrathecal Methotrexate plus Ara-C (IT MTX/Ara-C)

Age	MTX	Ara-C	Volume	Alternate Volumes
1 - 1.99 yr	8 mg	20 mg	8 ml	5 ml
2 - 2.99 yr	10 mg	30	10	6
3 - 8.99 yr	12 mg	40	12	8
≥ 9 yr	15 mg	40	15	10

6.525 **Intrathecal Therapy (IT MTX/Ara-C)** doses and volumes are age-dependent (see section 6.524). Each drug should be made up in 1/2 of the final total volume, using preservative-free saline. The drugs are then pooled in one syringe prior to administration. The volume of CSF removed should be equal to the volume of medication delivered. Following administration, the patient should lie prone or in Trendelenberg position for 30 minutes to enhance drug delivery to the head.

6.6 Duration of Therapy

Therapy will continue until 24 months of CCR (approximately 108 weeks total therapy).

7.0 EVALUATION CRITERIA

7.1 Evaluation Criteria

7.11 Evaluation of complete response (CR) - no evidence of disease (for T-ALL patients see Appendix I).

7.12 For Lymphoblastic NHL Patients:

7.121 Complete remission will be defined as disappearance of all evidence of disease from all sites. This will be determined by physical exam and appropriate imaging studies. If blasts were present in the bone marrow at diagnosis, they should be < 5% and there should be no blasts in the peripheral blood. Patients with residual mediastinal mass lesions which meet the criteria for PR and who otherwise are in CR should be presumed to be in CR and not taken off study unless there is biopsy proof of failure to achieve complete remission.

7.122 Partial response ≥ 50% decrease in the sum of the products of the maximum perpendicular diameter of the lesions. No new lesions.

7.123 No response - failure to qualify for a PR. No new lesions.

7.124 Progressive disease ≥ 25% increase in the size of any lesions.

7.2 Evaluation of toxicity will be according to Appendix II.

7.3 Relapse is a recurrence of disease at any site.

8.0 OFF-STUDY CRITERIA

8.1 Failure to achieve CR by day 43.

8.2 Relapse at any site.

8.3 Second malignancy.

8.4 Death in remission.

8.5 Development of intolerable, unacceptable toxicity (≥ gr.4) not amenable to dosage modification (contact study coordinator).

8.6 Bone marrow transplantation is not an off-study criterion. Removal from the therapeutic protocol for marrow transplantation will constitute a protocol violation.

9.0 REGISTRATION AND STUDY MONITORING

9.1 **Registration:** All patients will be registered on the WWW 24 hours, 7 days per week. If you have problems with registration, call 352-392-5198. During business hours, dial extension 0 for the Receptionist. After hours, follow the instructions given by the auto attendant in order to page the individual on call.

Lymphoblastic NHL - Pathology material must be submitted as per section 5.2.

T-Cell ALL - Register on POG 9900 within two days of mailing samples (Registration date is day 1). By day 6 (day 8 if day 6 is on a week-end) patient must be registered on POG 9404. The patient, having previously registered on POG 9400 or POG 9900 is registered as an old (or existing) patient when being registered on this present (#9404) study. During the period until January 15, T-Cell leukemia patients entering 9404, where no 9400 or 9900 registration was made enter as "New Patients"

9.2 Forms

Except where noted below, send two copies of the following forms, scheduled per the following table, to the COG Research Data Center, 104 N. Main St. Suite 600, Gainesville, FL 32601-3330.

FORM	**DUE**
Patient Identification Form	During patient registration in RDE.
Prestudy for Newly Diagnosed ALL (Study Numbers 9200+)	T-ALL: Within 3 weeks of registration on 9404. Label prestudy as 9404 (not 9900).
Untreated Non-Hodgkin's Lymphoma Prestudy	Lymphoma: Within 3 weeks of registration.
NHL Pathology Sample Inclusion Form (App. VIII)	Submit with pathology samples to Dr. Hutchison.
POG 9404 Flowsheets	Every 2 months while on therapy.
POG 9404 Roadmaps	Every 2 months while on therapy - to match the period of time described on the flow sheet (occasionally may require submission of a partially complete roadmap).
Pathology Review (NHL)	See section 5.0
Echocardiogram for POG 9404 (App. VI)	Due within three weeks of testing. Also send form to Dr. Steven Lipshultz (Address page ii). ***See Appendix V, Sect. 4.0.***
Markers for Myocardial Injury for POG 9404 from (App. VI)	Due with serum samples ***See Appendix V, Sect. 3.1.***
Quantitative Troponin T Shipping Log (App. VI)	Due with serum samples ***See Appendix V, Sect. 3.1.***
Response Documentation Form for ALL and NHL	Within 3 weeks of completion of induction.
Quality Assurance Documentation	See Appendix IV
Off Protocol Therapy Follow-Up Report	At completion of protocol therapy and every six months until four years from registration; annually thereafter (to be discontinued only if the patient subsequently enters another POG/COG treatment study or dies).
New ALL Off Study/Relapse Report	**For T-ALL**: Within three weeks of such an event. See back of form for conditions requiring a resubmission of this form.
Off Study Summary/Relapse Report	**For Lymphoma**: Within three weeks of such an event. See back of form for conditions requiring a resubmission of this form.
Secondary Malignancy Reporting Form (page 1 of 3) and NCI/CTEP Secondary AML/MDS Report Form (Pages 2 and 3)	Page 1 (for all secondary malignancies): Within 3 weeks of such an event, mail two copies to the COG Research Data Center if the patient is on study. Otherwise mail one copy. Pages 2 and 3 (Only for secondary AML/MDS): Within 3 weeks of such an event, mail one copy to the COG Operations Office, and one copy to the COG Research Data Center.
CNS ADR Reporting Form. For neurotoxicity $\geq$ grade 2.	Within 3 weeks of such an event. Mail 1 copy to the COG Operations Office, two copies to the COG Research Data Center and 1 copy to the IDB of CTEP (address in section 9.3). Include copies of all CNS Imaging Study Reports.
Notice of Patient Death	Within 3 weeks of patient death.

9.3 Requirements for Protocol 9404

As of January 1, 2001, certain adverse events experienced on protocols using **CTEP(NCI)-sponsored investigational agents** require expedited reporting to CTEP using its Web-based AdEERS. This study requires expedited adverse event reporting using AdEERS. NCI's guidelines for expedited adverse event reporting for protocols using NCI investigational agents can be found at:

http://ctep.info.nih.gov/AdEERS/Downloads/NCIAEReportingGdlnv3.0Jan01,2001.pdf

CTEP(NCI)-sponsored investigational agent: Dexrazoxane NSC #169780

ATTRIBUTION	ADVERSE EVENT									
	GRADE 1		GRADE 2		GRADE 3 and/or Hospitalization*		GRADE 4 and/or Hospitalization*		GRADE 5∀	
	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED
UNRELATED					*	*	AdEERS	AdEERS	AdEERS	AdEERS
UNLIKELY					*	*	AdEERS	AdEERS	AdEERS	AdEERS
POSSIBLE			AdEERS		AdEERS	*	AdEERS	AdEERS	AdEERS	AdEERS
PROBABLE			AdEERS		AdEERS	*	AdEERS	AdEERS	AdEERS	AdEERS
DEFINITE			AdEERS		AdEERS	*	AdEERS	AdEERS	AdEERS	AdEERS

* **For Hospitalization Only – Any medical event equivalent to CTC Grade 3 or 4 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for Phase of study, expected or unexpected and attribution.**

∀ **All deaths within 30 days of the last dose of treatment with an investigational agent require expedited reporting, regardless of attribution. Deaths attributed to the agent (possible, probable or definite) require expedited reporting.**

Unexpected Grade 4 and 5 adverse events must be **telephoned within 24 hours** to the Investigational Drug Branch at 301-230-2330 (available 24 hr daily, recorder 5 pm to 9 am EST), with an AdEERS report to follow.

Expedited reports are to be submitted using AdEERS or the AdEERS paper templates available at http://ctep.info.nih.gov. **within 7 working days**.

Expedited reporting may not be appropriate for certain protocols where an adverse event is expected. Exceptions to the above table for the POG 9404are provided below. A listing of "expected" (i.e., known) adverse events for the investigational agent Dexrazoxane is provided on the reverse side.

The adverse events which do NOT require expedited AdEERS reporting for this protocol are the expected toxicities listed in Section 3.0 and the exceptions listed below.

Category	Adverse Events
Allergy/Immunology	Grade 3 and 4 allergic reaction, with or without hospitalization
Blood/Bone Marrow	Grade 3 and 4 anemia, leukopenia, neutropenia, thrombocytopenia, with or without hospitalization Grade 3 and 4 transfusion, with or without hospitalization
Coagulation	Grade 3 and 4 fibrinogen, with or without hospitalization Grade 3 and 4 thrombosis/embolism, with or without hospitalization
Gastrointestinal	Grade 3 and 4 constipation, with or without hospitalization Grade 3 and 4 diarrhea, with or without hospitalization Grade 3 and 4 stomatitis, with or without hospitalization Grade 3 and 4 pancreatitis, with or without hospitalization Grade 3 and 4 vomiting, with or without hospitalization
Hepatic	Grade 4 transaminases (SGOT, SGPT)
Infection/Febrile neutropenia	Grade 3 and 4 febrile neutropenia, with or without hospitalization Grade 3 and 4 infections, with or without hospitalization
Metabolic	Grade 3 and 4 hyperglycemia
Neurology	Grade 3 and 4 seizure, with or without hospitalization Grade 3 and 4 mood alteration, with or without hospitalization
Pain	Grade 3 and 4 headache, with or without hospitalization

Questions regarding AdEERS reporting requirements for this study may be directed to Susan Caso at the Group Operations Office. In addition, NCI guidelines for expedited adverse event reporting requirements protocols using NCI investigational agents can be found at:

http://ctep.info.nih.gov/AdEERS/Downloads/NCIAEReportingGdlnv3.0Jan01,2001.pdf

9.4 ADVERSE EVENT REPORTING FOR COMMERICAL AGENTS

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the following procedures should be followed:

9.4.1 What To Report: Any life-threatening (Grade 4) or fatal (Grade 5) adverse event with an attribution of possible, probable or definite to a study drug that is **also unexpected** (not listed in the package label).

