

Combined Modality Therapy for Adults With Small Noncleaved Cell Lymphoma (Burkitt's and Non-Burkitt's Types)

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Between June 1979 and June 1984 18 adult patients with small noncleaved cell lymphoma (SNCL) (diffuse undifferentiated lymphoma, Burkitt's and non-Burkitt's types of the Rappaport classification) were treated with high-dose cyclophosphamide, doxorubicin, vincristine, prednisone, midcycle high-dose methotrexate, and intrathecal methotrexate. Early in the course of treatment, hyperfractionated radiotherapy (125 cGy, every two days, for 1,500 to 2,250 centigray [cGy]) was administered to unresected masses > 10 cm in their greatest dimension. Chemotherapy was administered every 21 days for six to ten cycles. Treatment was generally well tolerated; however, one patient died of probable tumor lysis syndrome. With a median follow-up of 1.2 years, actuarial survival was 66.8% and relapse-free survival (RFS) was 71.3% for the entire group. All treatment failures and deaths occurred in patients with stage D disease. RFS

projected at 2 years was 100% for stages A and AR and 60.6% for stage B, C, and D ($P = .13$ Gehan). Two-year RFS for patients with stage A, AR, B, or C disease was 100 v 41% for those with stage D disease. Patients with adverse prognostic features ($n = 7$)—unresected bulk measuring > 10 cm, pretreatment serum lactate dehydrogenase (LDH) 500 IU/L (normal, 200) or involvement of CNS or bone marrow—had a projected RFS of 28.6% compared with 100% for those patients without these features ($P = .002$ Gehan). Too few patients received induction radiotherapy to assert its role in therapy. By using aggressive multiagent therapy, cure can be expected in a high percentage of adults with SNCL. In the subset with adverse prognostic features, more effective therapy is necessary.

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S MALL noncleaved cell lymphoma (SNCL) is one of three high-grade lymphomas designated by the Working Formulation of the Non-Hodgkin's Lymphomas.¹ The 58 patients included in the Working Formulation report had a bimodal age distribution with a median age of 29.8 years. The 5-year survival and freedom from relapse rates were both approximately 25%, with a median survival of only 0.7 years. As is the case in the Rappaport, Lukes-Collins, and World Health Organization classifications, within the Working Formulation classification SNCL retains the distinction between Burkitt's lymphoma (BL) and non-Burkitt's diffuse undifferentiated lymphoma (NBL).²⁻⁴ However, the importance of this distinction remains controversial. Some investigators have defined clinicopathologic features that distinguish BL from NBL, the former tending to present in younger patients in abdominal and gastrointestinal sites, and the latter tending to present in older patients with peripheral adenopathy and bone marrow involvement.^{5,6} Nevertheless, others have emphasized that clinical features may overlap considerably, that histologic distinctions can be subtle and unreliable, and that the two tumors may be

ultrastructurally, cytochemically, and immunologically indistinguishable.⁷

Therapeutic experience has been chiefly derived from pediatric patients. Multiagent chemotherapy and CNS prophylaxis can achieve high rates of remission.⁸⁻¹⁰ Using an aggressive multiagent regimen in 51 children and young adults with SNCL, Magrath et al reported an overall long-term relapse-free survival (RFS) of 51%. A long-term remission rate of 88% was achieved in patients with early stage disease.¹¹ Other series suggest that children with either BL or NBL can achieve remission at high rates.^{8,10,12} Advanced stage, elevated serum lactic dehydrogenase (LDH), or uric acid, and bone marrow involve-

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ment were recognized as adverse prognostic factors. Although adults with NBL may also have high response rates with chemotherapy,¹³ no series has reported the long-term results of therapy among adults with SNCL.

In 1979 we initiated a treatment protocol for adults with SNCL adapted from that of the National Cancer Institute (NCI) Pediatric Oncology Branch. This report will demonstrate that although a high rate of cure can be achieved, an unfavorable subpopulation of patients can be identified for which more effective therapy is needed.

MATERIALS AND METHODS

Between June 1979 and June 1984, 18 patients with SNCL were evaluated by the Division of Medical Oncology of the Stanford University Medical Center. No study patient had received prior chemotherapy. All biopsy material was reviewed by the Stanford Laboratory of Surgical Pathology and subclassified as either Burkitt's-type or non-Burkitt's type according to established histologic criteria.^{1-3,5,7,14-17} These comprised of cells of intermediate size (larger than lymphocytes of small lymphocytic lymphoma but smaller than the large non-cleaved cells of large-cell lymphoma), with nuclear size approximately equal to that of benign macrophages. Nuclear shape was usually uniform and round to oval. Chromatin was coarsely or finely distributed, with two to five nucleoli, and mitotic figures were numerous. Cells of SNCL had a moderate amount of amphophilic and intensely pyroninophilic cytoplasm, usually devoid of glycogen; squaring-off of the cytoplasm of adjacent cells was considered a characteristic feature of SNCL. The principle histologic features distinguishing non-Burkitt's type were of greater variability in size and shape of the lymphoma cells and prominence of the nucleoli.

