Medical and Pediatric Oncology 29:526–533 (1997)

Fractionated Cyclophosphamide and Back to Back High Dose Methotrexate and Cytosine Arabinoside Improves Outcome in Patients With Stage III High Grade Small Non-Cleaved Cell Lymphomas (Snccl): A Randomized Trial of the Pediatric Oncology Group

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Background. The Pediatric Oncology Group (POG) conducted a two-arm, randomized study for the treatment of children and adolescents with stage III small, non-cleaved cell lymphoma (SNCCL). Regimen A, based on the group's previous best treatment for this group of patients, included cyclophosphamide (CTX) and high-dose methotrexate (MTX), as well as vincristine (VCR), prednisone (PRED), and intrathecal (IT) chemoprophylaxis. Regimen B, based on a single institution pilot study (Total B therapy), consisted of two rapidly alternating chemotherapy combinations (CTX, VCR, doxorubicin; MTX, and cytarabine (Ara-C) plus coordinated IT chemotherapy.

Procedure. One hundred thirty-four consecutive patients were entered on this study. Seventy patients were randomized to Regimen A, and 64 patients to Regimen B. One hundred and twenty-two patients are eligible for response.

Results. Complete remission (CR) was achieved by 81% (52/64) of patients on Regimen A, and 95% (55/58) of patients on Regimen B (p = 0.014 one-sided). The two-year event-free survival (EFS) is 64% (SE = 6%) on Regimen A, and 79% (SE = 6%) on Regimen B (p = 0.027 by one-sided logrank test). No patient has relapsed on either regimen after a year from diagnosis, although one patient had a second malignancy at day 371. Severe, but manageable, hematologic toxicity was seen in the majority of patients on both regimens, but was more frequent on Regimen B.

Conclusions. We conclude that the cure rate in stage III SNCCL is significantly improved with the use of a short, six-month chemotherapy regimen of fractionated CTX alternated with coordinated MTX and Ara-C. Results suggest that drug schedule, not simple drug selection, influences outcome. Med. Pediatr. Oncol. 29:526–533, 1997.

Key words: fractionated cyclophosphamide; high-dose methotrexate; small non-cleaved cell lymphoma; dose intensification

INTRODUCTION

High-grade small non-cleaved cell lymphomas (SNCCL) are characterized by extranodal tumors usually affecting the abdominal, pelvic, and/or retroperitoneal viscera. As with many other malignancies, outcome in SNCCL is influenced by extent of disease. While 80–90% of patients presenting with localized SNCCL (Murphy stage I and II) are cured, even with treatments of the late 70's, disease-free survival (DFS) for those with advanced-stage disease (Murphy stage III or IV) has historically been <50%. More recently however, regimens that included CTX and high-dose MTX with leucovorin rescue, in addition to other chemotherapeutic agents, enabled the vast majority of patients to achieve remission. This progress resulted in a 69% event-free survival (EFS) for patients with stage III SNCCL treated on a six-month, five-agent regimen, POG protocol (#8106), conducted between January 1982 and October 1986 [1].

At approximately the same time, investigators led by Murphy piloted a novel regimen referred to as ''Total B'' therapy [2]. The strategies employed in this innovative study included fractionated doses of CTX alternated with escalating high doses of intravenous cytarabine and in-

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Contract grant sponsor: National Institutes of Health, National Cancer Institute; Contract grant numbers: CA 28383, CA 41573, CA 33625, CA 33603, CA 31566, CA 29139, CA 30969.

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Received 23 October 1996; Accepted 9 April 1997

TABLE I. Patient Characteristics at Presentation

	Regimen A	Regimen B
Median Age (Years)	9.0	8.5
Sex		
Males	58	48
Females	7	10
Primary Site		
Abdomen	61	53
Head/Neck	2	4
Mediastinum	2	1
Median LDH (IU/L)	806	898

termediate dose MTX coordinated with intrathecal (IT) therapy. CTX was fractionated with the goal to encompass the generation time of the tumor, as well as to provide a smoother induction with fewer metabolic complications. In addition, the Total B regimen included an early switch to non-cross resistant antimetabolites, each given by infusion to catch rebounding cells entering S phase, to penetrate extramedullary sites, and to promote synergistic drug effects. This single institution study resulted in a DFS rate of 85% for 26 patients with stage III disease [2].

