

TREATMENT OF CHILDREN AND YOUNG ADULTS WITH EARLY-STAGE NON-HODGKIN'S LYMPHOMA

MICHAEL P. LINK, M.D., JONATHAN J. SHUSTER, PH.D., SARAH S. DONALDSON, M.D., COSTAN W. BERARD, M.D.,
AND SHARON B. MURPHY, M.D.

ABSTRACT

Background Children and young adults with early-stage non-Hodgkin's lymphoma have an excellent prognosis, but treatment is prolonged and is associated with many side effects. We performed two studies to determine whether therapy could be simplified.

Methods Between 1983 and 1991, we conducted two consecutive trials in children and young adults (age, <21 years) with early-stage non-Hodgkin's lymphoma. In the first trial, patients were treated for 9 weeks with induction chemotherapy consisting of vincristine, doxorubicin, cyclophosphamide, and prednisone, followed by 24 weeks of continuation chemotherapy with mercaptopurine and methotrexate. Half the patients were randomly assigned to receive involved-field irradiation. In the second trial, after the 9 weeks of induction chemotherapy, the patients were randomly assigned to receive 24 weeks of continuation chemotherapy or no further therapy.

Results A total of 340 patients were enrolled in the two trials, 12 of whom did not have complete remissions. One hundred thirteen patients received nine weeks of chemotherapy without radiotherapy, 131 received eight months of chemotherapy without radiotherapy, and 67 received eight months of chemotherapy with radiotherapy. At five years, the projected rates of continuous complete remission were 89, 86, and 88 percent for the three groups, respectively. At five years, event-free survival among the patients with early-stage lymphoblastic lymphoma was inferior to that among the patients with other subtypes of lymphoma (63 percent vs. 88 percent, $P < 0.001$). Continuation therapy was effective only in patients with lymphoblastic lymphoma.

Conclusions A nine-week chemotherapy regimen without irradiation of the primary sites of involvement is adequate therapy for most children and young adults with early-stage, nonlymphoblastic non-Hodgkin's lymphoma. (N Engl J Med 1997;337:1259-66.)

©1997, Massachusetts Medical Society.

THE improvement over the past two decades in the outcome for children and young adults with non-Hodgkin's lymphoma is one of the success stories of pediatric oncology. Nearly three fourths of all children and young adults with this disease who undergo current therapeutic regimens are cured, including most of those who present with local or regional (early-stage)

disease confined to sites associated with a favorable prognosis.¹⁻⁷

Because of a desire to spare young patients with early-stage non-Hodgkin's lymphoma from the adverse acute and late effects of therapy, we conducted two consecutive studies designed to maintain the high cure rate while reducing the intensity and duration of therapy. The first trial demonstrated that an eight-month chemotherapy regimen without irradiation of the primary sites of involvement was as effective as chemotherapy plus radiotherapy.⁶ The second trial was designed to determine whether six months of continuation treatment with two drugs is a necessary component of the regimen. We report the results of this study, as well as the updated results of the first trial.

METHODS**Patients**

Children and young adults were enrolled in the first trial between April 1983 and May 1987 and were enrolled in the second trial between June 1987 and November 1991 at all institutions that are members of the Pediatric Oncology Group (see the Appendix). Previously untreated children and adults younger than 21 years of age who had biopsy-confirmed non-Hodgkin's lymphoma of any histologic type were eligible for enrollment.

Studies and procedures performed to determine the stage of disease included a history taking and physical examination, blood counts, bone marrow aspiration, lumbar puncture for examination of a cytocentrifuged specimen of cerebrospinal fluid, chest radiography, and radionuclide bone scanning. Additional studies, including computed tomography or magnetic resonance imaging, were performed in some patients, particularly those with primary tumors in the head and neck region or abdomen. The clinical stage was determined according to a staging system described previously.⁸ Patients meeting the criteria for early-stage disease were eligible for the trials. Specifically, eligible patients were those who had stage I disease, with lymphoma confined to a single nodal or extranodal area (whether resected or not), or stage II disease, with a single tumor and regional lymph-node involvement, two or more sites of disease confined to one side of the diaphragm, or lymphoma of the gastrointestinal tract that had undergone grossly complete (>90 percent) resection. Excluded were patients with more advanced

From the Departments of Pediatrics and Radiation Oncology, Stanford University School of Medicine and the Lucile Salter Packard Children's Hospital, Stanford, Calif. (M.P.L., S.S.D.); the Department of Statistics, University of Florida, and the Pediatric Oncology Group Statistical Office, Gainesville, Fla. (J.J.S.); the Department of Pathology, Saint Jude Children's Research Hospital and the University of Tennessee, Memphis (C.W.B.); and the Department of Pediatrics, Northwestern University School of Medicine and Children's Memorial Hospital, Chicago (S.B.M.). Address reprint requests to Dr. Link at the Department of Pediatrics, Stanford University School of Medicine, 300 Pasteur Dr., Stanford, CA 94305-5208.