Evaluation and Staging

All patients received hematologic and blood chemistry evaluation, chest radiographs, bipedal lymphography, computerized axial tomography (CAT) of abdomen, pelvis and chest, and radionuclide scans as indicated. Bone marrow biopsies and lumbar punctures were obtained before the initiation of therapy. Pleural effusions or ascites, if present, were aspirated for cytologic analysis. If a diagnosis was obtained from an extraabdominal site and noninvasive studies subsequently defined intraabdominal disease, the patient was not subjected to laparotomy and surgical debulking. Patients were assigned stages according to the system of the Pediatric Oncology Branch of the NCI (PB stage) (Table 1).^{17,18} Patients were assigned stage AR if the abdomen was the initial and only site of presentation, and if, by the surgeon's estimation and by subsequent radiographic studies, > 90% of tumor was resected. Patients were also assigned a stage based on the Ann Arbor criteria.¹⁹

Treatment

The treatment regimen is represented in Table 2. Allopurinol 300 mg/d orally was begun before initiating therapy; when nec-

Table 1. Staging (NCI Pediatric Oncology Branch)¹⁸

Stage A	A single extraabdominal tumor site
Stage AR	Completely resected intraabdominal tumor (tumor volume reduced by more than 90%)
Stage B	Multiple extraabdominal sites
Stage C	Intraabdominal tumor without involvement at other sites
Stage D	Intra- and extraabdominal sites

essary, the drug was delivered intravenously (IV). In all patients with residual disease, elevated serum uric acid or azotemia, vigorous hydration, and urine alkalinization were instituted before the first chemotherapeutic cycle. Patients with bulky disease were treated as inpatients and carefully monitored for the tumor lysis syndrome.²⁰

Radiotherapy was administered before or during the first cycle of chemotherapy to all patients with abdominal masses radiographically measuring > 10 cm in their greatest dimension. Using either a 4 or 6 meV linear accelerator, anterior and posterior or bilateral opposed fields were treated with a midplane dose of 125 centigray (cGy) twice daily to a total dose of 1,500 to 2,250 cGy. Fields included the mass with a margin of at least one cm. Kidney dose was limited to 1,500 cGy. Doxorubicin was omitted from the first cycle if radiotherapy was administered concurrently; otherwise, the doses and scheduling of chemotherapy were not altered.

Chemotherapy consisted of cyclophosphamide (1,200 mg/m² [IV] on day 1), doxorubicin (40 mg/m² IV on day 1), vincristine (1.4 mg/m², to a maximum dose of 2 mg IV, on day 1), prednisone (40 mg/m² orally or IV for five days from day 1). Methotrexate (3 g/m² IV over six hours) infusions were administered on day 10 or at midcycle of the first five cycles and were followed 24 hours later by folic acid rescue (25 mg/m² orally or IV every six hours for 12 doses). Methotrexate was delayed until the total leukocyte count exceeded 1,000/ μ L and was eliminated if the serum creatinine was \geq 1.5 mg/dL, or if the creatinine clearance was < 60 mL/min. With the initial cycle, methotrexate and serum creatinine levels were obtained at 48 hours. Folic acid rescue was extended as described by Bleyer.²¹ Cycles were repeated at 21-day intervals.

CNS prophylaxis consisted of methotrexate 12 mg administered intrathecally via lumbar puncture on day 1 of each cycle and again during the midcycle at the time of IV methotrexate infusion for a total of ten administrations.

In patients with limited disease (stages A, AR, and B) six full cycles of chemotherapy were administered. Eight to nine cycles were planned for patients with extensive disease (stages C and D).

Response and Toxicity Criteria

History, physical examination, chest and abdominal plane films, hemograms, and chemistries were obtained with each cycle. A hemogram and serum creatinine were obtained before each administration of high-dose methotrexate. Complete response was defined by the total resolution of all indicator lesions and the failure to detect any new tumor over a period of 2 months. Partial response was defined as a reduction > 50% of the product of the longest perpendicular dimensions of each index lesion.

Table 2. Schedule of Regimen

Drug	Cycle				
	1		2-5		6-9*
	d1	d10	d1	d10	d1
CTX	x		x		x
ADR	o		x		x
VCR	x		x		x
PRED	x		x		x
ALLO	x		p		
HDMTX		x		x	
ITMTX	x	x	x	x	
XRT	*****				

NOTE. Twenty-one day cycles: CTX, cyclophosphamide 1,200 mg/m² IV; ADR, doxorubicin 40 mg/m² IV; VCR, vincristine 1.4 mg/m² (maximum, 2.0 mg) IV; PRED, prednisone 40 mg/m² orally per day × 5 (days 1-5); ALLO, allopurinol 300 mg orally or IV per day; HDMTX, 3 gm/m² over six hours with leucovorin rescue (see text); ITMTX, 12 mg/m² intrathecally; XRT, radiation therapy; x, day drug administered; o, doxorubicin omitted from first cycle if concurrent radiotherapy is delivered; p, administered as needed; *****, 125 cGy twice daily for six to nine days for unresected abdominal mass of 10 cm.