In an attempt to improve outcome in children with stage III SNCCL, investigators of the POG proposed to evaluate the ''Total B'' therapy in a prospective randomized multicenter trial (POG #8616). Here we report a significant superiority of the Total B regimen and cure of eight out of ten children and adolescents with stage III SNCCL.

MATERIALS AND METHODS

Patients

Between October 1986 and November 1991, 134 consecutive newly diagnosed patients under the age of 21 years were entered into this multi-institutional cooperative group trial after informed consent was obtained. Pathology was confirmed by central review, as diffuse, undifferentiated NHL, small, non-cleaved cell (Burkitt or non-Burkitt), and all had stage III disease, according to the staging system described by Murphy [3].

Most patients had extensive primary intra-abdominal disease, and many had ascites and pleural effusions.

After central pathology review, 11 of the 134 registered patients were deemed ineligible, leaving 123 patients eligible for study. The median age of patients was 8.6 years (ranging from 2.3–20.2 years). There were 106 males and 17 females (Table 1).

Staging Studies

Patients were staged with a thorough physical examination, hematologic evaluation, examination of a percutaneous bone marrow aspiration and biopsy, cerebrospinal fluid (CSF) examination, including a search for tumor cells on a cytocentrifuged smear, chest radiogram, and a computerized axial tomography scan to delineate areas of primary tumor involvement. Gallium and bone scanning were not mandatory. Cytogenetic and immunophenotypic studies, performed at the local institutions, were encouraged, but not mandatory.

Treatment

All patients were randomized to receive either Regimen A or Regimen B (Figures 1 and 2). Investigators were encouraged to initiate therapy expeditiously, within 72 hours of admission, to provide adequate hydration and alkalinization, and to control elevated serum uric acid levels with allopurinol.

Patients on Regimen A (Figure 1) underwent a one-month induction with high-dose CTX (day 1), MTX (days 24 and 31), VCR (weekly for five weeks) and daily oral prednisone (PRED) for 28 days. Subsequently, they received consolidation chemotherapy for 22 weeks: CTX on days 52 and 102 and high-dose MTX on days 74, 81, 124, and 131. VCR was given one hour prior to each high-dose MTX. Finally, during maintenance therapy (11 weeks), VCR and high-dose MTX were given on days 174 and 216. Central nervous system (CNS) prophylaxis on Regimen A included doses of intrathecal (IT) Ara-C on days 0, 1, 21, and 22, and IT MTX on days 3 and 23. IT MTX, Ara-C and hydrocortisone, referred to as TIT, was given on days 45, 73, 102, 123, 173, and 215. Thus, IT therapy was coordinated with high-dose MTX on five occasions in an effort to maintain therapeutic levels of MTX in the CSF for at least 48 hours.

Patients on Regimen B (Figure 2) first received fractioned CTX with VCR and doxorubicin (DOX) during induction (or primary phase). Then, as soon as mucosal recovery and returning marrow function (as evidenced by an absolute phagocyte count of $\geqslant$500 per microliter and a platelet count of $\geqslant$100,000 per microliter) were documented, sequential continuous infusions of MTX and Ara-C were administered (infusion phase). A course of therapy was defined as one cycle each of the primary and infusion phase. A total of four courses of therapy was given to each patient randomized to Regimen B, with the dosage of the Ara-C being doubled with each succeeding course from an initial dose of 400 mg/m^2 to a maximum of 3.2 gm/m^2. IT MTX and Ara-C were given on two occasions during the initial induction course (days 1 and 4) and one (day 1) with each subsequent course.

All therapy was completed within seven months on both Regimens A and B. Second-look laparotomy was