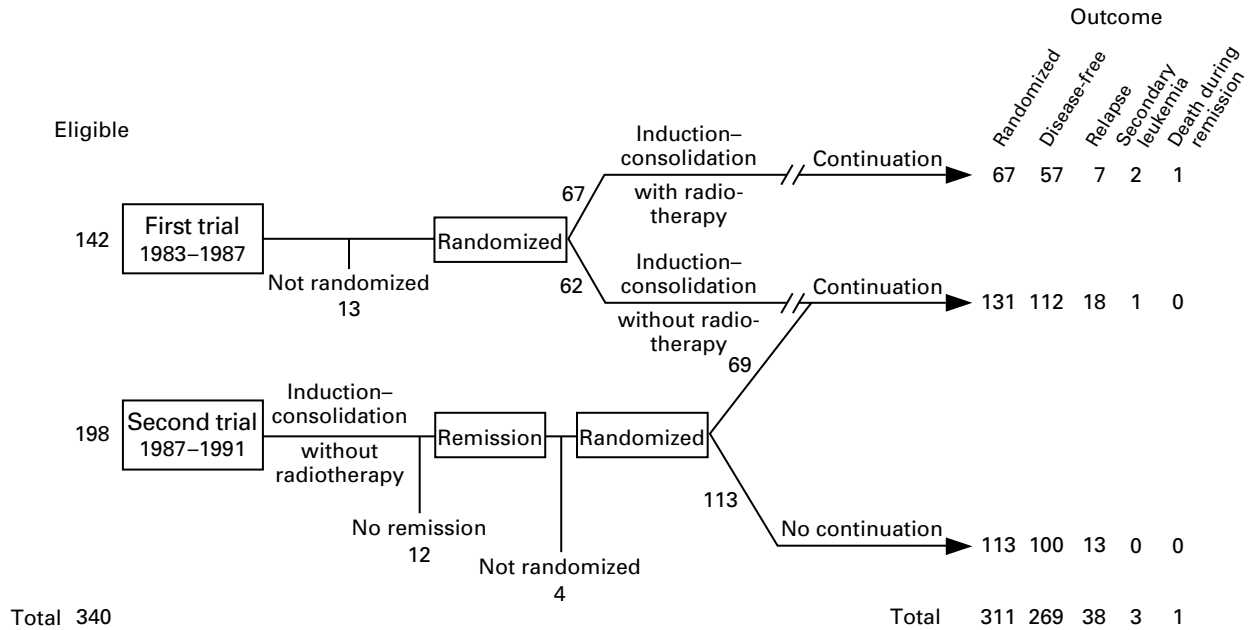


Figure 1. Design of Two Consecutive Trials of Therapy for Patients with Early-Stage Non-Hodgkin's Lymphoma, with the Treatment Assignments and Outcomes Shown for All 340 Eligible Patients.

disease (stage III or IV), including those with mediastinal or massive intraabdominal primary tumors, lymphoma on both sides of the diaphragm, or involvement of the bone marrow or central nervous system. The histologic findings were reviewed centrally, and the diagnostic specimens were classified according to the working formulation for clinical use.⁹

Randomization and Treatment

The design of the two trials is shown in Figure 1. In the first trial,⁶ patients were randomly assigned to receive either eight months of chemotherapy with radiotherapy or eight months of chemotherapy alone. Radiotherapy, which was administered during induction chemotherapy, consisted of irradiation of the involved field with a total dose of 27 Gy in 18 150-cGy fractions during a period of three and a half weeks. In the second trial, all patients received identical regimens of induction and consolidation chemotherapy for nine weeks without irradiation. Remission was assessed after the nine-week period by clinical examination and repeated staging studies. Patients with complete remissions at this time were then randomly assigned to receive an additional 24 weeks of chemotherapy with mercaptopurine and methotrexate, as administered in the first trial, or no further therapy.

The chemotherapy regimens are shown in Table 1. Induction-consolidation chemotherapy consisted of four drugs given for 9 weeks, and continuation chemotherapy consisted of daily oral mercaptopurine and weekly oral methotrexate given for 24 weeks. Central nervous system prophylaxis was administered only in patients with primary tumors in the head and neck region. The drugs, doses, and schedule of administration were identical in the two trials, except for central nervous system prophylaxis. The protocols were approved by the institutional review board at each participating center, and all patients or their parents gave informed consent.

Statistical Analysis

We had demonstrated in the first trial that irradiation of primary sites can be safely omitted from the treatment of children

with early-stage non-Hodgkin's lymphoma.⁶ The second trial was designed to investigate the contribution of 24 weeks of continuation therapy as used in the earlier trial. In addition, we planned a comparison of the efficacy of eight months of chemotherapy combined with radiotherapy (the standard treatment in the first trial) with nine weeks of chemotherapy alone (the least intensive of the treatments) to assess any loss of overall efficacy resulting from two successive reductions in treatment. This analysis was intended to protect against the possibility that two small decrements in efficacy, neither one significant alone, would result in a significant overall decrement in efficacy when combined.