*Six cycles planned for stages A, AR, and B; eight to nine cycles planned for stages C and D.

Toxicity was graded according to criteria of the Northern California Oncology Group (Palo Alto, Calif). Cardiac status was evaluated by clinical examination; gated blood-pool scintigraphy was obtained in patients at risk for anthracycline-related cardiomyopathy.

Analysis of Data

Survival and follow-up times were calculated from the date of initiation of therapy. Kaplan-Meier estimates of survival and response duration were obtained.²² Comparisons of curves were based on the Gehan generalized nonparametric test statistic.²³ Because of the limited size of our sample, logistic regression analysis was not used.

RESULTS

The pretreatment characteristics of the 18 patients are summarized in Tables 3 and 4. Seven women and 12 men ranged in age from 15 to 75 years (median age, 25 years). Ten patients had SNCL-NBL, and eight had SNCL-BL. Median follow-up was 1.2 years from study entry. Follow-up after completion of therapy was a minimum of 6 months.

Clinical Findings and Staging

The most common site of initial presentation was the gastrointestinal tract with seven patients

found to have ileal, duodenal, or gastric involvement (Table 5). The bowel was the only site of involvement in four patients. Two patients presented with abdominal tumors that had been completely resected (patients no. 2 and 9, staged AR). Two patients presented with nasopharynx and regional nodal involvement. One patient had massive involvement of the thyroid gland. A resected area of skin was an isolated site of involvement in a single patient (patient no. 11).

As described in the Patients and Methods section, no patient with an established diagnosis of SNCL was subjected to resection of known disease. Seven patients (38.9%) had limited disease (three stage A, two stage AR, and two stage B); 11 patients (61.1%) had extensive disease (two stage C and nine stage D). Five patients, all with stage C or D disease had pretreatment serum LDH levels elevated above 500 IU/L (normal, 200 IU/L). The pretreatment serum uric acid exceeded 9 mg/dL in four patients, all having stage C or D disease. Two patients with bulky abdominal disease had bone marrow involvement at the time of initial staging. No patient presented with CSF cytology positive for lymphoma; however one patient had presumed CNS involvement based on the presence of multiple cranial nerve palsies despite negative cytologic examinations of multiple samples of CSF cytologies.

Response to Therapy

Five patients received radiotherapy. One of these (patient no. 8) received whole-brain irradiation as emergency therapy of multiple cranial nerve palsies. A second patient (patient no. 10), who had presented in bulky axillary nodes, had completed mantle radiotherapy at another institution before initiating chemotherapy. Three patients received induction hyperfractionated radiotherapy as prescribed by the protocol: two (patients no. 6 and 14) received 1,500 cGy to the whole abdomen and one (patient no. 15) received 1,500 cGy to the pelvic field.

Response to therapy is summarized in Table 6. Fourteen patients achieved a complete response. Three had only a partial response; the fourth patient died on the second day of therapy and is considered a treatment failure. Although it is difficult to precisely ascertain the time of complete response by conventional clinical and radiologic means, remissions were achieved in 2 to 16

Table 3. Patient Characteristics

Patient No.	Sex/Age	Histology	Stage		Primary site	Response/Outcome
			PB	AA		
1	F/27	BL	A	IEA	Thyroid	CR/alive
2	F/15	BL	AR	IEB	Ileum	NE/alive
3	M/19	BL	B	IIEB	Nasopharynx, nodes	CR/alive
4	F/28	BL	B	IIA	Nasopharynx, nodes	CR/alive
5	F/75	BL	D	IIA	Abdominal soft tissue	PR/dead
6	M/25	BL	D	IIIA	Ileum	CR/alive
7	M/24	BL	D	IVEB	Nodes, bone marrow	TD
8	F/35	BL	D	IVA	Nodes, bone marrow, cranial nerve palsies (cytology negative)	PR/dead
9	M/24	NBL	AR	IEA	Small bowel	NE/alive
10	M/24	NBL	A	IA	Axillary node	NE/alive
11	M/42	NBL	A	IEA	Skin (single site)	NE/alive
12	M/24	NBL	C	IEA	Stomach	CR/alive
13	M/44	NBL	C	IVB	Small bowel	CR/alive
14	M/42	NBL	D	IVA	Duodenum, abdominal soft tissue	CR/dead*
15	M/20	NBL	D	IIIE	Colon	PR/dead
16	F/57	NBL	D	III	Neck mass	CR/alive
17	M/25	NBL	D	III	Soft tissue masses	CR/alive
18	M/23	NBL	D	IVA	Soft tissue masses	CR/alive

Abbreviations: PB, NCI Pediatric Branch¹⁸; AA, Ann Arbor staging¹⁹; CR, complete response; PR, partial response; NE, not evaluable; TD, toxic death (probable tumor lysis).

*Stable abdominal CAT scan; progressed on therapy.

weeks (median, 6 weeks). One patient (patient no. 14) was thought to have had a complete response based on the stability of abdominal CAT scan; however, he subsequently relapsed in multiple abdominal soft tissue sites. All three patients who had a partial response died within 6 months of study entry (Table 7).