9.4.2 When To Report: These events should be reported within ten (10) working days.

9.4.3 Where To Report: These adverse events with commercial agents must be reported to the FDA and a copy provided to the NCI using the MedWatch form. A copy of the MedWatch form can be obtained from the FDA's MedWatch Web site (see below) or the CTEP home page in Appendix 12 of the Investigator's Handbook. The MedWatch report can be sent by the following mechanisms:

To the FDA:	NCI:	C.O.G:
On Line: www.fda.gov/medwatch	Copy	Copy
Mail: MedWatch 5600 Fishers Lane Rockville, MD 20852-9787	Mail: Investigational Drug Branch P.O. Box 30012 Bethesda, MD 20824	C.O.G RDC
Fax: 1-800-332-0178	Fax: 301-230-0159	Study Coordinator: see page 2 for address and/or fax number

9.5 Neurotoxicity - RDE CNS ADR Report
For CNS toxicity ≥ grade 2, use the RDE CNS ADR Report in lieu of the FDA Form 3500 Medwatch and the DCT Adverse Reaction Form for Investigational Agents. Send copies to IDB at CTEP (P.O. Box 30012, Bethesda, MD 20824). Submit during protocol therapy and until two years after the end of protocol therapy.

10.0 STATISTICAL CONSIDERATIONS

This is a 2X2 Factorial Trial of the Dana Farber Cancer Institute (DFCI) Regimen, with or without High Dose MTX, and with or without Zinecard. The Zinecard question is primarily designed as a cancer control effort to test if abnormalities seen in echocardiograms can be reduced under Zinecard.

Treatments:
1. DFCI
2. DFCI+Zinecard
3. DFCI+MTX
4. DFCI+Zinecard+MTX

10.1 Accrual Rates and Endpoints

Primary Question 1: High Dose MTX Addition:

Based on historical considerations, POG is expected to accrue 140 patients per year to T-Cell ALL/ advanced lymphoblastic NHL protocols. Of these, we expect to divert 15 patients per year to a pilot study, leaving 125 in the main pool. Since all patients receive the same induction, the endpoint will be CCR , i.e. complete continuous remission (the time to failure for any cause among patients achieving a complete response).

Hence the net accrual will be 120 patients (5 losses for failure to achieve a CR).

This question will drive the sample size requirements for the trial, while the power considerations for the Zinecard questions will be based on sensitivity for these numbers. In an earlier draft of the protocol, we did separate sample size calculations, where all Zinecard questions required fewer patients than the MTX question. Hence, this revision effectively increases the power of the Zinecard questions.

Primary Question 2: Zinecard Addition:

Although other echocardiograms will be used, the endpoint will be abnormalities in the 31 week and the year 3 echocardiograms (i.e. year 1 off therapy). Secondarily, we shall compare the CCR rates for the two treatment regimens, in a two sided fashion. However, we cannot expect to make a definitive conclusion about the "negative question" that there is "no difference in the CCR curves". Other echocardiograms will be used for late effects monitoring.

10.2 Planning Parameters and Design Issues for the MTX Question

The randomization will be stratified for the four strata below. This is to balance the randomization rather than for specific subset inference, which will lack sufficient power. We shall assume the overall result holds in all strata unless a significant qualitative interaction is detected (P<.05) by the method of Simon and Gail.

Strata: **1=T-Cell ALL** (No CNS disease)(71/year expected)
2=T-Cell ALL (CNS disease) (9/year expected)
3=Stage 3/4 Lymphoblastic NHL (No CNS) (41/year expected)
4=Stage 3/4 Lymphoblastic NHL (CNS) (4/year expected)

Sample Size Assumptions:

-Proportional Hazards
-Post 4 year hazard = 0.25 Pre 4 year hazard on average
-DFCI 4 year CCR=65%
-Improvement planned to be detected 10% (to 75%)
-Power 80%
-Sidedness 1-sided (If MTX addition has no significant efficacy or has worse efficacy, the same management decision will be made)
-Annual accrual (achieving CR) 120
-Method: logrank test (post-stratified for Zinecard use)
-Final analysis: Per POG studies, 4 years after accrual is complete. POG Patients are all afforded the opportunity to reach the trial endpoint unless the study is closed by the data monitoring committee.
-Sequential Monitoring Method=O'Brien-Fleming (Has virtually no impact on operating characteristics)

Sample Size Requirement: 474 Patients achieving a CR(3.95 years of accrual) (494 patients total)

10.3 Planning Parameters and Design Issues for the Zinecard Question

In order to maximize compliance, POG has adopted the design strategy to target a pragmatic but functionally efficient set of outcome measures for the entire group and target a wider set of measures for a limited number of institutions, as a pilot study. We shall discuss the required measures in the section.

(A) Cardiac Troponin-T Levels: Pretreatment and 24-72 hours after the first doxorubicin dose. While most baseline levels will be near zero, a small percentage will be significant. An increase of 0.03 μg/l or greater will be considered an adverse event.

(B) Echo variables: LV fractional shortening, LV Mass, LV Wall thickness, LV End diastolic dimension, LV afterload, or major clinical symptom. These will be collected at baseline, prior to the second dose of doxorubicin, after completion of doxorubicin therapy (week 31), year 3 and year 6 of the study.

While we shall analyze each parameter, the main inference will be made on the basis of an "adverse event": A Z-score of 2.33 or more in the adverse direction (signifying in the lowest 1% of normals) or a cardiac adverse drug reaction, whether on or after completion of therapy. Cardiac events secondary to post relapse Phase II therapy will not be counted as adverse cardiac events (% fractional shortening would be -2.33;dimension, thickness, and mass would be 2.33).

10.31 Power Estimate for Troponin-T

The actual method will use a Wilcoxon Test with dependent variable change from baseline.

In the Dana-Farber study, 40% had elevations of 0.02 μg/l or higher. The actual distribution is unavailable, and hence we shall calculate the necessary sample size on the basis of binomial considerations (as if all we use is whether or not the change exceeds 0.02 μg/l). Clearly, this sample size calculation is conservative. Assuming these required studies will be available on 90% of patients achieving a CR, (474*90%)=427 patients, we shall have the following sensitivity.

Event rates:	40% control, 25.5% Zinecard
P-Value:	0.01 (one-sided)
Power:	80%

10.32 ECHO

We shall conduct three cross-sectional analyses. The first two will be for inference purposes while the third will be for late effects monitoring.

For the two points of inference, we shall utilize a one-sided P-value of 2% to define statistical significance.

Week 31: Assuming that 90% of patients who achieve a CR reach week 31, and of these 90% have the required studies, the annual net accrual is expected to be 97 patients per year. (Total 3.95*97=383 patients)

Year 3: Assuming that 75% of the patients who achieve a CR reach 3 years, and of these, 85% have the required studies, the annual net accrual is expected to be 69 patients per year. (Total=3.95*69=273 patients)

Time	Purpose	Adverse Events Planning Sensitivity (80% Power)
Week 31	Inference	6% (Zinecard) vs. 15%
Year 3*	Inference	8% (Zinecard) vs. 20%
Year 6*	Late Effects	N/A

*Year 3 and year 6 refer to years 3 and 6 of the study.

10.33 Event-Free Survival

We view this as a secondary issue, but it is important for safety monitoring. Also, since Zinecard administration is completed by week 31, and is not designed as a cytotoxic agent, it is expected that any impact on event-free survival will be relatively early. Late failures are likely to be pure noise with respect to the Zinecard EFS question, and hence inclusion of these is expected to detract from the statistical operating characteristics.

We shall compare the arms with respect to two year event-free survival, stratified for methotrexate arms, using Kaplan-Meier estimates. A Two-sided 90% confidence interval will be utilized. Assuming the average two year EFS will be in the 80% range, the confidence interval will be bounded by the estimated difference plus or minus six percent.

Note that this implies that if Zinecard is associated with a 6% reduction (or increase) in two year EFS, power to detect this will be only 50%.

10.34 Footnotes on the Zinecard Question

- Overall p-value for Zinecard is controlled to be under 5%.
- Reminders for cardiac testing will be posted on the POG Bulletin Board (beginning four months prior to the timed event) and will be published as an addendum to the POG delinquency list which comes out every other month, for 1-2 issues prior to the timed event.
- The cardiology co-coordinator and local institution cardiologists will be blinded as to treatment regimen.
- Cardiology data will be sent electronically every three months from Dana-Farber to the Statistical Office.

– All inferences will be made by statistical tests, but as in all POG analyses, these will be supplemented by confidence limits corresponding to the P-values used.

10.4 Safety Monitoring

10.41 Event-Free Survival

This study will be monitored by the O'Brien-Fleming method every six months starting after the 25th of the expected 156 adverse events occurs, until one year after accrual has been completed. The critical Z-value will be 2.24/sqrt(Information fraction), where the information fraction is given by the number of observed deaths/156. This monitoring has virtually no impact on either the type I error or power, as described in the fixed sample size calculation of 10.2. This monitoring will apply to both questions.

This monitoring will be one-sided (MTX question) and two-sided (Zinecard question). However, we shall also compute the conditional power of the study for the MTX question at each interim analysis. A value below 10% would lead to flagging the study for possible discontinuation of the MTX question. Such a value would suggest that likelihood of a significant difference favoring higher MTX would be low. It would not necessarily mean that higher dose MTX is inferior.

10.42 Cardiac Data

Since the bottom line of this study is to investigate the efficacy of Zinecard in terms of cardiac endpoints, while attempting to obtain as tight estimates of the EFS difference as possible, we shall monitor only for clinical cardiac events, reported as ADRs to the data monitoring committee. No formal stopping rule can be formulated, in view of the interplay between cardiac toxicity and EFS.