Since the disease is rare, we elected to include patients from the first trial in the analysis of the second trial and used a study design in which two patients were randomly assigned to nine weeks of chemotherapy without radiotherapy for each patient assigned to eight months of chemotherapy without radiotherapy. Because the study question is negative (Is a less intensive therapy as effective?), we considered a one-sided P value of 0.10 or less in favor of eight months of chemotherapy as evidence of the efficacy of continuation therapy. We planned for a power of 90 percent to detect this difference. Allowing for the data already accrued, assuming a 95 percent rate of continuous complete remission at two years for the patients receiving continuation therapy and an 85 percent rate for those not receiving continuation therapy, and assuming an enrollment of 36 patients per year, we determined that an additional 183 patients would be required, with a final analysis planned two years after the completion of enrollment. The two-to-one randomization scheme increased the power obtained with the usual one-to-one randomization and also increased the power of the secondary comparison (eight months of chemotherapy with radiotherapy vs. nine weeks of chemotherapy without radiotherapy).

The analysis is based on follow-up data as of April 1996. All eligible patients were evaluated according to the treatment assigned at randomization. The dependent variable for efficacy was complete continuous remission — the time from a complete remission to the last contact, a relapse at any site, the development of a second cancer, or death, whichever came first. In the analysis of the

TABLE 1. TREATMENT REGIMENS FOR PATIENTS WITH EARLY-STAGE NON-HODGKIN'S LYMPHOMA.

THERAPY	ROUTE OF ADMINISTRATION	SCHEDULE			
		1-YR-OLDS	2-YR-OLDS	3-8-YR-OLDS	≥9-YR-OLDS
Induction and consolidation therapy (9 weeks)					
Vincristine	Intravenous	1.5 mg/m ² of body-surface area weekly for 7 weeks			
Doxorubicin	Intravenous	40 mg/m ² on days 1, 22, and 43			
Cyclophosphamide	Intravenous	750 mg/m ² on days 1, 22, and 43			
Prednisone	Oral	40 mg/m ² daily on days 1-28 and 43-47			
Continuation therapy (24 weeks)					
Mercaptopurine	Oral	50 mg/m ² daily			
Methotrexate	Oral	25 mg/m ² weekly			
Central nervous system therapy*					
		Age-adjusted doses given on days 1, 8, 22, 43, and 64 of induction-consolidation therapy and every six weeks during continuation therapy			
Methotrexate	Intrathecal	8 mg	10 mg	12 mg	15 mg
Cytarabine	Intrathecal	16 mg	20 mg	24 mg	30 mg
Hydrocortisone	Intrathecal	8 mg	10 mg	12 mg	15 mg

*Intrathecal methotrexate alone (12 mg/m²) was used in the first trial.

outcome according to the histologic subtype of lymphoma, the dependent variable was event-free survival — the time from the initiation of therapy to treatment failure for any reason or the last contact, whichever came first. All comparisons were made with the use of the log-rank test,¹⁰ and life tables for continuous complete remission, event-free survival, and overall survival were constructed according to the method of Kaplan and Meier,¹¹ with standard errors calculated as described by Peto et al.¹² All comparisons of efficacy were conducted as one-sided tests. Comparisons of outcome according to histologic type were omnibus (all-sided) tests. One-sided confidence intervals for the outcome in the patients treated with nine weeks of chemotherapy without radiotherapy (the least intensive of the treatments) were also determined.

RESULTS

Patients

Between April 1983 and May 1987, 150 patients were enrolled in the first trial, and between June 1987 and November 1991, 205 patients were enrolled in the second trial. Fifteen patients were found to be ineligible on review and were excluded from the analysis: in seven, the diagnosis of non-Hodgkin's lymphoma could not be confirmed, and eight did not have early-stage disease. The 340 eligible patients in the two trials included 243 males (71 percent) and 97 females (29 percent), with a median age of 10 years (range, 16 months to 20 years; mean, 10 years). One hundred thirty-eight patients had stage I non-Hodgkin's lymphoma, and 202 had stage II disease. The distribution of cases according to the primary site of tumor and histologic subtype is shown in Table 2.

Twenty-nine patients were not randomly assigned

to a treatment group. Seven patients in the first trial had primary lymphomas of bone and, according to the design of that trial,⁶ were excluded from randomization and treated with chemotherapy for eight months and radiotherapy (total dose, 37.5 Gy). Six other patients were not randomized: one was treated with irradiation, and five were treated without irradiation. In the second trial, 12 patients did not have complete remissions and were thus ineligible for random assignment, and 4 patients declined randomization. Data from these 29 patients are not included in any of the randomized comparisons of treatment efficacy but are included in other analyses of outcome in which the treatment assignment was not relevant.

A total of 311 patients were randomly assigned to treatment in the two studies (Fig. 1). In the second trial, 113 patients were randomly assigned to receive nine weeks of chemotherapy alone, and 69 were assigned to receive eight months of chemotherapy. (The imbalance in the treatment assignments reflects the two-to-one randomization scheme.) In the analysis of the outcome, the 62 patients from the first trial who were assigned to treatment with eight months of chemotherapy without radiotherapy were included with the 69 patients assigned to this treatment in the second trial, so that a total of 131 patients were assigned to this treatment. Finally, 67 patients from the first trial were randomly assigned to receive eight months of chemotherapy and radiotherapy, and this treatment served as the standard against which the other treatments were evaluated.