Survival

Life table analyses of survival and RFS are presented in Figure 1. RFS for the entire group was estimated at 71.3% (SE = 10.9%) beyond 1 year. No relapses were observed beyond 0.97 years. Actuarial survival was 66.8% at 2 years (SE = 12.8%), and no death occurred beyond 1.2 years.

Projected (RFS) rates for eight patients with BL and ten patients with NBL were 62.5% and 80%, respectively ($P = .51$). There was no significant difference in projected survival rates for the two groups (BL, 60%; NBL, 80%; $P = .83$).

Stage D patients had significantly worse prognoses than all others (RFS 41.7% v 100%, $P = .013$; survival 38% v 100%, $P = .016$) (Figs 2 and 3). Otherwise, grouping by stage alone was not an accurate discriminator of the outcome of therapy (Table 8). Actuarial (RFS) for limited

disease (PB stage A and AR) was 100%; RFS for stage B, C, and D patients was 60.6% ($P = .13$). Overall survival was 100% for stages A and AR v 53.8% for stages B, C, and D ($P = .14$). If the two stage B patients are regrouped with stages A and AR, and compared against stages C and D, the differences in RFS (100% v 53%, $P = .049$) and in survival (100% v 45.5%, $P = .055$) approach statistical significance.

Table 4. Histology, Staging, and Outcome of Therapy of All Patients

	n	Relapse	Toxic Death	No Evidence of Disease (%)
PB Stage				
A	3	0		3
AR	2	0		2
B	2	0		2 (100)
C	2	0		2
D	9	4	1	3 (33.3)
Ann Arbor				
I	6			6
II	4	2		2 (84.6)
III	3			3
IV	5	2	1	2 (40)
Histology				
BL	8	2	1	5 (62.5)
NBL	10	2		8 (80)

Table 5. Principal Sites of Involvement at Presentation

Skin	1
Thyroid	1
Nasopharynx	2
Lymph node	3*
Gastrointestinal	7
Stomach	1
Small bowel	5
Colon	1
Multiple soft tissue sites	4
Total	18

*Includes one patient with bone marrow involvement and one with bone marrow and symptomatic cranial nerve involvement.

Although stage D patients performed significantly worse than all others (Table 8), stage and adverse prognostic features were associated (Table 9). Eight patients had one or more recognized poor prognostic features—mass measuring > 10 cm in its largest dimension, LDH > 500 (normal, 200), uric acid > 9 mg/dL, or bone marrow involvement.³⁰ These eight had an RFS of 37.5% projected beyond 1 year. Patients without these features had 100% RFS ($P = .006$) (Fig 4). Survival for these two groups was 33.3% compared with 100% ($P = .01$; Fig 5). However, only a single patient (patient no. 12) had an elevated uric acid without other adverse prognostic features and this patient has maintained a complete response in excess of 1 year. Thus, there is insufficient data to demonstrate that elevated uric acid alone is associated with a poor prognosis. Patients with elevated pretreatment LDH alone (four stage D and one stage C patient) performed significantly worse than did those patients without LDH elevations 500 IU/L, with RFS of 20% v 92.3% ($P = .007$) and actuarial survival at 1 year, 40% v 92.3% ($P = .008$). The LDH was

Table 6. Response to Therapy

	n	%
Completely resected (SR)	4	22
Disease present following surgery	14	78
NR	1	7*
PR	3	21
CR	10	71
Unmaintained complete response (SR and CR)	14	78

Abbreviations: NR, no response to therapy; PR, partial response; CR, complete response.

*Death during induction therapy.

not elevated beyond 500 IU/L in only one patient with massive stage D disease, and this patient did not relapse. Thus, stage and high LDH were found empirically to be strongly associated with a poor prognosis. The patient population defined by either stage C or stage D and LDH elevated > 500 IU/L also included both bone marrow positive patients and all patients with massive disease. This group had distinctly worse RFS—28.6% v 100% ($P = .002$)—and survival—21.4% v 100% ($P = .003$).

Patterns of Failure

Of the four patients who had progression of disease, three had achieved only a partial response; the fourth was thought to be in complete remission after CT of the abdomen (Table 7). All four ultimately progressed in abdominal or soft tissue sites 3 to 7 months after completion of chemotherapy.

The meninges were the site of initial progression in two patients, one of whom had presented with cranial nerve palsies and normal cerebrospinal fluid cytologies (patient no. 8). Her progression occurred while undergoing systemic chemotherapy and maintenance intraventricular methotrexate administration six months after combined intraventricular methotrexate, cranial irradiation, and systemic chemotherapy had cleared her systemic disease and cranial neuropathies. Further salvage with intrathecal cytosine arabinoside and methotrexate was attempted, but within 10 weeks disease recurred in the maxilla and multiple soft tissue sites. In another patient (patient no. 14), lumbar radicular pain and cranial nerve palsies occurred while the patient was believed to have had a complete response in massive abdominal disease after abdominal radiotherapy and three cycles of systemic chemotherapy. Systemic therapy was continued, but within 12 weeks he progressed in the testes and soft tissues. Craniospinal and testicular irradiation was begun, but disease control was not achieved.