10.43 Monitoring CR rate for Zinecard

Based on historical considerations, we expect a 95% CR rate. At each meeting, starting after the study has been opened for six months we shall flag the study if the CR rate in the Zinecard arm falls below 95% at $P<.05$ one-sided, as judged by the O'Brien-Fleming method in continuous time. The information fraction will be patients/247, where the denominator is the total expected number of patients to be randomized to the Zinecard arm. A Z-value greater than 1.96/sqrt(IF), where IF=information fraction, will flag the study. There is less than a 5% chance of flagging the trial if the true CR rate is 95% or higher.

10.44 Toxicity Monitoring

Since MTX has been associated with neurotoxicity, we shall flag the study, if at any six month cutoff, the actuarial projected grade 3 or higher neurotoxicity to the end of consolidation is above 7%, or more than 10% in total. These actuarial projections will be applied to the higher dose arm, and to the combined arms. All ADRs will be reported in tabular unblinded fashion to the Data Monitoring Board.

Cardiac toxicity will be monitored per 10.42.

10.5 Troponin Amendment of 8/98

An unscheduled review of the troponin data after the first doxorubicin use had insufficient variation to continue this aspect (See 10.3A and 10.31).

Hence, Troponin results will not be employed to evaluate the Phase III objectives of the trial, but will be relegated to being a secondary evaluation.

We shall employ the Troponin data in two ways. The first issue is to determine if there are a sufficient fraction of patients with clinically detectable troponin levels at the cumulative doses of 120, 240, and 330 mg/m^2 to plan a future investigation? We shall use the first 50 post amendment patients to screen the variability. Any parameters with fewer than 20% with detectable levels will be eliminated. The protocol will be amended to eliminate such troponin levels and the secondary comparison would be based on the remaining (i.e. future) patients, and be restricted to the single time point with the most variation (assuming one or more pass the test). No patient used to screen variables will be used in the efficacy comparison. This prevents creating and testing hypotheses on the same data.

10.6 6/00 Amendment

Based on the ongoing data, it has become clear that the projected overall outcome of 65% vs. 75% at four years was overly pessimistic. In reality, the 4 year overall EFS is projected to be about 80%. Consequently, the event-free survival comparisons, if conducted as in the original design, will have fewer events than planned and hence lower power. Under the same assumptions above, if the design parameters for 4 year EFS are 76% vs. 84% at 4 years (Hazard ratio of 1.57 rather than 1.50 per the original), the study will require 549 eligible patients.

Accrual as of 4/10/00: 407 eligible patients

Current Accrual rate: 110 eligible patients per year Additional Eligible Patients Needed: 142 (15.5 months) Projected Closure: July, 2001.

Since the extension is based on aggregate outcome, not on arm specific outcome, this does not bias the type I and type II error rates for the study.

10.7 9/27/00 Amendment

The methotrexate randomization was closed based on the Data Monitoring Committee recommendation. The stopping barrier was exceeded, indicating that we have sufficient evidence to conclude that the addition of high dose methotrexate is associated with improved event-free survival. The Zinecard randomization remains open.

11.0 GENDER/MINORITY ANALYSIS

We shall study the subpopulations (a) within males; (b) within females; (c) within Caucasians; (d) within Blacks; and within (5) Hispanics. Since power within subgroups is limited, we shall obtain confidence interval for treatment effect in each of the subgroups by Cox regression (Survival endpoints, logistic regression, [binary endpoints], and ordinary regression [Troponin T]. This will help us in the design of future trials.

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APPENDIX I

REMISSION DEFINITIONS - ALL IN CHILDHOOD

Bone Marrow

M_1	0 - 5% Blasts in count of at least 200 cells
M_2	>5 - 25% blasts; at least 200 cells counted
M_3	> 25% blasts: at least 200 cells counted

For initial remission: M_1 marrow MUST be achieved; M_3 marrow at day 28 OR either M_2 or M_3 marrow (if M_2 at day 28) day 42 means an induction failure.

Extramedullary Disease

Any histologically or pathologically identified extramedullary disease signifies either induction failure or relapse depending on timing.

The following definitions are used:

INITIAL REMISSION: M_1 marrow with no extramedullary disease as above; demonstrated 28 or 42 days after start of induction.

INDUCTION FAILURE: M_3 marrow on day 28; M_2 or M_3 marrow day 42 OR the presence of histopathologically documented disease elsewhere on these same dates.

RELAPSE: M_3 marrow or histopathologically documented disease in the CNS, testis(es) or elsewhere at any time after initial remission.

CONTINUING REMISSION: Any living patient who achieved initial remission and has never had a relapse as defined above.

TOXICITY AND COMPLICATIONS CRITERIA

(For studies #8850, #8862, #8866, and > #8900)

Death due to toxicity should be coded as Grade 5

		O/WNL	1 (mild)	2 (moderate)	3 (severe)	4 (unacceptable)
CBC & MARROW	WBC/m*l* ANC/m*l* LYMPHS/m*l* PLT/m*l* HGB g/d*l*	≥4.0 ≥2.0 ≥2.0 WNL WNL	3.0 - 3.9 1.5 - 1.9 1.5 - 1.9 75.0 - normal 10.0 - normal	2.0 - 2.9 1.0 - 1.4 1.0 - 1.4 50.0 - 74.9 8.0 - 10.0	1.0 - 1.9 0.5 - 0.9 0.5 - 0.9 25.0 - 49.0 6.5 - 7.9	<1.0 <0.5 <0.5 <25.0 <6.5
	MARROW CELLULARITY	normal	mildly hypo. 25%	mod. hypo. 50%	marked hypo. 75% – 3 wks to recovery	aplastic >3 wks to recovery
COAGULATION	HEMORRHAGE THROMBOSIS	none none	mild/no transfusion local	gross - 1-2 trans/episode superficial	gross - 3-4 trans/episode deep vein	massive - >4 trans/episode major event organ dysfunction
	FIBRINOGEN PT PTT	WNL WNL WNL	0.99 - 0.75 x N 1.01 - 1.25 x N 1.01 - 1.66 x N	0.74 - 0.50 x N 1.26 - 1.50 x N 1.67 - 2.33 x N	0.49 - 0.25 x N 1.51 x 2.00 x N 2.34 - 3.00 x N	≤.24 x N >2.00 x N >3.00 x N
	INFECTION*	none	mild	moderate	severe	life threatening
	ALLERGY	none	transient rash	mild bronchospasm	mod. bronchospasm serum sickness	hypotension, anaphylaxis
	FEVER	<38°C	38°C - 40°C	>40°C <24 hrs	>40°C >24 hrs	--
	SKIN CONJUNCTIVITIS/ CORNEA	no chg or WNL none	scattered eruption or erythema, asympt. mild irritation, redness	urticar/scattered erupt., sympt. sig. inflamm., mild photophobia	generalized eruption, req. Rx severe inflamm., mkd photophobia	exfol/ulcer dermatitis erosion
	LOCAL	none	pain	pain/swelling with inflammation/phlebitis	ulceration	plastic surgery indicated
	ALOPECIA	no loss	mild hair loss	marked/total hair loss	--	--
GASTROINTESTINAL	STOMATITIS NAUSEA VOMITING DIARRHEA CONSTIPATION PANCREAS (CL) PANCREAS (IMAGING)	none none none none no chg none none	erythema, or mild soreness reasonable intake 1x/day 2-3 stools/day mild ileus -- somnolency	painful/edema, can eat decreased intake 2-5x/day 4-6 stools/day mod. ileus symptomatic size increased <2x local somnolency	cannot eat or drink no sig. intake 6-10x/day 7-9 stools/day or severe cramps severe ileus hosp. req'd ≥2x size increased x 2 general somnol.	requires parenteral or enteral support -- >10x/d or IV req'd. -≥10 stools/day bloody, parenteral support req'd. ileus >96 hrs parenteral support hemorrhage pseudocyst
LIVER	TOTAL BILI. SGOT, SGPT ALK. PHOSPHATASE LIVER-CLIN. PROTEIN *g/l* ALBUMIN g/d	WNL WNL WNL WNL WNL WNL	-- ≤2.5 x N ≤2.5 x N -- >5.0 - 6.0 >3.0 - 5.0	<1.5 x N 2.6 - 5.0 x N 2.6 - 5.0 x N -- >4.5 - 5.0 >2.5 - 3.0	1.5 - 3.0 x N 5.1 - 20.0 x N 5.1 - 20.0 x N precoma >4.0 - 4.5 >2.0 - 2.5	>3.0 x N >20.0 x N >20.0 x N hepatic coma <4.0 <2.0
KIDNEY/ BLADDER	CREATININE PROTEINURIA HEMATURIA CREAT. CLEAR. FANCONI SYN	WNL neg neg WNL none	<1.5 x N 1 +/or < 3 *g/l* micro only 75% --	1.5 - 3.0 x N 2-3 +/or 3-10 *g/l* gross, no clots 50-74% --	3.1-6.0 x N 4+/or >10 *g/l* gross + clots 25-49% reversible	>6.0 x N nephrotic synd. trans. req'd. <25% irreversible

* Clinical judgment will have to be used. Usually grade 3 infection would require hospitalization and/or IV antibiotics, where grade 2 could be managed by outpatient oral therapy, etc.