TABLE 2. DISTRIBUTION OF PATIENTS WITH EARLY-STAGE NON-HODGKIN'S LYMPHOMA ACCORDING TO THE PRIMARY SITE AND HISTOLOGIC SUBTYPE OF TUMOR.

PRIMARY SITE	TYPE OF TUMOR				TOTAL
	SMALL NONCLEAVED CELL	LARGE CELL	LYMPHO- BLASTIC	OTHER*	
	no. of patients (%)				
Gastrointestinal tract	77	11	0	3	91 (27)
Cervical node	37	23	18	4	82 (24)
Tonsil	34	10	0	8	52 (15)
Nasopharynx or sinuses	28	7	3	0	38 (11)
Peripheral node	5	18	8	1	32 (9)
Scalp	0	0	12	1	13 (4)
Bone	1	7	3	2	13 (4)
Other†	3	5	6	5	19 (6)
Total	185 (54)	81 (24)	50 (15)	24 (7)	340

*Other histologic subtypes were follicular and diffuse large-cell lymphoma (in eight patients), diffuse mixed lymphoma (in eight), follicular and diffuse mixed lymphoma (in two), and follicular and diffuse undifferentiated lymphoma (in one); five patients had unspecified subtypes.

†Other sites were the subcutaneous tissue in eight patients, parotid gland (in three), orbit (in four), thigh (in two), larynx (in one), and tongue (in one).

Outcome

The outcome for all patients is shown in Figures 1 and 2 and Table 3. A total of 54 patients had adverse events. Twelve did not have complete remissions, 38 had recurrent lymphoma after a complete remission, 1 died of sepsis during a complete remission, and 3 had secondary leukemia (acute nonlymphocytic leukemia in 1 patient, biphenotypic leukemia in 1, and secondary T-cell acute lymphoblastic leukemia in 1 patient with small-noncleaved-cell lymphoma). Of the 38 patients who had relapses, 10 had recurrences at the primary site, 7 in the bone marrow, 5 in the central nervous system, 3 in the testis, and 13 in various nodal and extranodal sites.

The results of a life-table analysis of the outcome according to the treatment are shown in Figure 2. At five years, the mean (\pm SE) projected rate of continuous complete remission was 89 ± 4 percent for patients treated with nine weeks of chemotherapy without radiotherapy, 86 ± 4 percent for those treated with eight months of chemotherapy without radiotherapy, and 88 ± 4 percent for those treated with eight months of chemotherapy with radiotherapy (Fig. 2A). There was no difference in the outcomes for patients receiving nine weeks of chemotherapy without radiotherapy and those receiving eight months of chemotherapy without radiotherapy ($P=0.66$). Nor was there a difference in the outcomes for patients receiving nine weeks of chemotherapy without radiotherapy and those receiving our previous stand-

ard therapy — eight months of chemotherapy with radiotherapy ($P=0.48$) (Table 3). A life-table analysis of overall survival according to treatment is shown in Figure 2B. The 12 patients who did not have complete remissions and the 17 who were not randomly assigned to a treatment group (all of whom have had continuous complete remissions) are not included in the life-table analyses shown in Figure 2. Although the overall results must be viewed as inconclusive, one can infer that nine weeks of chemotherapy without radiotherapy is sufficient, because we can state with 95 percent confidence that with this therapy, the projected five-year survival exceeds 94 percent and the five-year rate of continuous complete remission exceeds 83 percent.

Considering that all 142 eligible patients enrolled in the first trial had complete remissions, we were concerned that induction therapy was unsuccessful in 12 of 198 patients in the second trial. An analysis of the characteristics of the patients enrolled in the two trials failed to account for this difference, and it remains unexplained. To assess the likelihood that our conclusions would have been altered had we included in the analysis the 12 patients who did not have complete remissions, we analyzed the data with the 12 patients assigned to treatment in the two-to-one ratio prescribed by our design. Only if all 12 of these patients had been assigned to nine weeks of chemotherapy without continuation therapy (a circumstance with a probability of less than 1 percent) would the P value have been less than 0.10.

When all 340 eligible patients are considered together, the projected event-free survival at five years was 85 ± 2 percent, and only 4 patients (of 211 at risk) had adverse events more than five years after the diagnosis (Fig. 3A). Salvage therapy was apparently successful for more than half the patients who did not have complete remissions or had recurrent disease. The projected overall survival nine years after the diagnosis of non-Hodgkin's lymphoma was 92 ± 3 percent (Fig. 3B).