Two other patients progressed only in the soft tissues of the pelvis and retroperitoneum: one (patient no. 5) accepted palliative radiotherapy and a single cycle of cytosine arabinoside and etoposide; the other (patient no. 15) refused any other therapeutic interventions. No patient survived longer than 9 months after disease progression.

Table 7. Patterns of Disease Progression and Salvage Therapy

Patient No.	Histology/Stage	Response	Time to Disease Progression	Initial Site of Progression	Subsequent Sites of Progression	Salvage Therapy	Survival After Relapse
5	BL/D	PR	6 mo*	Paralumbal soft tissues		Radiotherapy; cyclophosphamide, etoposide (one cycle)	4 mo
8	BL/D	PR	6 mo†‡	Meninges	Maxilla soft tissues (3 mo after CNS progression)	Intrathecal cytosine arabinoside, intrathecal methotrexate, radiotherapy to maxilla	7 mo
14	NBL/D	CR§	12 wk†	Meninges	Abdomen, soft tissues, testis	Craniospinal radiotherapy, continued regimen, testicular radiotherapy	5 mo
15	NBL/D	PR	13 wk*	Iliac nodes	Pelvis	Refused	1 mo

*Measured from completion of therapy.

†CNS recurrences during therapy, measured after initiation of systemic chemotherapy.

‡Initially presented with cranial nerve palsies, CSF cytology negative.

§Stable abdominal CAT scan.

Toxicity

There was one therapy-related death in a 24-year-old man (patient no. 7) with extensive involvement of stomach, duodenum, ileum, and colon. Twenty-four hours after the first treatment, the patient became suddenly disoriented and pulseless. Attempts at resuscitation were unsuccessful, and autopsy was refused. Despite the administration of allopurinol and aggressive hydration and monitoring of serum electrolytes, it is suspected that he died of acute tumor lysis rather than perforation of a viscus.

Leukopenia was the major toxicity observed. In 115 cycles of therapy delivered, 17 cycles

(14.7%) were accompanied by total WBC counts between 1,500/ μ L and 2,000/ μ L. In ten cycles (8.7%), the WBC count was < 1,000/ μ L, but there was only one episode of sepsis requiring hospitalization.

Nausea and vomiting were generally mild and well-tolerated; one patient required inpatient supportive care on one occasion for this reason. In one alcohol-using patient, endoscopically proven benign gastric ulceration was observed at the site of his treated tumor mass (patient no. 12). He was treated medically without complication. No life-threatening or dose-limiting mucositis was observed.

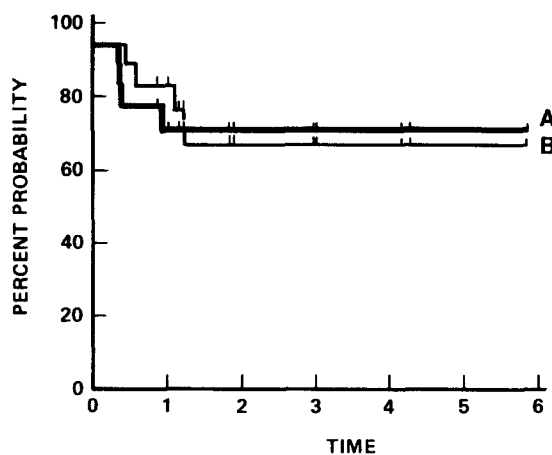


Fig 1. (A) RFS, all patients; (B) survival, all patients.

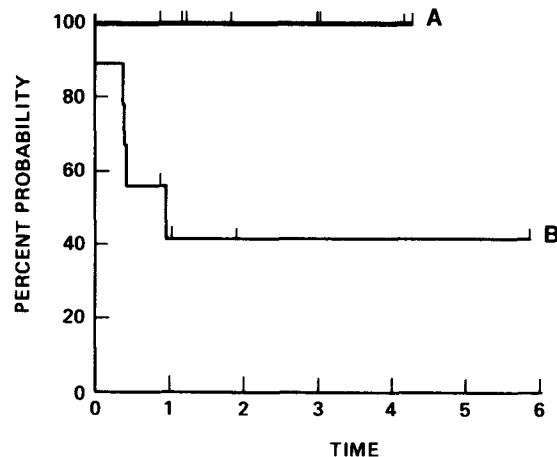


Fig 2. RFS, stages A, AR, B, and C v D. (A) SNCL, stages A, AR, B, and C; (B) SNCL, stage D.

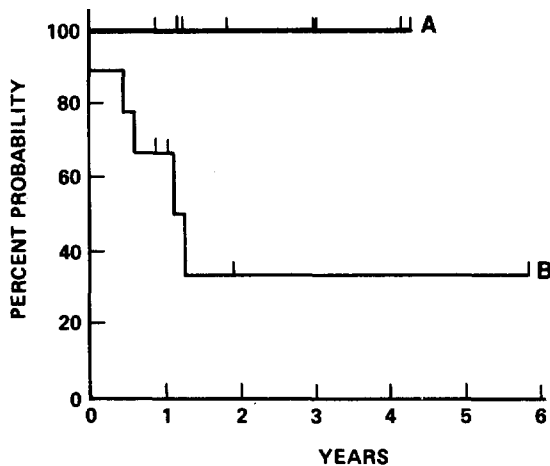


Fig 3. Survival, stages A, AR, B, and C v D. (A) SNCL, stages A, AR, B, and C; (B) SNCL, stage D.