METAB/LYTES	Ca mg/dl	WNL	8.4-7.8/10.6-11.5	7.7-7.0/11.6-12.5	6.9-6.1/12.6-13.5	≤6.1/≥13.5
	Mg mEq/l	WNL	1.4-1.2	1.1-0.9	0.8-0.6	≤0.5
	K mEq/l	WNL	¯3.1-3.4/5.5-5.9	2.6-3.0/6.0-6.4	2.1-2.5/6.5-6.9	<2.0/>7.0
	Na mEq/l	WNL	¯130-134/146-149	125-129/150-155	116-124/156-164	<115/>165
	Glu mg/dl	WNL	55-64/116-160	40-54/161-250	30-39/251-500	<30/>500/ketoacid
	AMYLASE	WNL	<1.5 x N	1.5-2.0 x N	2.1-5.0 x N	>5.0 x N
CARDIOVASCULAR	CARD. RHYTHM	WNL	asympt./transient no Rx required	recur./persist. no Rx required	requires treatment	hypotension V tach/fibrillation
	CARD. FUNCTION	WNL	asymptomatic/ ¯ ej. fr. ≤20%	asymptomatic/ ¯ ef. fr. >20% baseline	mild CHF/ responds to Rx	severe or refractory CHF
	ECHO: %FS	>30	24-30	20-24	<20-24	--
	%STI	<0.35	--	<0.40	>0.40	--
	CARD. -ISCHEMIA	NONE	non-specific T-wave flattening	asymptomatic EKG chg sugg ischemia	angina/without evid. of infarction	acute myocardial infarction
	CARD. -PERICARD. -EFFUSION	NONE	asympt. effusion no Rx required	pericarditis	drainage required	tamponade; drainage urgently required
	HYPERTENSION	no chg	asympt./transient ↯20%, no Rx req'd.	recur./persist. ↯20%, no Rx req'd.	requires therapy	hypertensive crisis
	HYPOTENSION	no chg	no Rx req'd.	Rx but no hosp.	Rx = hosp. <48 hrs. after stop agent	Rx = hops. >48 hrs after stop agent
PULMONARY	CLINICAL	no chg	abn PFTs/asymp.	dyspnea on sig exert.	dyspnea at N activ.	dyspnea at rest
	VITAL CAP.	WNL	10-20%¯	21-35%¯	36-50%¯	>51%
	p A02	>90	80-89	65-79	50-64	<49
	DLCO	100-75%	74-65%	64-55%	54-40%	<40%
	FUNCTIONAL	normal	tachypnea	dyspnea	O_2 req'd.	assist vent.
	02 SAT	>95%	94-95%	91-93%	86-90%	≤85%
NEUROLOGICAL	MOOD	no chg	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
	HEADACHE	no chg	mild	transient/mod/severe	severe, unrelenting	--
	CORTICAL	no chg	mild somnolence/agitation	mod. somnolence/agitation	severe somnol/agit. confusion/halluc.	coma/seizures/toxic psychosis
	SENSORY	no chg	mild paresthesias, loss tendon reflex	mod. sensory loss, mod. parasthesias	interferes with function	--
	MOTOR	no chg	subj weakness/no obj. findings	mild obj weakness/no signif. impair	obj weakness/function impair	paralysis
	CEREBELLA	no chg	slight incoordination/ dysdiadokinesis	intention tremor/ dysmetria/slurred speech/nystagmus	locomotor ataxia	cerebellar necrosis
	HEARING -subj	no chg	loss on audiometry only	tinnitus, soft speech	loss correctable with hearing aid	deafness not correctable
	obj	no chg	20-40db loss >4KHz	>40db loss 4KHz	>40db loss >2KHz	>40db loss <2KHz
	VISION	no chg	--	--	subtotal vision loss	blindness
	WEIGHT CHANGE	<5.0%	5.0-9.9%	10-19.9%	≥20.0%	--
	PERFORMANCE (Karnofsky %) ECOG	normal (90-100)	mild restriction (70-<90)	ambulatory up 50% (50-<70)	bed or wheelchair (30-<50)	no self care (<30)

* Clinical judgment will have to be used. Usually grade 3 infection would require hospitalization and/or IV antibiotics, where grade 2 could be managed by outpatient oral therapy, etc.

NUMERIC CODES FOR COMMON TOXICITY AND COMPLICATIONS

CBC/MARROW	
WBC	101
ANC	110
APC	115
LYMPHS	120
PLATELETS	130
HEMOGLOBIN	140
MARROW CELLULARITY	150
BLEEDING/CLOTTING	
HEMORRHAGE	160
THROMBOSIS	165
FIBRINOGEN	170
PT	180
PTT	190
INFECTION	
INFECTION NOS/UNK	200
SEPSIS, BACTERIA	201
PNEUMONIA, BACTERIA	202
URI/OTITIS	210
ABSCESS	220
OTHER BACTERIAL	230
VIRAL NOS/UNK	250
VIRAL GENERALIZED	251
VIRAL PNEUMONIA	252
VARICELLA	253
ZOSTER	254
OTHER VIRAL	256
FUNGAL NOS/UNK	270
FUNGAL SEPSIS	271
FUNGAL ABSCESS	272
FUNGAL STOMATITIS	273
FUNGAL ESOPHAGITIS	274
PROTOZOA NOS/UNK	290
P. CRINII	291
ALLERGIC/TOXIC	
ALLERGIC REACTION	300
FEVER (DRUG)	310
SKIN	320
GENERALIZED	321
LOCAL	322
ALOPECIA	340
ENDOCRINE/WT	
2° SEX CHARACTERISTICS	350
SPERM PRODUCTION	353
OVARIAN FUNCTION	358
HYPOTHYROIDISM	370
WT LOSS	380
GROWTH FAILURE	390
GI	
STOMATITIS	400
NAUSEA	410
VOMITING	420
DIARRHEA	430
CONSTIPATION	440
PANCREAS (CLINICAL)	445
PANCREAS (IMAGING)	446
AMYLASE	447
LIVER	
LIVER (CLINICAL)450	
BILIRUBIN	460
PROTEIN	465
ALBUMIN	466
SGOT, SGPT	470
ALK. PHOSPHATASE	480
KIDNEY/BLADDER	
ANURIA	500
CREATININE	501
CREATININE CLEARANCE	502
PROTEINURIA	510
HEMATURIA	520
FANCONI SYNDROME	530
METAB/LYTES	
CA	550
MG	555
K	560
NA	565
GLUCOSE	570
CARDIAC	
RHYTHM	600
FUNCTION	610
ECHO: FS	620
STI	621
CARDIAC ISOTOPE SCAN	625
ISCHEMIA	630
PERICARDITIS/EFFUSION	640
HYPERTENSION	650
HYPOTENSION	651
NUCLEOTIDE SCAN	660
PULMONARY	
CLINICAL	670
VITAL CAPACITY	671
PAO_2	672
DLCO	673
FUNCTIONAL	674
OXYGEN SATURATION	675
CNS	
MOOD	800
HEADACHE	801
CORTICAL	810
INTELLIGENCE	811
SENSORY	820
MOTOR	830
CEREBELLAR	840
HEARING (SUBJECT.)	860
HEARING (OBJECT.)	861
VISION	870
PNS	890
MUSCULOSKELETAL	
MUSCULAR ATROPHY/FIBROSIS	900
MUSCLE CONTRACTURE	910
ANKYLOSIS	920
BONE SHORTENING	930
OSTEOPOROSIS/PENIA	940
PATHOLOGIC FRACTURE	950
KARNOFSKY PERFORM SCORE	990
PSYCHOSOCIAL	999

Codes for Toxicity Effect:
0=none 1=delay 2=decrease
3=delay/decrease 4=change/omission 5=stop permanently

POG #9404
Appendix III

T-4 OPEN STUDY
TREATMENT 1

INDUCTION							CONSOLIDATION								
WK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
	VCR DOX x2 MTX PDN **x 21 days**	VCR	VCR	VCR DOX			VCR DOX			VCR DOX			VCR DOX		
				6MP **x 14 days**			PDN**x5d** 6-MP **x 14 days**			PDN**x5d** 6MP **x 14 days**			PDN**x5d** 6MP **x 14 days**		
	IT Ara-C	IT Ara-C*	IT Ara-C	ASP IT MTX/ Ara-C	ASP	ASP	ASP IT MTX/ Ara-C	ASP	ASP	ASP IT MTX/ Ara-C	ASP	ASP	ASP	ASP	ASP

CONSOLIDATION															
WK	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
	VCR DOX PDN**x5d** 6MP **x 14 days** ASP IT MTX/ Ara-C*	ASP	ASP	VCR DOX PDN**x5d** 6MP **x 14 days** ASP	ASP	ASP	VCR DOX PDN**x5d** 6MP **x 14 days** ASP IT MTX/ Ara-C XRT	ASP	ASP	VCR DOX PDN**x5d** 6MP **x 14 days** ASP	ASP		VCR DOX PDN**x5d** 6MP **x 14 days**		

CONSOLIDATION				CONTINUATION									UNTIL 24 MOS CCR		
WK	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**
	VCR DOX PDN**x5d** 6MP **x 14 days**			VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX	VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX	VCR PDN**x5d** 6MP **x** IT MTX/ Ara-C**	MTX **14 days**	MTX	VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX

INDUCTION	
VCR	1.5 mg/m^2 days 1, 8, 15 (max 2.0 mg)
VCR	2 mg/m^2 day 22 (max 2.0 mg)
PDN	40 mg/m^2/day (in 3 divided doses) x 21
DOX	30 mg/m^2 days 1, 2, 22
MTX	40 mg/m^2 day 2
6MP	50 mg/m^2/day x 14: wks 4 and 5
IT Ara-C	Ara-C (Dose by age) day 1 of wk 1, 3
IT Ara-C*	CNS (*) [POG CNS 2 & 3] Wk 2
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 4

CONSOLIDATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day (in 3 divided doses) x 5 q 3 weeks
DOX	30 mg/m^2 q3wks (total dose 360 mg/m^2)
6MP	50 mg/m^2/day x 14 q 3 weeks
ASP	25,000 IU/m^2 IM q wk x 20 (wks 7-26)
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 7, 10, 22
IT MTX/ Ara-C*	CNS (*) [POG CNS 2 & 3] Wk 16
XRT	1800 cGy to cranium (Begin week 22)

CONTINUATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day(in 3 divided doses) x 5 q 3 weeks
MTX	30 mg/m^2 weekly (max 40 mg) Omit wks 40, 58, 76, 94
6MP	50 mg/m^2/day x 14 q 3 weeks
IT MTX/ Ara-C**	MTX/Ara-C (Dose by age) Weeks 40, 58, 76, 94 ONLY