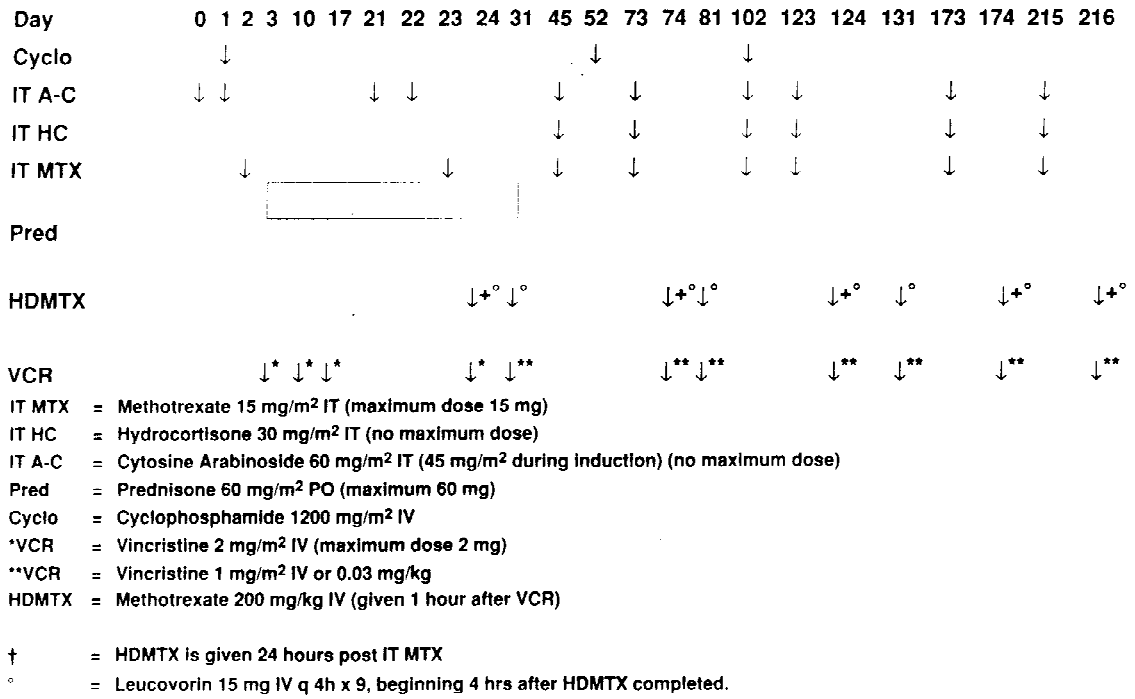

Fig. 1. Treatment Schema Regimen A.

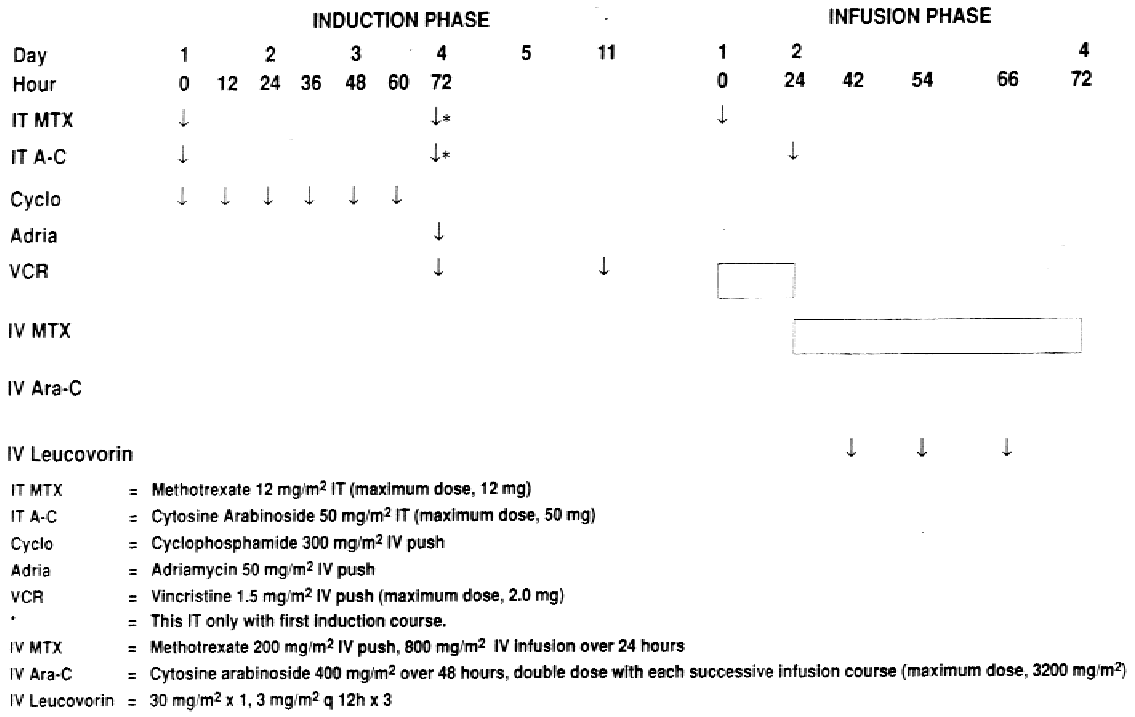

Fig. 2. Treatment Schema Regimen B.

discouraged except to confirm persistent disease before removing patients from study. No patients received radiotherapy. As of 1988, all patients received trimethoprim-sulfamethoxisole three days per week for prophylaxis against *Pneumocystis carinii* infection. Hematopoietic growth factors were not utilized.