Transient asymptomatic chemical arachnoiditis occurred in two patients; there were no other episodes of subacute or chronic neurotoxicity. No alteration of intellect was detected in any patient. No cardiomyopathy was observed.

Drug Dose Modifications

Toxicity of the regimen is summarized in Table 10. One hundred fifteen cycles were delivered to 18 patients. Fifteen patients (83.3%) received more than 75% of the projected total of each cytotoxic agent. Three patients (15.8%) received part of their therapy at institutions other than Stanford. One of these patients (patient no. 18) was treated with our regimen and then received 4 months of maintenance cytosine arabinoside and thioguanine. Although considered a

major violation of protocol, he is nevertheless included in our analysis.

Bone marrow suppression limited chemotherapy dosage in a patient (patient no. 13) with acquired immunodeficiency syndrome and stage C disease. A second patient who was homosexual (patient no. 11) with stage A disease and biopsy-proven chronic active hepatitis, experienced an exacerbation of hepatitis, with transaminases and DNA polymerase increasing fivefold. His therapy was discontinued after the third cycle, and he remains without evidence of disease 14 months after therapy.

Doxorubicin and cyclophosphamide were decreased below 85% of total ideal dose in two patients because of myelosuppression. Vincristine was eliminated from the regimen of an elderly patient (patient no. 5) with scleroderma and severe esophageal dysmotility. Severe nausea, vomiting, and myalgias were associated with the administration of IV methotrexate in two patients (patients no. 5 and 9), and methotrexate was eliminated from their regimens after three cycles.

Although the protocol called for a total of ten administrations of intrathecal methotrexate, only six patients received ten or more intrathecal injections. Nine patients received six injections, but toxicity was responsible for discontinuation in only two patients; after four administrations in one patient who developed evidence of chemical arachnoiditis, and after three administrations in one patient who developed headache, nausea, and vomiting. Neither experienced a CNS relapse. Patient or physician preference, rather than specific toxicity, limited the number of intrathecal injections in the other patients.

DISCUSSION

One of the significant achievements of cancer therapy has been the progress in treatment of childhood diffuse non-Hodgkin's lymphomas, particularly African and American BL^{9,24-28} and undifferentiated lymphoma.^{11,12} The undifferentiated lymphomas of adults, termed SNCL in the Working Formulation, are characterized by their aggressive course, brief median survival, and low rates of long-term survival.¹ Although frequently included among adult patients with diffuse histiocytic lymphoma (Rappaport),¹³ or among younger patients with non-lymphoblastic

Table 8. RFS and Survival for All Patients, Grouped by Stages

Stages	2-yr RFS		Actuarial Survival	
	Probability (%)	P (Gehan)	Probability (%)	P (Gehan)
A, AR	100	.13	100	.14
v				
B, C, D	60.6		53.8	
A, AR, B	100	.049	100	.055
v				
C, D	53		45.5	
A, AR, B, C	100	.013	100	.016
v				
D	41.7		33.3	

Table 9. Adverse Prognostic Features*

Patient No.	Histology	Stage	BM	CSF	Bulk†	LDH	Uric Acid
No adverse prognostic features							
1	BL	A	—	—	8 × 6 cm	235	3.9
2	BL	AR	—	—	—	173	2.3
3	BL	B	—	—	—	174	5.8
4	BL	B	—	—	5 cm	161	3.1
9	BL	AR	—	—	—	174	4.2
10	NBL	A	—	—	4 cm	114	6.7
11	NBL	A	—	—	—	174	5.6
12	NBL	C	—	—	8 × 10 cm	221	9.3
16	NBL	D	—	—	5 × 5 cm	232	3.4
17	NBL	D	—	—	—	186	4.5
18	NBL	D	—	—	—	205	7.7
With adverse prognostic features							
5	BL	D	—	—	—	511	5.4
6	BL	D	—	—	massive	145	5.0
7	BL	D	+	—	massive	1,345	22.0
8	BL	D	+	‡	12 × 15 cm	1,128	10.1
13	NBL	C	—	—	8 cm	537	11.9
14	NBL	D	—	—	massive	725	7.7
15	NBL	D	—	—	23 cm	213	5.8

*Unresected bulk measuring > 10 cm in greatest dimension, pretreatment serum LDH > 500 IU/L, bone marrow involvement, and CNS involvement.

†For all sites > 3 cm; massive = > 10 cm in greatest dimension, exact extent not measurable.

‡Multiple cerebrospinal fluid cytologies negative, presented with cranial nerve palsies.

diffuse lymphoma,¹¹ no large series composed primarily of adult patients with SNCL has been reported. Adapted from the NCI Pediatric Oncology Branch protocol of Magrath et al,¹¹ the Stanford regimen is an attempt to achieve similarly high rates of remission and cure in adult patients with SNCL.