T-4 OPEN STUDY
TREATMENT 2

INDUCTION / CNS PROPHYLAXIS							CONSOLIDATION								
WK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
	VCR DOXx2 MTX PDN **x 21 days**	VCR	VCR	VCR DOX 6MP **x 14 days**			VCR DOX PDN**x5d** 6MP **x 14 days** ASP	ASP	ASP	VCR DOX PDN**x5d** 6MP **x 14 days** ASP	ASP	ASP	VCR DOX PDN**x5d** 6MP **x 14 days** ASP	ASP	ASP
	IT Ara-C DZR x 2	IT Ara-C*	IT Ara-C	IT MTX/ Ara-C DZR			IT MTX/ Ara-C DZR			IT MTX/ Ara-C DZR			DZR		

CONSOLIDATION															
WK	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
	VCR DOX PDN**x5d** 6MP **x 14 days** ASP IT MTX/ Ara-C*	ASP	ASP	VCR DOX PDN**x5d** 6MP **x 14 days** ASP	ASP	ASP	VCR DOX PDN**x5d** 6MP **x- 14 days** ASP IT MTX/ Ara-C	ASP	ASP	VCR DOX PDN**x5d** 6MP **x 14 days** ASP	ASP		VCR DOX PDN**x5d** 6MP **x 14 days**		
	DZR			DZR			DZR XRT			DZR			DZR		

CONSOLIDATION				CONTINUATION									UNTIL 24 MOS CCR		
WK	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**
	VCR DOX PDN**x5d** 6MP **x 14 days** DZR			VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX	VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX	VCR PDN**x5d** 6MP **x 14 days** IT MTX/ Ara-C**	MTX	MTX	VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX

INDUCTION	
VCR	1.5 mg/m^2 days 1, 8, 15 (max 2.0 mg)
VCR	2 mg/m^2 day 22 (max 2.0 mg)
PDN	40 mg/m^2/day(in 3 divided doses) x 21
DOX	30 mg/m^2 days 1, 2, 22
MTX	40 mg/m^2 day 2
6MP	50 mg/m^2/day x 14: Weeks 4 and 5
IT Ara-C	Ara-C (Dose by age): day 1 of wk 1, 3
IT Ara-C*	CNS (*) [POG CNS 2 & 3] Wk 2
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 4
DZR	DZR 300 mg/m^2 IVP **pre-DOX**

CONSOLIDATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day(in 3 divided doses) x 5 q 3 weeks
DOX	30 mg/m^2 q3wks (total dose 360 mg/m^2)
6MP	50 mg/m^2/day x 14 q 3 weeks
ASP	25,000 IU/m^2 IM q wk x 20 (wks 7-26)
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 7, 10, 22
IT MTX/ Ara-C*	CNS (*) [POG CNS 2 & 3]
XRT	1800 cGy to cranium (Begin week 22)
DZR	DZR 300 mg/m^2 IVP **pre-DOX**

CONTINUATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day (in 3 divided doses) x 5 q 3 weeks
MTX	30 mg/m^2 weekly (max 40 mg) Omit wks 40, 58, 76, 94
6MP	50 mg/m^2/day x 14 q 3 weeks
IT MTX/ Ara-C**	MTX/Ara-C (Dose by age): Weeks 40, 58, 76, 94 ONLY

T-4 OPEN STUDY
TREATMENT 3

INDUCTION							CONSOLIDATION								
WK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
	VCR DOX x2 MTX PDN **x 21 days**	VCR	VCR	VCR DOX HDM 6MP **x 14 days**			VCR DOX HDM PDN**x5d** 6MP **x 14 days**			VCR DOX HDM PDN**x5d** 6MP **x 14 days**			VCR DOX HDM PDN**x5d** 6MP **x 14 days**		
	IT Ara-C	IT Ara-C*	IT Ara-C	IT MTX/ Ara-C			ASP IT MTX/ Ara-C	ASP	ASP	ASP IT MTX/ Ara-C	ASP	ASP	ASP	ASP	ASP

CONSOLIDATION															
WK	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
	VCR DOX PDN**x5d** 6MP **x 14 days**			VCR DOX PDN**x5d** 6MP **x 14 days**			VCR DOX PDN**x5d** 6MP **x 14 days**			VCR DOX PDN**x5d** 6MP **x 14 days**			VCR DOX PDN**x5d** 6MP **x 14 days**		
	ASP IT MTX/ Ara-C*	ASP	ASP	ASP	ASP	ASP	ASP IT MTX/ Ara-C XRT	ASP	ASP	ASP	ASP				

CONSOLIDATION				CONTINUATION									UNTIL 24 MOS CCR		
WK	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**
	VCR DOX PDN**x5d** 6MP **x 14 days**			VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX	VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX	VCR PDN**x5d** 6MP **x 14 days** IT MTX/ Ara-C**	MTX	MTX	VCR MTX PDN**x5d** 6MP **x 14 days**	MTX	MTX

INDUCTION	
VCR	1.5 mg/m^2 days 1, 8, 15 (max 2.0 mg)
VCR	2 mg/m^2 day 22 (max 2.0 mg)
PDN	40 mg/m^2/day(in 3 divided doses) x 21
DOX	30 mg/m^2 days 1, 2, 22
MTX	40 mg/m^2 day 2
6MP	50 mg/m^2/day x 14: wks 4 and 5
IT Ara-C	Ara-C (Dose by age): day 1 of wk 1, 3
IT Ara-C*	CNS (*) [POG CNS 2 & 3] Wk 2
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 4
HDM	5 gm/m^2 wk 4

CONSOLIDATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day (in 3 divided doses) x 5 q 3 weeks
DOX	30 mg/m^2 q3wks (total dose 360 mg/m^2)
6MP	50 mg/m^2/day x 14 q 3 weeks
ASP	25,000 IU/m^2 IM q wk x 20 (wks 7-26)
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 7, 10, 22
IT MTX/ Ara-C*	CNS (*) [POG CNS 2 & 3] Wk 16
XRT	1800 cGy to cranium (Begin week 22)
HDM	5 gm/m^2 wks 7, 10, 13

CONTINUATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day (in 3 divided doses) x 5 q 3 weeks
MTX	30 mg/m^2 weekly (max 40 mg) Omit wks 40, 58, 76, 94
6MP	50 mg/m^2/day x 14 q 3 weeks
IT MTX/ Ara-C**	MTX/Ara-C (Dose by age): Weeks 40, 58, 76, 94 ONLY

T-4 OPEN STUDY
TREATMENT 4

INDUCTION / CNS PROPHYLAXIS							CONSOLIDATION								
WK	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
	VCR DOX x2 MTX PDN **x 21 days** IT Ara-C DZR x 2	VCR IT Ara-C* 	VCR IT Ara-C 	VCR DOX HDM 6MP **x 14 days** IT MTX/ Ara-C DZR			VCR DOX HDM PDN**x5d** 6MP **x 14 days** ASP IT MTX/ Ara-C DZR	 ASP 	 ASP 	VCR DOX HDM PDN**x5d** 6MP **x 14 days** ASP IT MTX/ Ara-C DZR	 ASP 	 ASP 	VCR DOX HDM PDN**x5d** 6MP **x 14 days** ASP DZR	 ASP 	 ASP

CONSOLIDATION															
WK	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
	VCR DOX PDN**x5d** 6MP **x 14 days** ASP IT MTX/ Ara-C* DZR	 	 	VCR DOX PDN**x5d** 6MP **x 14 days** ASP DZR	 	 	VCR DOX PDN**x5d** 6MP **x 14 days** ASP IT MTX/ Ara-C DZR XRT	 	 	VCR DOX PDN**x5d** 6MP **x 14 days** ASP DZR	 	 	VCR DOX PDN**x5d** 6MP **x 14 days** DZR	 	

CONSOLIDATION				CONTINUATION									UNTIL 24 MOS CCR		
WK	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**
	VCR DOX PDN**x5d** 6MP **x 14 days** DZR	 	 	VCR MTX PDN**x5d** 6MP **x 14 days**	 MTX 	 MTX 	VCR MTX PDN**x5d** 6MP **x 14 days**	 MTX 	 MTX 	VCR PDN**x5d** 6MP **x 14 days** IT MTX/ Ara-C**	 MTX 	 MTX 	VCR MTX PDN**x5d** 6MP **x 14 days**	 MTX 	 MTX

INDUCTION	
VCR	1.5 mg/m^2 days 1, 8, 15 (max 2.0 mg)
VCR	2 mg/m^2 day 22 (max 2.0 mg)
PDN	40 mg/m^2/day (in 3 divided doses) x 21
DOX	30 mg/m^2 days 1, 2, 22
MTX	40 mg/m^2 day 2
6MP	50 mg/m^2/day x 14: Weeks 4 and 5
IT Ara-C	Ara-C (Dose by age): day 1 of wk 1, 3
IT Ara-C*	CNS (*) [POG CNS 2 & 3] Wk 2
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 4
DZR	DZR 300 mg/m^2 IVP **pre-DOX**
HDM	5 gm/m^2. wk 4

CONSOLIDATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day (in 3 divided doses) x 5 q 3 weeks
DOX	30 mg/m^2 q3wks (total dose 360 mg/m^2)
6MP	50 mg/m^2/day x 14 q 3 weeks
ASP	25,000 IU/m^2 IM q wk x 20 (wks 7-26)
IT MTX/ Ara-C	MTX/Ara-C (Dose by age) Wk 7, 10, 22
IT MTX/ Ara-C*	CNS (*) [POG CNS 2 & 3] Wk 16
XRT	1800 cGy to cranium (Begin week 22)
DZR	DZR 300 mg/m^2 IVP **pre-DOX**
HDM	5 gm/m^2. wks 7, 10, 13

CONTINUATION	
VCR	2 mg/m^2 q3wks (max 2.0 mg)
PDN	120 mg/m^2/day(in 3 divided doses) x 5 q 3 weeks
MTX	30 mg/m^2 weekly (max 40 mg) Omit wks 40, 58, 76, 94
6MP	50 mg/m^2/day x 14 q 3 weeks
IT MTX/ Ara-C**	MTX/Ara-C (Dose by age): Weeks 40, 58, 76, 94 ONLY

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APPENDIX IV
Cranial Radiation Therapy Boost

1.0 Equipment

1.1 Modality: X-ray beams with a nominal energy between 4 and 6 MV.

1.2 Calibration: The calibrations of therapy units used in this protocol shall be verified by the Radiological Physics Center.