Evaluation Criteria

Intent to treat was utilized in all our analyses [4]. EFS, the primary endpoint of this study, was measured from the time of initial therapy. An event was defined as induction death, progressive disease, relapse, death in re-

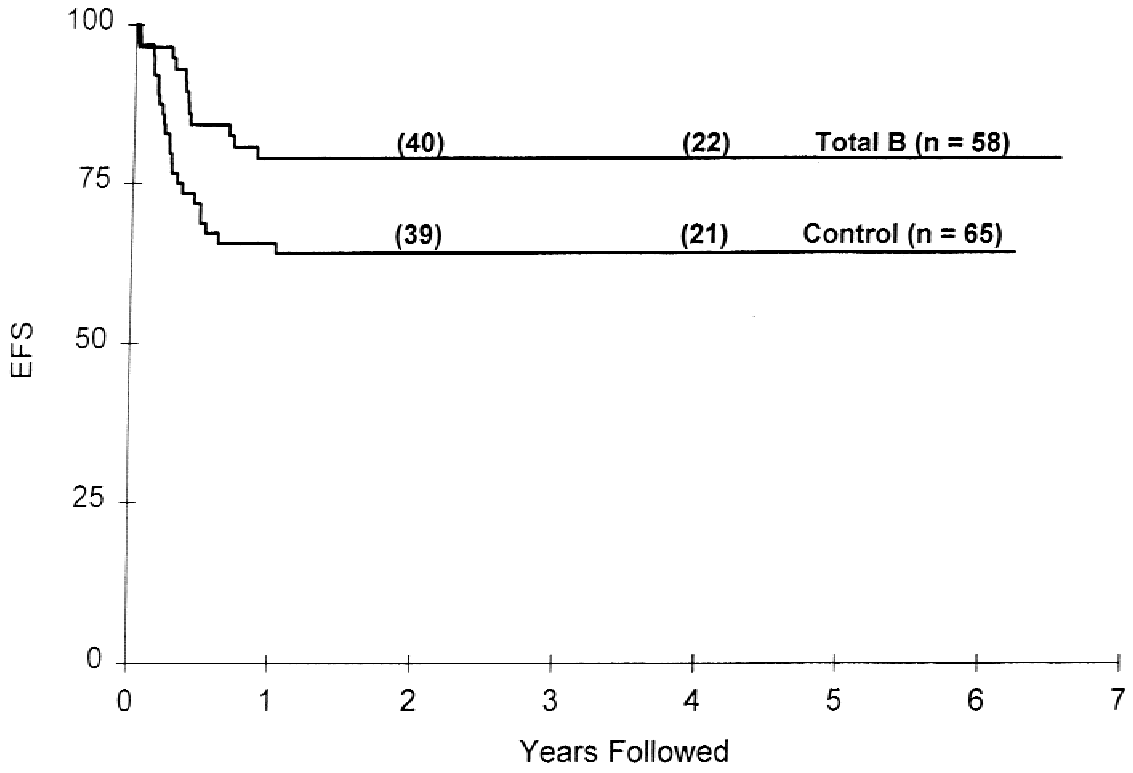

Fig. 3. Event-free survival (EFS) for patients treated on the control arm (Regimen A) and total B therapy (Regimen B). EFS was measured from time of initial therapy, utilizing the logrank method. EFS was superior for patients on total B therapy ($P = 0.027$).

mission, or second malignancy. Patients who did not have an adverse event were censored at last contact. A secondary goal of this study was to evaluate response. Complete response (CR) was defined as the disappearance of all evident disease by physical examination and appropriate imaging studies. In addition, pleural and peritoneal fluid collections had to be resolved and patients had to have recovered from treatment-induced mucosal and bone marrow toxicities. Response was evaluated after induction. Patients with small residual masses after induction who were felt to be free of tumor by clinical and biochemical parameters were designated as being in ''provisional CR'', and continued on study unless there was histopathologic evidence of persistent lymphoma or subsequent tumor progression. An analysis of treatment toxicities and prognostic factors is also included.