Analysis of the results of treatment according to the histologic subtype of non-Hodgkin's lymphoma revealed important differences (Fig. 3). Although induction therapy was successful in all 50 patients with early-stage lymphoblastic lymphoma (as compared with a success rate of 96 percent for those with other histologic subtypes), the event-free survival for these patients was inferior to that for patients with other subtypes of lymphoma. Only 63 percent of the patients with early-stage lymphoblastic lymphoma were projected to survive without a recurrence of disease for five years, as compared with a projected 89 percent of patients with small-noncleaved-cell lymphomas and 88 percent of those with large-cell lymphomas ($P<0.001$). It is apparent that among patients with lymphoblastic lymphoma, those who receive eight months of chemotherapy (including six

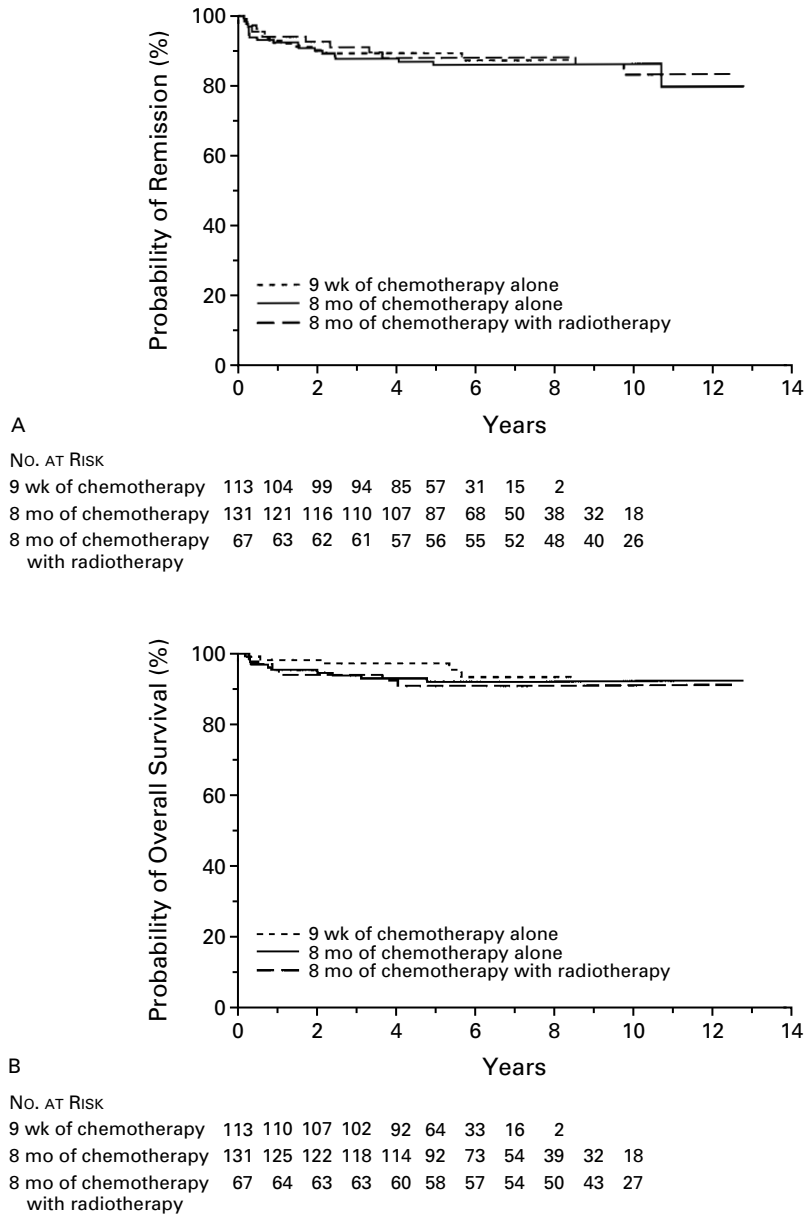


Figure 2. Life-Table Analysis of Continuous Complete Remission (Panel A) and Overall Survival (Panel B) after Randomization in Patients with Early-Stage Non-Hodgkin's Lymphoma, According to Treatment Group.

The probability of continuous complete remission in the group of patients treated with nine weeks of chemotherapy without radiotherapy did not differ significantly from that in the groups treated with eight months of chemotherapy without radiotherapy ($P=0.66$) or eight months of chemotherapy with radiotherapy ($P=0.48$).

months of continuation chemotherapy with or without radiotherapy) have a better outcome than those who receive nine weeks of chemotherapy without continuation chemotherapy (Table 3). In contrast, for the majority of patients with other subtypes of non-Hodgkin's lymphoma, no significant benefit was derived from six months of continuation ther-

apy (Table 3). We can conclude (with 95 percent confidence) that the five-year rate of continuous complete remission for patients with nonlymphoblastic lymphoma who receive nine weeks of chemotherapy (4 failures among 89 patients) exceeds 92 percent. Salvage therapy for the patients with early-stage lymphoblastic lymphoma who had relapses ap-

TABLE 3. OUTCOME OF EARLY-STAGE NON-HODGKIN'S LYMPHOMA, ACCORDING TO TREATMENT AND HISTOLOGIC SUBTYPE OF TUMOR.

TYPE OF TUMOR	EIGHT MONTHS OF CHEMOTHERAPY ALONE			NINE WEEKS OF CHEMOTHERAPY ALONE				EIGHT MONTHS OF CHEMOTHERAPY WITH RADIOOTHERAPY			P VALUE‡	P VALUE§
	NO. OF PATIENTS	NO. OF FAILURES	NO. EXPECTED*	NO. OF PATIENTS	NO. OF FAILURES	NO. EXPECTED*	NO. EXPECTED†	NO. OF PATIENTS	NO. OF FAILURES	NO. EXPECTED†		
Small noncleaved cell	63	6	3.8	69	2	4.2	4.5	39	5	2.5	0.94	0.98
Lymphoblastic	22	7	10.6	14	8	4.4	5.4	10	3	5.6	0.02	0.06
Large cell	37	5	3.9	20	2	1.8	0.9	15	2	3.1	0.63	0.09
Other	9	1		10	1			3	0			
Total	131	19	17.8	113	13	14.2	12.9	67	10	10.1	0.66	0.48

*The number of expected failures is the actuarially adjusted expected number of failures in a log-rank analysis comparing nine weeks of chemotherapy without radiotherapy with eight months of chemotherapy without radiotherapy.