2.0 Target Volume

2.1 Cranial Irradiation: The target volume consists of the entire brain and meninges, including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve superior to the vertex and posterior to the occiput. The caudal border shall be below the skull at the C2 vertebral level.

2.2 Localization: The planning target volumes shall be defined by means of simulator.

3.0 Target Dose

3.1 Prescription Point: The prescription point is in the center of the target volume.[1] For multi-convergent beams, the prescription point is usually at the intersection of the beam axes.

3.2 Dose Definition: The absorbed dose is specified as cGy-to-water.

3.21 Tissue heterogeneity: No corrections for attenuation shall be made. Institutions that customarily correct for heterogeneities must calculate monitor units or time of irradiation without this option.

3.3 Prescribed Dose and Fractionation:

3.31 The total dose to the prescription point shall be 1800 cGy in 9 fractions. The patient shall be treated with one fraction per day of 200 cGy.

3.4 Dose Uniformity: The variation of the dose shall be kept within +7% and -5% of the dose to the prescription point.[2] The cranial field shall extend sufficiently

[1] 1. This follows the recommendations of ICRU Report 50. If your institution's practice differs, a conversion may be necessary. For instance, if you prescribe to a certain isodose line, adjust this (departmental) prescription so that the (protocol) prescribed dose is given to the (protocol) prescription point. Contact QARC if assistance is needed.

[2] In accordance with ICRU Report 50, small high dose volumes can be excluded from the evaluation of the dose uniformity but not small low-dose volumes.

beyond the head so that the dose in the target volume is not affected by the decreased dose in the penumbrae.

3.5 Treatment Interruptions: No corrections shall be made for treatment interruptions less than seven days. For interruptions greater than seven days, please contact the radiation oncology coordinator.

4.0 Treatment Technique

4.1 Patient Position: The patient shall be treated in the supine position.

4.2 Beam Configuration: Equally weighted, opposing beams are recommended.

4.3 Field Shaping: The base of the field will extend from the supraorbital ridge, the lateral canthus of the orbit, through the tip of the mastoid process, which is 1.5 - 2 cm below the external auditory meatus back to the C1-C2 vertebral interspace. The field shall extend at least 1 cm beyond the periphery of the scalp. Any supplemental field-shaping should be done with divergent blocks at least 5 HVL thick, if required.

4.4 Eye Protection: A simple method to minimize lens irradiation, while irradiating the posterior halves of the eyes, is to let the central axes of the horizontal cranial beams go through both orbits. The anterior edges of the beams are defined by an external block or by an independently controlled collimator and meet at a point 1 cm anterior to the frontal lobe meninges. Shielding blocks over the anterior halves of the eyes and protect the nose and mouth.

5.0 Dose Calculations and Reporting

5.1 Prescription Point: The monitor units required to deliver the prescribed dose to the prescription points shall be calculated and submitted using the “RT-1 Dosimetry Summary” form.

5.2 Dose Uniformity: The maximum and minimum doses in the target volumes shall be calculated and reported on the “RT-Dosimetry Summary” form. These may be extracted from isodose diagrams or calculated separately.[3]

6.0 Quality Assurance Documentation

6.1 Within three days of the start of radiotherapy, the following data shall be submitted for on-treatment review.

6.11 Copies of simulation films for each field.

6.12 Copies of verification (portal) films for each field.

[3] The 50% decrement lines of a photon beam are defined as the lines passing through the points at each depth where the dose is 50% of the central Axis dose for each depth.

6.13 Photographs of the patient in the treatment position with the fields marked.

6.14 The "RT-1 Dosimetry Summary" form, for each target volume.

6.15 Copies of worksheets and/or printouts used for calculations of monitor settings to give the prescribed dose.

6.2 Within one week of the completion of radiotherapy, the following data shall be submitted.

6.21 Copies of additional simulation films and verification (portal) films for any major field modification made subsequent to the initial reporting of data for on-treatment review.

6.22 An "RT-1 Dosimetry Summary" form if changes have been made subsequent to submission of on-treatment data.

6.23 The "RT-2 Radiotherapy Total Dose Record" form.

6.24 A copy of the patient's radiotherapy record including the prescription, and daily and cumulative doses to all required areas and dose specification points.

6.25 Copies of calculations performed subsequent to the submission of the on-treatment data.

6.3 Data should be forwarded to T.J. Fitzgerald, MD. Any questions regarding dose calculation should be directed to the POG Protocol Dosimetrist. Questions regarding the radiotherapy section of this protocol should be directed to Ed Halperin, MD. (All addresses are located on page ii and iii.)

7.0 Definitions of Deviations in Protocol Performance

7.1 Prescription Dose

Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%.

Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%.

7.2 Dose Uniformity

Minor Deviation: the variation of dose in one of the target volumes exceed +7%, -5%, but is within $\pm$ 10%

Major Deviation: The variation of dose in one of the target volumes exceeds $\pm$ 10%.

7.3 Volume

Minor Deviation: Margins less than specified, or field(s) excessively large.

Major Deviation: Transecting tumor or potentially tumor-bearing area(s).

8.0 TESTES

8.1 EQUIPMENT

8.11 Modality: High-energy photon or electron beams. The selection of energy is determined by the dose uniformity criterion, and with electrons, the lowest possible energy should be used to spare tissues outside the target volume.

8.12 Calibration: The calibrations of therapy machines used in this protocol shall be verified by the Radiological Physics Center.

8.2 PLANNING TARGET VOLUME

The planning target volume consists of the testes in the scrotal sac. (N.B. Cremasteric reflex may move testes high up in the inguinal canal.)

8.3 TARGET DOSE

8.31 Prescription Point: The prescription point is at or near the center of the planning target volume[4].

8.32 Dose definition: The absorbed dose is specified as centigrays (cGy)-to-water.

8.33 Prescribed Dose and Fractionation: The total dose to the prescription point shall be 2400 cGy in 12 fractions. The patient shall be treated with one fraction per day of 200 cGy.

8.34 Dose Uniformity: The variations of dose within the planning target volume shall be within +7%, -5% of the dose to the prescription point[5]. The uniformity requirement can be in general be met with an electron beam of appropriate energy provided bolus is used, which is the simplest

[4] This follows the recommendations of ICRU Report 50. If your institution's practice differs, a conversion may be necessary. For instance, if you prescribe to a certain isodose line, adjust this (departmental) prescription so that the (protocol) prescribed dose is given to the (protocol) prescription point. Contact QARC if assistance is needed.

[5] In accordance with the ICRU Report 50, small high-dose volumes can be excluded from the evaluation of the dose uniformity but not small low-dose volumes.

technique. Bolus may also be needed for photon beams to fulfill the dose uniformity requirement.

8.35 Treatment Interruptions: No corrections shall be made for treatment interruptions less than seven days. For interruptions greater than seven days, please contact the radiation oncology coordinator.

8.4 TREATMENT TECHNIQUE

8.41 Patient Position: The patient shall be treated in the supine position.

8.42 Field-shaping: Field shaping can be done with blocks of at least 5 HVL thick.

8.5 NORMAL TISSUE SPARING AND DOSE SPECIFICATION POINTS

8.51 Perineum: The testes shall be supported posteriorly and, if possible, extended caudally in order to minimize perineal irradiation. The field shall not be angled towards the perineum.

8.52 Penis: The penis shall be excluded from the field by fixing it to the skin over the symphysis pubis.

8.53 Dose Specification Points: To ensure dose uniformity specified in section 5. The dose at two points shall be calculated and submitted with the Quality Assurance documentation.

Point A: 0.5 cm. from the anterior surface of the testes.

Point B: 0.5 cm. from the posterior surface of the testes.

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

8.6 DOSE CALCULATIONS AND REPORTING

8.61 Prescription Point: The monitor units or time of irradiation required to deliver the prescribed dose to the prescription points shall be calculated and submitted using the "RT-1 Dosimetry Summary" form.

8.62 Dose Uniformity: The maximum and minimum doses in the target volumes shall be calculated and reported on the "RT-1 Dosimetry Summary" form. These may be extracted from isodose diagrams or calculated separately.

8.63 Dose Specification Points: The daily dose to dose specification points shall be calculated and reported on the "RT-1 Dosimetry Summary" form. The total dose shall be calculated and reported on the "RT-2 Radiotherapy Total Dose Record"

8.7 QUALITY ASSURANCE DOCUMENTATION

8.71 Within three days of the start of radiotherapy, the following data shall be submitted for on-treatment review.

8.711 Copies of simulation films for each field.

8.712 Copies of verification (portal) films for each field.

8.713 Photographs of the patient in the treatment position with the fields marked.

8.714 The "RT-1 Dosimetry Summary" form, one for each target volume.

8.715 Copies of worksheets and/or printouts used for calculations of monitor settings to give the prescribed dose.

8.72 Within one week of the completion of radiotherapy, the following data shall be submitted.

8.721 Copies of additional simulation films and verification (portal) films for any major field modifications made subsequent to the initial reporting of data for on-treatment review.

8.722 An "RT-1 Dosimetry Summary" form if changes have been made subsequent to submission of on-treatment data.

8.723 The "RT-2 Radiotherapy Total Dose Record" form.

8.724 A copy of the patient's radiotherapy record including the prescription, and daily and cumulative doses to all required areas and dose specification points.