STATISTICAL CONSIDERATIONS

Our design called for a one-sided test asking if Total-B therapy (Regimen B) was superior to the control therapy (Regimen A) carried from POG 8106. Based on a proportional hazards model, a study of 123 eligible patients has at least 80% power [4] to detect a 20% improvement in EFS from 65% (historical control), at $P = 5\%$, one-sided. The power to detect a 15% improvement is at least 58%. The power numbers are exact if failure after two years is deemed impossible, and is higher if such failures can occur. The logrank test [5] was specified for use in the protocol.

Comparisons of EFS and survival utilized the logrank method [5], while comparison of achievement of a complete response was conducted by the exact unconditional Z-test [6]. These comparisons were one-sided, as specified in the protocol. Toxicity was compared by two-sided exact unconditional Z-tests.

Prognostic factors were studied univariately by the stratified logrank test [5], post stratifying for treatment. A Cox forward stepwise analysis [7] was also conducted with treatment forced into the model. Actuarial EFS curves were constructed by the method of Kaplan-Meier [8] with standard errors of Peto and co-workers [9]. Finally, a second look at the EFS comparison, stratified for factors found in the Cox analysis, was taken.

RESULTS

Sixty-five patients were randomized to Regimen A, and 58 patients to Regimen B. One patient (Regimen A) refused therapy one day after registration. The cut-off date for analysis was October 20, 1994.

CR and EFS

One hundred and seven patients achieved CR, for an overall CR rate of 88% (Table II). CR was obtained by

TABLE II. Treatment Comparison

	Regimen A			Regimen B			
	N	Failed	Expected	N	Failed	Expected	*P*-Value
Achieve CR[a]	64	12	7.9	58	3	7.1	.014
EFS[b]	65	23	17.3	58	12	17.7	.027***
Survival[b]	65	19	16.0	58	12	15.0	.14

[a]One patient was inevaluable for response. One sided exact unconditional Z-test was employed.
[b]By one-sided logrank test.
***P-value, stratified for LDH over vs under 500; $p = .012$.

52/64 (83%) of patients on Regimen A, and 55/58 (95%) of patients on Regimen B ($P = 0.014$). The two-year EFS was 64% (SE = 6%) and 79% (SE = 6%) for patients on Regimen A and B respectively ($P = 0.027$) (Fig. 3).

Relapse

All 19 patients who relapsed after achieving CR (ten randomized to Regimen A, and nine to Regimen B) did so within one year of diagnosis. Local recurrence accounted for 6/10 relapses on Regimen A, and 7/9 relapses on Regimen B, while primary bone marrow relapse was noted in four patients on Regimen A, but none on Regimen B. Only two patients (<5%) experienced first relapse in the CNS, both treated on Regimen B.

Prognostic Factors

No prognostic significance was found for sex, race, age, presenting white blood cell count, or the presence of pleural effusions (Table III). However, patients presenting with an LDH level of >500 IU/L fared significantly worse than those with an initial LDH ⩽500 IU/L ($P = 0.01$) (Table III). Treatment arm and LDH at presentation retained prognostic significance in multivariate analysis (Table III).

Toxicity

Four patients suffered early death during induction therapy. One patient, on Regimen A, died of septic shock on day 10 of therapy, and one died with pneumonia on day 10. Two patients on Regimen B died of metabolic complications secondary to tumor lysis syndrome (one on day 3, and one on day 7 of therapy). Four additional patients required dialysis for reversible renal failure due to tumor lysis syndrome.

As expected, the most frequent and predictable toxicity was hematopoietic, which was nearly universal. Grades 3 and 4 hematologic toxicities were noted for 74% of patients on Regimen A and 97% of patients on Regimen B ($P < 0.001$). Regimen B also resulted in a significantly higher rate of grades 3 and 4 infectious complications (81% vs 51%, $P = <.001$) and stomatitis (19% vs 6%, $P = <.035$). Regimen A on the other hand, was shown to be more neurotoxic (17% vs 5%, $P = .042$), although persistent neurologic impairment has not been encountered on either arm.

DISCUSSION

Over the past decade, several studies have reported encouraging results in the treatment of advanced stage childhood B-cell lymphomas [1,10–18]. Some of these reports involve small numbers of patients, often from a single institution, and therefore require confirmation in multicenter trials. Our results are comparable to those reported. For example, Schwenn et al [10], reported a two-year actuarial EFS rate of 75% in 20 patients with stage III and IV Burkitt lymphoma or B-cell acute lymphoblastic leukemia (ALL) treated with a two-month chemotherapy regimen utilizing intensive CTX, high-dose MTX, high-dose Ara-C, and VCR. Finlay et al [12], utilizing an eight-drug regimen for 48–84 weeks, reported an EFS of 76.7% in 30 children and adolescent patients with ''poor prognosis'' non-lymphoblastic lymphoma, including both SNCC and large cell histologies.