At the start of this protocol, it was perceived that because of age, medical condition, unresectability, or because surgery would delay the start of chemotherapy excessively, many adults with advanced-stage or bulky SNCL were not candidates for debulking laparotomy. The Stanford regimen differed from the NCI Pediatric Oncolo-

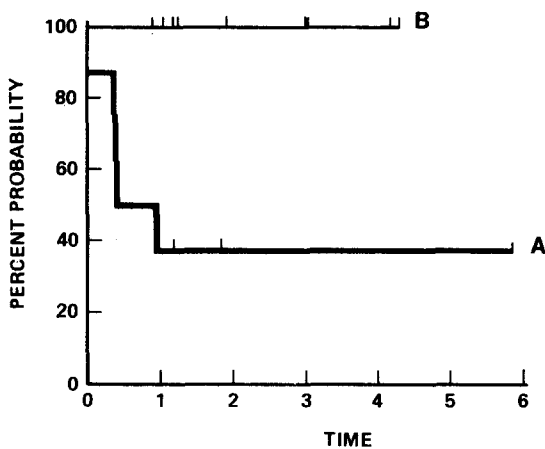


Fig 4. RFS, patients with and without adverse prognostic features. (A) SNCL with adverse prognostic features; (B) SNCL without adverse prognostic features (see text).

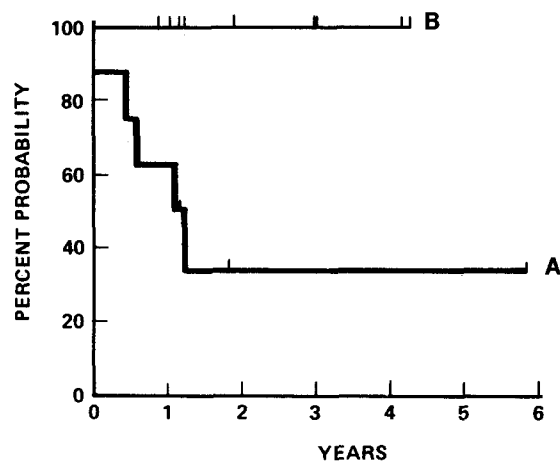


Fig 5. Survival, patients with and without adverse prognostic features. (A) SNCL with adverse prognostic features; (B) SNCL without adverse prognostic features (see text).

Table 10. Toxicity

	No. of Patients (%)	No. of Events (% total cycles)*
Tumor lysis (probable)	1 (5.6)	
Hematologic		
WBC 1,500–2,000	9 (50)	17 (15)
WBC 1,500	7 (39)	10 (8.7)
Platelets 100,000/ μ L	0 (0)	
Arachnoiditis	2 (14.3)	
Nausea†		
Grade 4	1 (5.6)	2 (1.7)
Grade 2–3	2 (11)	2 (1.7)
Stomatitis (grade 2)‡	2 (11)	2 (1.7)

*Total, 115 cycles.

†Grade 2, nausea and vomiting controlled by antiemetics; grade 3, intractable vomiting; grade 4, requires hospitalization.

‡Grade 2, patchy mucositis, brief erythema; grade 3, fibrinous mucositis (confluent); grade 4, ulcerative mucositis, necrosis, or hemorrhage requiring hospitalization.

gy Branch protocol in the addition of hyperfractionated radiotherapy without the use of surgical debulking in patients with an established diagnosis and large abdominal bulk. Other modifications included decreasing the duration of IV infusion of methotrexate (42 hours to six hours) so that it could be administered in an outpatient setting, decreasing the planned number of intrathecal injections (19 to ten), and eliminating the use of intrathecal cytosine arabinoside.

In this series, high rates of disease-free survival were achieved in patients with limited disease and in some patients with advanced stage. When patients were grouped in the fashion of the NCI Pediatric Branch, their projected relapse-free survival rates of 100% for stages A and AR and 53.8% for stages B, C, and D compared well with 88% and 43%, respectively, achieved among children and young adults with SNCL treated on the NCI Pediatric Oncology Branch,¹¹ as well as other aggressive regimens.^{8,10,12,27,28} All relapses and deaths occurred in patients with PB stage D disease.

Tumor burden has been recognized as an adverse prognostic factor in BL.^{9,18,24,29,30} To a degree, staging is independent of measurement of bulk, although among patients with African BL, tumor burden and prognosis were reflected by measurements of LDH, uric acid, delayed cutaneous hypersensitivity, and stage.³⁰ In addition to PB stage, four clinical features were analyzed:

direct measurement of bulk > 10 cm, CNS involvement, bone marrow involvement, or elevated pretreatment serum LDH. Elevated uric acid can not be evaluated as an independent adverse feature because in only one patient (patient no. 12) was the pretreatment uric acid elevated in the absence of other adverse clinical features. In the two patients who presented with CNS and/or bone marrow involvement, other adverse features were present, and bone marrow and meningeal involvement could not be demonstrated as independent prognostic indicators. Despite the small number of patients in this series, pretreatment serum LDH was an important prognostic indicator: patients with LDH > 500 IU/L had a 1-year RFS of 20% v 92.3% in those with levels < 500 IU/L ($P = .007$).