8.725 Copies of dose calculations performed subsequent to the submission of the on-treatment data.

8.73 The data should be sent to:

T. J. Fitzgerald, MD
Director
Quality Assurance Review Center
825 Chalkstone Avenue
Providence, RI 02908-4735
Telephone: (401) 456-6500
FAX: (401)456-6550

8.74 Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
Quality Assurance Review Center
825 Chalkstone Avenue
Providence, RI 02908-4735
Telephone: (401) 456-6500
FAX: (401) 456-6550

8.75 Questions regarding the radiotherapy section of this protocol should be directed to:

E.C. Halperin, MD
Box 3085
Duke University Medical Center
Durham, NC 27710
Telephone: (919) 660-2115
FAX: (919) 684-3953

8.8 DEFINITIONS OF DEVIATION IN PROTOCOL PERFORMANCE

8.81 Prescription Dose

8.811 Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%.

8.812 Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%.

8.82 Dose Uniformity

8.821 Minor Deviation: The variation of dose in one of the target volumes exceeds +7%, -5%, but is within ±10%.

8.822 Major Deviation: The variation of dose in one of the target volumes exceeds ±10%.

8.83 Volume

8.831 Minor Deviation: Margins less than specified, or field(s) excessively large.

8.832 Major Deviation: Transecting tumor or potentially tumor-bearing area(s).

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APPENDIX V

1.0 Late Cardiotoxicity associated with the Dana-Farber Cancer Institute (DFCI) Leukemia Studies

Long-term follow-up data was assessed on 79 of 115 previously reported patients with ALL who had been treated with doxorubicin [19]. Changes in left ventricular (LV) structure and function at three time points were compared: 1) before doxorubicin therapy; 2) at 6.4 years after doxorubicin [1]; and 3) at 11 years after doxorubicin. LV fractional shortening fell from normal at time 1 to significantly depressed at time 2, and stable (depressed) at time 3. LV mass and wall thickness were normal at time 1 and significantly abnormal at times 2 and 3 ($p=0.01$ and 0.03, respectively). LV end-diastolic dimension was normal for body surface area at times 1 and 2 and fell significantly at time 3 ($p=0.03$). LV afterload increased from time 1 to time 2 and remained stable at time 3. We conclude that bolus administration of doxorubicin resulted in a fall in LV dimension with increasing follow-up, a pattern seen in restrictive cardiomyopathy with a loss of capacity of the left ventricle to dilate. Restrictive cardiomyopathy has also been suggested by echocardiographic [3,20-23], hemodynamic and histopathologic data [24] in late anthracycline cardiotoxicity. Little is known about the cause, outcome, prevention, or treatment of restrictive cardiomyopathy, especially in children [25,26]. Few studies are under way because of the general lack of accessible pediatric patients. If the continuation of our study confirms that the long-term effects of doxorubicin are those of a restrictive cardiomyopathy, then we will be better able to delineate the natural history and prognosis of this type of heart disease and to apply potential therapies to reduce its incidence or progression.

Long-term cardiotoxicity in pediatric doxorubicin recipients at DFCI has two distinct forms: 1) depressed contractility, resulting from increased cumulative doxorubicin dose and female gender and 2) increased afterload resulting from decreased LV mass and wall thickness; this latter form of cardiotoxicity is related to length of follow-up, age at treatment, and the individual doxorubicin dose rate. Cardiotoxicity is also a function of the length of exposure to doxorubicin.

Little is known regarding risk factors for late cardiotoxicity. Female gender and higher individual doxorubicin dose (mg/m^2/dose) constituted independent risk factors for abnormalities of cardiac mechanics after doxorubicin treatment in childhood, at DFCI.[2] These factors were in addition to previously documented risk factors of cumulative dose and age at the time of doxorubicin treatment. Prevalence and severity of abnormalities of cardiac growth and mechanics increased with longer follow-up. The risk factors for abnormal contractility were different from those for reduced wall thickness and mass, and elevated afterload, suggesting separate mechanisms for these two forms of cardiotoxicity.

Determination of myocardial injury in children is important for the identification of, treatment, and prevention of myocyte damage, yet reliable and specific assessment of myocyte damage in children has been difficult. Acute myocardial toxicity will be measured clinically by echocardiography, ECG criteria, as well as by the determination of levels of cardiac troponin T(cTnT), a protein that is elevated after myocardial damage [10-18]. cTnT may be more sensitive than conventional measures of acute myocardial toxicity, such as echocardiography,

EKG, relatively non-specific enzymes (e.g. CPK), and the more recently reported "gold standard," creatine kinase (CK) MB isozyme [10-18]. cTnT is a thin-filament contractile protein that is released from damaged cardiomyocytes and is highly sensitive for the detection of acute myocardial infarction and unstable angina in adults. [10-12,15,18] Unlike CK-MB and myoglobin, cTnT is not found in serum from healthy people, thus facilitating the detection of the minor myocardial-cell injury that may occur in patients treated with doxorubicin.

Since cTnT has developmentally regulated protein isoform diversity, it has been determined that serum cTnT levels are detectable in children of different ages following myocardial injury from doxorubicin chemotherapy or cardiac surgery. DFCI initiated an investigation of acute myocardial toxicity associated with doxorubicin by evaluating 290 serial serum samples from 5 children receiving doxorubicin for ALL (median, 29 samples/patients; range, 3 to 33) and 17 children undergoing cardiac surgery (median, 3.3 samples/patient; range 2-9) [34]. The CARDIAC T ELISA assay (Boehringer Mannheim) was used to determine cTnT levels. Creatine kinase MB isoform (CK-MB) was also measured by an ELISA assay. All but six patients had no detectable cTnT before Doxorubicin treatment or surgery; these 6 were ill or instrumented. All patients, ranging in age from 1 day to 34 years old, had high level elevations of cTnT following surgery (median, 4.16 μg/L; range, 0.29 to >17.7μg/L). In this group, the serum cTnT rise related to the severity of surgery. Of the 15 doxorubicin-treated children, 6 out of 10 currently receiving doxorubicin showed low level cTnT elevations (5/10 $\geq$ 0.04 μg/L $\pm$0.02 μg/L.

2.0 ZINECARD (DZR) Background

Cardioprotection using DZR will be tested. In adult patients with breast cancer who were treated with DZR before doxorubicin, acute cardiotoxicity was reduced without affecting the antitumor effects of doxorubicin, thus permitting significantly larger doses of doxorubicin to be administered [4-6]. However, in an unpublished trial in women with advanced breast cancer treated with fluorouracil, doxorubicin and cyclophosphamide (FAC), the response rate was statistically significantly lower with dexrazoxane, according to the manufacturer, than with placebo. In addition, leukopenia, granulocytopenia and thrombocytopenia were more severe in patients who received dexrazoxane. [35] DZR was well tolerated in a Phase II trial in 21 children with solid tumors and 35 children with acute leukemia [7]. A pilot study of 5 children with recurrent malignancy were treated with anthracyclines after pretreatment with DZR or no pretreatment showed significant cardioprotection from DZR [8]. Another study of 33 pediatric patients with sarcoma suggested that DZR was cardioprotective during chemotherapy without compromising antitumor efficacy; however, long-term cardioprotective effect is unknown [9].

3.0 Biochemical Assessment of Myocardial Injury

For children at POG institutions, tests on sera for biochemical markers of cardiac injury will be performed at the Children's Hospital, in Boston. The performance of such laboratory tests has been conducted under a grant by Boehringer Mannheim Corp., the manufacturer of the cTnT ELISA assay, to Children's Hospital. This same grant will hopefully provide for the testing of all studies' sera. Specific tests include 1) total CK, 2) CK-MB isozyme, 3) cTnT, and 4) myoglobin.

3.1 Serum Sample Collection and Shipment

A minimum of 0.5 ml of serum must be obtained in order to run the cTnT assay. If samples are to be run for CK, CK-MB, myoglobin and cTnT, 1 ml of serum is required (i.e. 2 ml blood). Blood should be placed in a red top, vacuum tube; spun, then serum separated and frozen at -70 degrees Celsius. Each tube should be labeled with the patient's POG number, the date and time of the draw and the name of the individual POG institution. Batching samples for monthly shipment to Children's Hospital is recommended. Every sample in the shipment should be documented on the shipping log, containing the patient's POG identification number, the date and the time of the draw. The local institution should retain the original log, as it will be the means of confirming the contents of the shipment with Lab Control, in Boston. The shipping log and POG "Marker of Myocardial Injury" forms should be enclosed in a ziplock storage bag and included in the shipment. Neither this form nor laboratory results will be returned to the local institution. The samples must be placed on dry ice, the package marked accordingly and sent by express mail to M.E. Harrison-Cortizas (Lab Control). **(NOTE: All addresses are on pages ii and iii.)**

Lab Control should be notified before a shipment is sent and should be called the following day to confirm the arrival of the samples. After the shipment's arrival is confirmed, Lab Control will fax the express mail airbill to the local institution.

The form 'Markers of Myocardial Injury' should also be sent to the POG Statistical Office (See section 9.2 and Appendix VI).

4.0 Cardiac Assessment of Myocardial Injury

4.1 Echocardiogram

To maximize reliability of cardiac measurements obtained at multiple sites in this study, we will employ central remeasurement using computer digital analysis, employing the same methodology previously used to establish normative data in a normal control population.[27] The intent is to reduce interobserver variability, based on results of our past work which found that the reliability of multicenter echo measurement of left ventricular wall thickness and fractional shortening is poor in the absence of central remeasurement.[28] Analysis of echocardiographic studies will occur in the research echocardiogram digitizing facility at the University of Rochester under the supervision of Drs. Colan and Lipshultz. POG institutions are requested to send *original* tracings from the echocardiograms to the central research echocardiogram digitizing facility at the University of Rochester for remeasurement, even if only partial data collections are available. Statistical comparison of both local and central echocardiogram measurements will provide quality assurance and outliers will be queried both locally and centrally for discrepancies. For study analyses, central measurements will be used exclusively. The reference laboratory has experience in training centers on multicenter echocardiographic studies of HIV and myocarditis.[27-31] Data will be reported as z-scores to adjust for the effects of variation in age and body size.