In a non-randomized multicenter study organized by the Children's Cancer Group (CCG), 68 children with disseminated, non-lymphoblastic lymphoma were treated with a cyclic chemotherapy regimen including CTX, VCR, DOX, and PRED (CHOP) plus IT chemotherapy. This resulted in an EFS rate of 86% for patients with stage III SNCCL and serum LDH ⩽500 IU/L. However, EFS was only 39% for those with either stage III disease and LDH >500 IU/L, stage IV patients or B-ALL [17]. The Berlin-Frankfurt-Munster (BFM) Group, utilizing a regimen consisting of dexamethasone, MTX, and IT therapy in each course, plus ifosfamide, Ara-C and etoposide alternating with CTX and DOX [18] reported an EFS of 79% for stage II patients (not resected) and stage III patients. The French Pediatric Oncology Society (SFOP) utilized high-dose fractioned CTX, high-dose MTX, and continuous infusion Ara-C, as well as VCR, DOX, and PRED with patients randomized to either four months or seven months of treatment, and reported an overall EFS for 167 patients with stage III disease of 80% [11]. Finally, the United Kingdom Children's Cancer Study Group (UKCCSG) treated 44 patients with stage III disease on either an eight-drug modified CHOP regimen, utilizing standard dose chemotherapy or a more dose-intensive five-drug regimen similar in design to the ''Total B'' regimen of POG 8616 [14]. Chemotherapy in the UKCCSG study was completed within six months. An overall actuarial EFS of 76% was obtained, with no difference between the two (eight vs five-drug) treatment groups. However, since patients were not randomly assigned to either regimen, it is difficult to assess the role of either drug schedule or dose intensity in the UKCCSG study.

TABLE III. Univariate Prognostic Factors for EFS

	Negative			Positive			
Factor	N	Failed	Expected	N	Failed	Expected	*P*-Value*
Female	106	32	30.0	17	3	5.0	.33
Black Race	113	33	31.9	10	2	3.1	.52
LDH > 500	31	3	9.7	85	29	22.3	.010
LDH > 1000	62	17	17.5	54	15	14.5	.85
WBC > 1000	77	22	22.0	45	12	12.0	.99
Pleural Effusion	83	20	22.5	38	13	10.5	.34
Age > 5.00 Yrs	27	5	7.3	96	30	27.7	.33
Age > 10.00 Yrs	75	21	21.8	48	14	13.2	.79

*By two-sided log rank test, stratified for treatment.

	Cox Stepwise Analysis[a] Forcing Treatment in the Model	
Adverse Variable	Estimated Hazard Ratio[b]	95% Confidence Limits
Treatment A	260%	115%–587%
LDH > 500	425%	129%–1411%

[a]No other variable entered model at $P < .05$.
[b]A hazard ratio estimate of 260% means that we estimate that the instaneous risk of failure under the adverse factor is 260% of that under the favorable factor.

POG 8616 was designed to prospectively compare the best arm of the previous POG study (8106) (1) with ''Total-B'' therapy, a regimen piloted from 1981 to 1985 at St. Jude Children's Research Hospital (SJCRH) (2). Comparison of the regimens shows a significantly better remission rate and EFS for Total-B. The superior EFS for Total-B, may, at least in part, be attributed to the recommendation to commence each chemotherapy cycle as soon as marrow recovery from the previous cycle was confirmed, rather than administering the drugs at fixed time intervals. The dose intensification undoubtedly also resulted in the significantly higher rate of hematologic toxicity and febrile episodes. The superior EFS on Total-B was primarily due to the significantly higher induction rate, suggesting that Total-B therapy provides superior initial cytoreduction critical to the likelihood of cure.

Only two of the 107 patients who achieved CR suffered an isolated CNS recurrence, suggesting that the combination of intensive IT prophylaxis and infusions of MTX and/or Ara-C, which penetrate the CNS, is highly effective in preventing meningeal spread of lymphoma in patients who do not have CNS (or bone marrow) involvement at diagnosis.