†The number of expected failures is the actuarially adjusted expected number of failures in a log-rank analysis comparing nine weeks of chemotherapy without radiotherapy with eight months of chemotherapy with radiotherapy.

‡P values (one-sided) are for the comparison of nine weeks of chemotherapy alone with eight months of chemotherapy alone.

§P values (one-sided) are for the comparison of nine weeks of chemotherapy alone with eight months of chemotherapy with radiotherapy.

peared to be effective, because an analysis of overall survival revealed no differences according to the histologic subtype ($P=0.24$) (Fig. 3B).

Side Effects

Fifteen of 131 patients (11 percent) had severe or life-threatening granulocytopenia during continuation therapy, and 2 had severe central nervous system toxic effects (hemiparesis in 1 patient and encephalopathy in the other). Two patients reported severe nausea and vomiting during continuation therapy; severe anemia, stomatitis, ileus, and marked elevations in serum aminotransferase concentrations were rare. Weekly blood counts were required in the patients receiving continuation therapy, and those with lymphomas originating in the head and neck region received four doses of intrathecal chemotherapy, in addition to the daily oral mercaptopurine and weekly methotrexate. The patients who received nine weeks of chemotherapy alone were spared these side effects and the additional diagnostic and therapeutic interventions associated with continuation chemotherapy.

DISCUSSION

The successful treatment of non-Hodgkin's lymphoma in children and young adults has evolved empirically since the early 1970s, when most patients with the disorder died. Although the use of intensive multimodal regimens proved to be successful in improving the prognosis for such patients,^{1,2,4,5,13-17} it became evident that patients with an early stage of disease had a more favorable prognosis than those with more advanced disease and might be curable with a reduction in treatment.^{3,6,7} We performed studies to identify the components of therapy that are necessary for a cure in patients with early-stage non-

Hodgkin's lymphoma, allowing us to eliminate the components that provide no benefit and only contribute to toxic effects. We have been cautious in choosing the modifications to be tested and conservative in designing our studies in an effort not to compromise the efficacy of therapy.

The results of our latest study extend the observation made by us and other investigators^{3,6,7,18} that patients with early-stage non-Hodgkin's lymphoma can be treated successfully with a short course of chemotherapy of lessened intensity without irradiation of the primary sites of involvement and without continuation therapy. This treatment strategy is likely to reduce the acute side effects and financial and psychological costs of therapy, as well as the risk of late side effects, although further follow-up is necessary to confirm that the excellent outcome will be sustained and that the incidence of late side effects will be reduced. It might be argued that the elimination of 24 weeks of therapy with mercaptopurine and methotrexate, as well as four doses of intrathecal chemotherapy, represents a very small gain, because these drugs are associated with few late effects. However, the continued use of therapy that cannot be demonstrated to confer a benefit is not justifiable.

Not all patients benefited equally from our approach. The event-free survival of the patients with early-stage lymphoblastic lymphoma — a histologic subtype that accounts for approximately 15 percent of early-stage non-Hodgkin's lymphomas in children and young adults — was inferior to that of the patients with other subtypes of lymphoma. Moreover, the patients with early-stage lymphoblastic lymphoma — unlike those with other subtypes — appeared to benefit from continuation therapy. Although salvage therapy for the patients with early-stage lymphoblastic lymphoma who have relapses appears to be excel-