Cardiac Anatomy: Full imaging from standard views should be done on one of the initial exams to exclude congenital heart disease. Subsequent exams are more focused to evaluate potential complications of therapy. In particular, the evaluation should address the presence of intracardiac mass, evidence of endocarditis, pericardial effusion, and valve dysfunction using standard methods. Patients with indwelling lines should undergo imaging of the length of the catheter for associated thrombus, stenosis, or obstruction.

Left Ventricular Systolic Structure and Function: M-mode assessment is invalid in the presence of abnormal left ventricular configuration, a critical decision which must be made at the time of exam. After assurance that short axis configuration of the left ventricle is circular throughout the cardiac cycle and qualitative assessment of regional wall motion abnormalities, data are obtained for assessment of function and if possible wall stress. Centers with experience and technical ability to perform the necessary measurements for wall stress analysis (tonometric pulse tracing, phonocardiogram, and non-invasive blood pressure) are requested to do so. Although complete measurements will not be possible in all instances and in all patients, **minimum required measurements in patients with normal left ventricular configuration include fractional shortening, dimension and thickness.**

Left Ventricular Diastolic Function: Evidence exists that left ventricular diastolic dysfunction may be important in doxorubicin cardiotoxicity.[3,20-23] Doxorubicin-treated ventricles do not dilate as much as is seen in other patients with a similar degree of depressed left ventricular dysfunction from other causes, suggesting a diminished ventricular compliance. Noninvasive assessment of left ventricular diastolic function will rely on indices derived from pulsed Doppler interrogation of the mitral valve and M-mode echocardiography.[32,33].

a) Equipment

High resolution ultrasound scanners employing 3.5 and 5.0, or 7.5 MHz frequency transducers with capabilities for pulsed Doppler, 2-D directed M-mode, ECG pulse and phono channels are recommended. Pulsed Doppler requirements include the ability for baseline shift and full spectral output. Hard copy capability for simultaneous 2-D directed M-mode, phono, pulse, and ECG are needed either in the form of a high quality trip chart recorder or a large format page printer. An indirect transducer (applantation tonometer), phonocardiogram, and automated blood pressure recorder are needed to obtain the data to calculate end-systolic wall stress.

All studies are recorded on 1/2" standard (or super) VHS recording transcribed and to standard 1/2" VHS videotape for record analysis and quality control. Tape studies are numbered with the examining center's initials, the preassigned POG code number for each patient recorded on the tape and clear reference to starting and ending times recorded.

b) Echocardiographic Methods

2-D and Doppler Exam: This portion of the exam is designed to detect masses associated with the heart and pericardial effusion, evaluate valve function and structural defects, and evaluate qualitatively regional left ventricular function. Valve morphology and function is assessed by imaging, spectral and color Doppler. Left ventricular regional wall motion is evaluated by scanning in parasternal long and short axis and apical 2 and 4 chamber views. Subxyphoid long and short axis views provide an alternative window in some patients.

Left Ventricular Function Exam: This part of the exam is designed to provide the physiologic data needed to calculate indices of ventricular function and to assess left ventricular loading conditions. The quality of the recording is highly dependent on the level of cooperation of the patient. It is uncommon for children below about three years of age to be able to cooperate sufficiently. It is usually necessary to sedate such patients.

High speed (100 mm/sec) stripchart hard copy or large format page printer of 2-D echo directed M-mode recordings of the left ventricular minor axis are obtained simultaneously with recordings of the electrocardiogram, phonocardiogram, indirect carotid or axillary pulse tracing, and peripheral blood pressure. Blood pressure is preferably obtained using an automated device such as the Dinamap Vital Signs Monitor. Centers without the capacity to obtain pulse and phonocardiographic recordings are asked to obtain strip chart or page print M-mode along with peripheral blood pressure. The following should be obtained:

1) Long and short axis views of the left ventricle from apex, left parasternal, and subxyphoid positions (in young patients) for documentation for regional wall motion abnormalities, calculation of LV mass and volume, and determination of circumferential stress. Technical note: Display the apical and subxyphoid images as they would be shown in an angiogram, that is, with the base of the heart on top, is preferred.

2) 2-D measurement of mitral diastolic (AP dimension from long-axis parasternal and lateral dimension from four-chamber apical) and aortic systolic (from long-axis parasternal) annulus sizes. Technical note: make 2 or 3 measurements during the study rather than on an off-line review station to avoid errors in scale entry and to enable use of the highest quality pictures. Zoom mode and cine loop mode is useful for those machines so equipped.

3) Pulsed Doppler just above the mitral and aortic valve annulus (from apical window) to document any valvular abnormalities a well as permitting calculation of Doppler outputs and Doppler indices of diastolic function. Phonocardiogram of the second heart sound (aortic valve closure) should be recorded if possible, to enable calculation of

isovolumic relaxation time. Technical note: Doppler should be recorded at 100 mm/sec paper speed, recording a simultaneous 2D image in large sector during the paper. The 2-D update trigger should be reduced to at least every 4-5 beats to allow at least 2 sequential beats to be recorded without blank space in the Doppler. Mitral sampling for diastolic indices is just apical to the level of the annulus, and is best achieved by using color Doppler to define the center of the inflow stream as the site of sampling during diastole.

4) Continuous wave Doppler just above the aortic valve (from high-right parasternal or suprasternal notch) with simultaneous recording of phonocardiogram, carotid pulse tracing, and automated blood pressure for calculation of left ventricular stroke volume, stroke work, and power. Centers without pulse recording capabilities are asked to record aortic Doppler alone. Technical note: As in #3, record on both media at high sweep speed. At least three blood pressure recordings are obtained, with the machine set to obtain recordings one per minute, preferably beginning before the data recording and continuing after.

5) 2-D directed M-mode is obtained from parasternal short axis and recorded at the minor diameter of the ellipse. Long axis imaging is performed first to assure that an angle of interrogation perpendicular to the long axis of the ventricle can be obtained. The transducer is then turned into the short axis at the same position to be certain that a true diameter of the circular short axis is taken. For those centers with pulse and phono capabilities, the M-mode is obtained simultaneously with electrocardiogram, phonocardiogram, pulse tracing, and automated blood pressure for calculation of left ventricular size, thickness, afterload, preload, contractility, and diastolic function indices. Technical note: As in #3, record on both media at high sweep speed and large 2-D sector size. Phono transducer filter and position is adjusted to optimize recording of aortic valve closure. At least four blood pressure recording are needed, preferably beginning before the data recording and continuing after (see below).

c) Blood Pressure Measurement

Blood pressure (BP) will be obtained simultaneously with function assessment or immediately thereafter in sedated and non-sedated patients. Recognizing that not all centers will perform wall stress measurements, physicians, nurses and technicians are strongly encouraged to nevertheless record blood pressure at the time of function assessment. If the patient moves, wakes up, or changes position, the hemodynamic conditions may change and effect the results of the final analysis. To facilitate this recording, the BP cuff should be applied to the patient at the beginning of the study. Monitor accuracy is dependent on use of proper cuff size.

Cuff Type	Range
Infant	8-11 cm
Child	12-16 cm
Small Adult	17-22 cm
Adult	23-33 cm

Position the artery mark on the cuff on the patient's artery before inflation. Four BP measurements will be taken simultaneously or immediately following the assessment of function. The first measurement will be excluded. The average of the remaining three BP measurements is then used.

1.0 OBJECTIVES

1.1 Primary Objectives

a. To determine, in a randomized trial, the effectiveness of high dose methotrexate (HD MTX) when added to a multi-agent chemotherapy backbone (DFCI 87-001) proven effective in T-Cell acute lymphoblastic leukemias (T-ALL) and advanced stage non-Hodgkin's lymphoma (Lymphoblastic NHL).

b. To determine, in a randomized trial, the role of the cardioprotectant Zinecard (DZR) in preventing cardiotoxicity in children with T-ALL and advanced stage Lymphoblastic NHL receiving an anthracycline based regimen.

1.2 Secondary Objectives

a. To study the biology of T-Cell lymphoid malignancies by accumulating data on the concurrent ALL classification study (POG 9900) and analyzing the data relative to outcome.

b. To evaluate the correlation of minimal residual disease with event-free survival utilizing the *TAL 1* proto-oncogene.

c. To determine the role of p53 and p16 tumor suppressor genes in T-ALL.

d. To determine if drug sensitivity profiles of blasts cells to Doxorubicin, methotrexate and cytarabine correlate with initial response and subsequent development of relapse.

2.0 BACKGROUND

2.1 Origin of the T-3 Study

T-Cell lymphoid malignancies have distinct biochemical, immunologic and clinical features which set them apart from non-T lymphoid malignancies.[1-3] The diagnosis of T-ALL portends a worse prognosis than most forms of non-T childhood ALL.[3-5]

Both *in vitro* and *in vivo* pharmacologic data have shown that T-Cell blasts respond differently to certain chemotherapeutic agents.[6-7] Utilizing this knowledge, new treatment strategies have been designed to exploit the characteristic differences in cell kinetics, drug sensitivity and biological properties of T-Cell disease which have improved the outlook for these high-risk patients. These regimens have in common intensive, high-dose multi-agent pulse chemotherapy, and have significantly improved event-free survival among patients with T-ALL from 15-20% to 40-60%.[8-9] The malignant cells from patients with Lymphoblastic NHL are very similar to T-ALL blasts. Similar strategies utilizing high doses of rotating chemotherapeutic agents have also been successful in treatment of patients with Lymphoblastic NHL.[10-12] It therefore seems reasonable to treat patients with advanced T-Cell malignancies on a common chemotherapy regimen which utilize drug combinations that have demonstrated efficacy in a variety of ongoing or previous protocols.