The prognostic importance of tumor burden as evidenced by LDH level at presentation, was confirmed. Other than treatment assigned and LDH, we were unable to identify other prognostic variables within this group of stage III patients.

The data reported here confirm, in a large randomized multi-institutional trial, that eight out of ten young patients with stage III SNCCL can be cured with a short (six month) intensive chemotherapy regimen. Based on these results, and that of other investigators [10], we intend to further reduce treatment duration. Further dose intensification, and the addition of other effective agents, such as ifosfamide and etoposide, combined with the use of hematopoietic growth factors, may improve survival for patients with stage III SNCCL beyond that reported in this study, and is the subject of further randomized trials in our group.

CONCLUSION

''Total-B'' therapy, which included fractionated CTX, VCR, and doxorubicin, alternating with back-to-back high-dose MTX and Ara-C, plus IT chemotherapy, was superior to the POG's previous best regimen for the treatment of children and adolescents with stage III SNCCL. Both regimens were effective in preventing CNS relapse. The prognostic importance of tumor burden, as evidenced by LDH level at presentation, was confirmed. Approximately 80% of pediatric patients with stage III SNCCL can be cured with the short, intensive ''Total-B'' regimen.

ADDENDUM

Following completion of this manuscript, a single patient on Regimen B has suffered a late recurrence at the primary tumor site 46 months after achieving CR. Although one cannot be certain that this is not a second

malignancy, the histology is unchanged from that at initial diagnosis.

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APPENDIX

INSTITUTION	GRANT NO.
Alberta Pediatric Oncology Consortium, Edmonton, Canada	
All Children's Hospital, St. Petersburgh, FL	
Baylor College of Medicine, Houston, TX	CA-03161
Bowman Gray School of Medicine, Winston, Salem, NC	CA-53128
Cancer Center of Hawaii, Honolulu, HI	
Carolinas Medical Center, Charlotte, NC	CA-69177
Children's Hospital and Health Center, San Diego, CA	CA-28439
Children's Hospital Greenville Health System, Greenville, SC	CA-69177
Children's Hospital of Michigan, Detroit, MI	CA-29691
Children's Hospital of New Orleans, LA	
Cook-Ft. Worth Children's Medical Center, Ft. Worth, TX	CA-33625
Cross Cancer Institute, Alberta, Canada	
Dana-Farber Cancer Institute, Boston, MA	CA-41573
Duke University, Durham, NC	CA-15525
Emory University School of Medicine, Atlanta, GA	CA-20549
Fairfax Hospital, Falls Church, VA	CA-28476
Hackensack Medical Center	
Johns Hopkins University, Baltimore, MD	CA-28476

(*Cont'd.*)

INSTITUTION	GRANT NO.
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Medical College of Virginia, Richmond, VA	
Miami Children's Hospital, Miami, FL	
Midwest Children's Cancer Center, Milwaukee, WI	CA-32053
Mount Sinai School of Medicine, New York, NY	CA-69428
Ochsner Clinic, New Orleans, LA	
Oklahoma University Health Sciences Center, Oklahoma City, OK	CA-11233
POG Operations Office, Chicago, IL	CA-30969
POG Statistical Office, Gainesville, FL	CA-29139
Roswell Park Memorial Institute, Buffalo, NY	CA-28383
Sacred Heart Children's Hospital, Pensacola, FL	
San Jorge Children's Hospital, Santure, PR	
Scott & White Memorial Hospital, Temple, TX	CA-33625
Stanford University Palo Alto, CA	CA-33603
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Swiss Pediatric Oncology Group, Lausanne	
Swiss Pediatric Oncology Group, Bern Switzerland	
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University of Florida, Gainesville, FL	
University of Groningen, Groningen, Netherlands	
University of Kansas, Kansas City, MO	
University of Miami School of Medicine, Miami, FL	
University of Mississippi Medical Center, Jackson, MS	CA-15989
University of Missouri, Columbia, MO	CA-05587
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University of Rochester Medical Center, Rochester, NY	
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University of Texas-Southwestern Medical School, Dallas, TX	CA-33625
University of Vermont College of Medicine, Burlington, VT	CA-29293
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Warren Clinics, Inc., Tulsa, OK	CA-11233
Washington University School of Medicine, St. Louis, MO	CA-05587
West Virginia University Health Science Center, Charleston, WV	CA-15525
West Virginia University Health Services Center, Morgantown, WV	CA-15525
Wichita CCOP (St. Francis)	
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