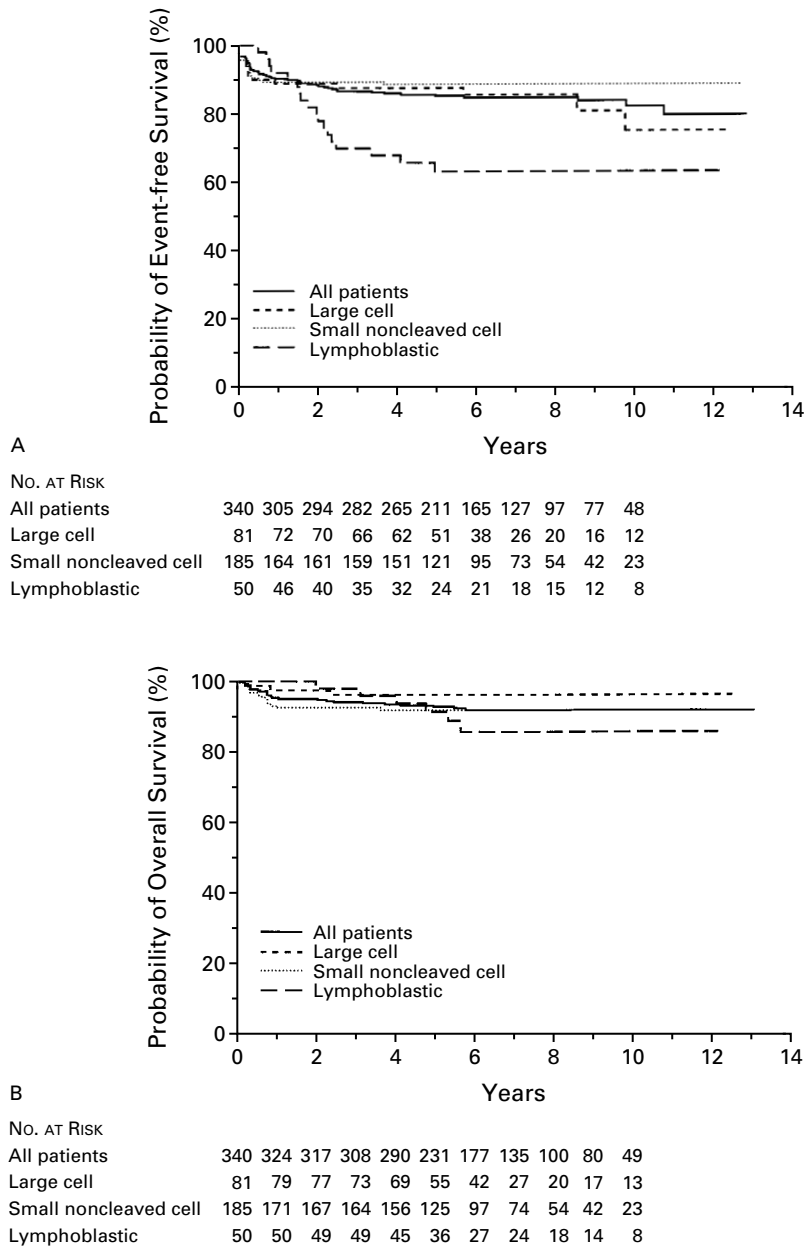


Figure 3. Life-Table Analysis of Event-free Survival (Panel A) and Overall Survival (Panel B) for All 340 Patients with Early-Stage Non-Hodgkin's Lymphoma, According to the Histologic Subtype. The event-free survival of patients with lymphoblastic lymphoma was significantly worse than that of patients with other histologic subtypes ($P < 0.001$). However, there were no significant differences in overall survival according to histologic subtype ($P = 0.24$).

lent (at least in the short term), further follow-up is necessary to determine whether they are cured. Other investigators have also recognized that patients with early-stage lymphoblastic lymphoma have a less favorable prognosis than those with other histologic subtypes and have treated such patients with more in-

tensive therapies designed for advanced-stage disease.^{7,17,19,20} However, the overall outcome does not appear to be much improved with this approach.

Supported in part by grants (CA-33603, CA-29139, CA-31566, and CA-30969) from the National Cancer Institute.

We are indebted to the physicians and nurses at the participating institutions who cared for the patients and to the clinical research associates who assisted with the submission and analysis of the data.

APPENDIX

The following members of the Pediatric Oncology Group participated in the study: Alberta Children's Hospital, Calgary, Alta., Canada; All Children's Hospital, St. Petersburg, Fla.; Baylor College of Medicine, Houston; Boston Floating Hospital, Boston; Bowman Gray School of Medicine, Winston-Salem, N.C.; Carolinas Medical Center, Charlotte, N.C.; Children's Hospital of San Diego, San Diego, Calif.; Children's Hospital of Michigan, Detroit; Children's Hospital of the Greenville Hospital System, Greenville, S.C.; Children's Memorial Hospital, Chicago; Children's Hospital of New Orleans, New Orleans; Cook-Fort Worth Children's Medical Center, Fort Worth, Tex.; Cross Cancer Institute, Edmonton, Alta., Canada; Dana-Farber Cancer Institute, Boston; Duke University Medical Center, Durham, N.C.; East Carolina University School of Medicine, Greenville, N.C.; Emory University School of Medicine, Atlanta; Fairfax Hospital, Fairfax, Va.; Hackensack Medical Center, Hackensack, N.J.; Johns Hopkins Hospital, Baltimore; Kaiser Permanente at San Diego, San Diego, Calif.; M.D. Anderson Cancer Center, Orlando, Fla.; Maine Children's Hospital, Portland; Massachusetts General Hospital, Boston; McGill University, Montreal; Medical College of Virginia, Richmond; Medical University of South Carolina, Charleston; Midwest Children's Cancer Center, Milwaukee; Mount Sinai Medical School, New York; Naval Medical Center, Portsmouth, Va.; Nemours Children's Clinic, Jacksonville, Fla.; Presbyterian Hospital, Charlotte, N.C.; Rhode Island Hospital, Providence; Roswell Park Memorial Institute, Buffalo, N.Y.; Sacred Heart Hospital, Pensacola, Fla.; Scott and White Memorial Hospital, Temple, Tex.; St. Christopher's Hospital for Children, Philadelphia; St. Francis Regional Medical Center, Wichita, Kans.; St. Jude Children's Research Hospital, Memphis, Tenn.; Stanford University School of Medicine, Stanford, Calif.; State University of New York at Syracuse, Syracuse; Swiss Pediatric Oncology Group, Bern, Geneva, and Lausanne, Switzerland; University of Alabama, Birmingham; University of Arkansas, Little Rock; University of California at Davis, Sacramento; University of California at San Diego, San Diego; University of Florida, Gainesville; University of Kansas Medical Center, Kansas City; University of Miami School of Medicine, Miami; University of Mississippi Medical Center, Jackson; University of Missouri Health Sciences Center, Columbia; University of New Mexico School of Medicine, Albuquerque; University of Oklahoma Health Sciences Center, Oklahoma City; University of Puerto Rico, San Juan; University of Rochester Medical Center, Rochester, N.Y.; University of South Alabama, Mobile; University of Texas Southwestern Medical School, Dallas; University of Texas at Galveston, Galveston; University of Vermont College of Medicine, Burlington; Walter Reed Army Medical Center, Washington, D.C.; Warren Clinics, Tulsa, Okla.; Washington University Medical Center, St. Louis; West Virginia University at Charleston, Charleston; West Virginia University at Morgantown, Morgantown; Wichita Community Clinical Oncology Program, Wichita, Kans.; and Yale University School of Medicine, New Haven, Conn.

REFERENCES

- Murphy SB, Fairclough DL, Hutchison RE, Berard CW. Non-Hodgkin's lymphomas of childhood: an analysis of the histology, staging, and response to treatment of 338 cases at a single institution. *J Clin Oncol* 1989;7:186-93.
- Murphy SB, Hustu HO. A randomized trial of combined modality therapy of childhood non-Hodgkin's lymphoma. *Cancer* 1980;45:630-7.
- Murphy SB, Hustu HO, Rivera G, Berard CW. End results of treating children with localized non-Hodgkin's lymphomas with a combined modality approach of lessened intensity. *J Clin Oncol* 1983;1:326-30.
- Anderson JR, Jenkin RDT, Wilson JF, et al. Long-term follow-up of patients treated with COMP or LSA₂-L₂ therapy for childhood non-Hodgkin's lymphoma: a report of CCG-551 from the Children's Cancer Group. *J Clin Oncol* 1993;11:1024-32.
- Hvizdala EV, Berard C, Callihan T, et al. Nonlymphoblastic lymphoma in children — histology and stage-related response to therapy: a Pediatric Oncology Group study. *J Clin Oncol* 1991;9:1189-95.
- Link MP, Donaldson SS, Berard CW, Shuster JJ, Murphy SB. Results of treatment of childhood localized non-Hodgkin's lymphoma with combination chemotherapy with or without radiotherapy. *N Engl J Med* 1990;322:1169-74.
- Meadows AT, Spoto R, Jenkin RDT, et al. Similar efficacy of 6 and 18 months of therapy with four drugs (COMP) for localized non-Hodgkin's lymphoma of children: a report from the Children's Cancer Study Group. *J Clin Oncol* 1989;7:92-9.
- Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol* 1980;7:332-9.
- The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer* 1982;49:2112-35.
- Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc [A]* 1972;135:185-207.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.
- Jenkin RDT, Anderson JR, Chilcote RR, et al. The treatment of localized non-Hodgkin's lymphoma in children: a report from the Children's Cancer Study Group. *J Clin Oncol* 1984;2:88-97.
- Magrath IT, Janus C, Edwards BK, et al. An effective therapy for both undifferentiated (including Burkitt's) lymphomas and lymphoblastic lymphomas in children and young adults. *Blood* 1984;63:1102-11.
- Weinstein HJ, Lack EE, Cassady JR. APO therapy for malignant lymphoma of large cell "histiocytic" type of childhood: analysis of treatment results for 29 patients. *Blood* 1984;64:422-6.
- Sullivan MP, Boyett J, Pullen J, et al. Pediatric Oncology Group experience with modified LSA₂-L₂ therapy in 107 children with non-Hodgkin's lymphoma (Burkitt's lymphoma excluded). *Cancer* 1985;55:323-36.
- Hvizdala EV, Berard C, Callihan T, et al. Lymphoblastic lymphoma in children — a randomized trial comparing LSA₂-L₂ with the A-COP+ therapeutic regimen: a Pediatric Oncology Group study. *J Clin Oncol* 1988;6:26-33.
- Patte C, Michon J, Leverger G, et al. High survival rate of childhood B-cell lymphoma and leukemia (ALL) as result of the LMB 89 protocol of the SFOP (French Pediatric Oncology Society). *Med Pediatr Oncol* 1993;21:531. abstract.
- Patte C, Kalifa C, Flamant F, et al. Results of the LMT81 protocol, a modified LSA₂-L₂ protocol with high dose methotrexate, on 84 children with non-B-cell (lymphoblastic) lymphoma. *Med Pediatr Oncol* 1992;20:105-13.
- Tubergen DG, Krailo MD, Meadows AT, et al. Comparison of treatment regimens for pediatric lymphoblastic non-Hodgkin's lymphoma: a Children's Cancer Group study. *J Clin Oncol* 1995;13:1368-76.