Stage was also a predictor of outcome. The nine patients with PB stage A, AR, B, or C disease had a 2-year RFS of 100% compared with 41.7% for stage D patients ($P = .016$). When regrouped according to the presence or absence of one or more of the four adverse clinical features, three stage D patients (patients no. 16, 17, and 18) with small burdens of unresected abdominal or soft-tissue disease were placed in the favorable prognostic group. Based on the presence of adverse prognostic features without regard to PB stage, the segregation of patients into favorable and unfavorable prognostic groups achieved statistical significance despite the relatively small number of patients in the series (Figs 4 and 5). However, those patients with stage C or D disease and pretreatment serum LDH > 500 IU/L had distinctly worse outcomes when treated with this regimen (Figs 6 and 7). When considered together, high PB stage and pretreatment LDH are excellent prognostic discriminators.

For treatment selection, it is useful to divide patients into high- and low-risk groups. In analyzing the results, low-risk patients are those with low stage (A, AR, and B) disease, as well as those with high stage (C and D) if pretreatment LDH is < 500 and if there is no massive disease or involvement of bone marrow or CNS. Patients with stage C or D disease with elevated serum LDH, massive disease, bone marrow, CNS involvement are at high risk of treatment failure.

Considering the prognostic importance of tumor burden in childhood SNCL, the therapeutic value of reductive surgery is suggested by the

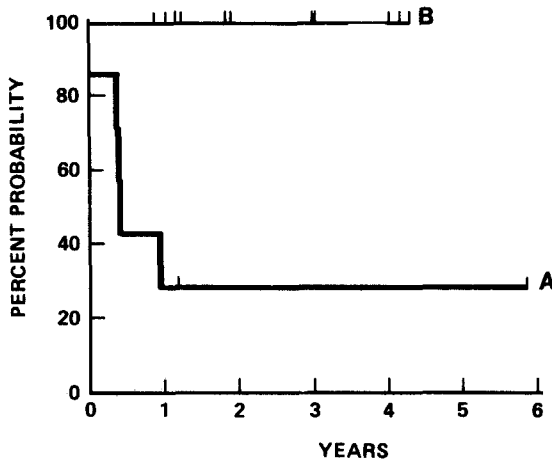


Fig 6. RFS, stage C or D, and high LDH (> 500 IU/L) v all others. (A) Stage C or D patients with high LDH; (B) all others.

experience with African BL^{18,22,26} and NBL.^{29,31} Combination chemotherapy has contributed to the management of advanced or bulky BL,^{9,28,29} presumably by increasing the fractional cell kill with the first cycle of therapy.³⁰ However, the benefit of conventionally fractionated radiotherapy is controversial. After induction chemotherapy, abdominal radiotherapy has been used without proven effectiveness.^{9,25,27,28,32} Hyperfractionation may improve the therapeutic index of radiotherapy in this rapidly growing tumor.³³ Despite the intent to substitute hyperfractionated radiotherapy for reductive surgery, the benefit of radiotherapy in the management of bulky unresected abdominal SNCL could not be demonstrated. Only three patients received 1,500 cGy to abdominal masses as prescribed by the protocol. One patient is alive after more than 5 years, but two later relapsed in abdominal soft tissue sites within irradiated fields. The apparent failure of hyperfractionated irradiation may be attributed to very large masses and tissue hypoxia, high growth fraction, relatively low cumulative doses of radiation, or to the elimination of doxorubicin from the first cycle despite the delivery of high doses of active agents. There may be other factors that are associated with these patients' inherently poor prognosis. It would seem reasonable to consider cytoreductive surgery and to reserve hyperfractionated radiotherapy if debulking is not possible, a decision that could be made before surgery.

CNS relapse is frequent not only among those presenting with CNS disease, but as the initial site of progression in those without known CNS disease.^{8,27,28,34} The value of aggressive intrathecal therapy and craniospinal irradiation for CNS prophylaxis has been demonstrated in childhood diffuse lymphomas.²⁸ Nevertheless, in other series CNS relapse occurred despite prophylaxis of initially uninvolved CNS in one of 18 patients²⁷ and six of 55 patients.³⁴ In this series, both patients (11%) who experienced CNS relapse were PB stage D and displayed one or more adverse prognostic features; one who had presumed meningeal involvement at presentation relapsed clinically and cytologically at 6 months. The second patient developed back pain and a positive CSF cytology. Systemic relapse followed quickly in both cases. No patient with limited disease and without adverse prognostic features experienced CNS relapse. Compared with the NCI Pediatric Oncology Branch protocol, the Stanford regimen called for fewer intrathecal administrations and eliminated cytosine arabinoside.¹¹ Results obtained with this intrathecal prophylaxis do not appear inferior to those obtained with more aggressive regimens,^{27,34} but the number of patients so treated is limited.

The toxicity of the regimen was moderate. One patient with massive abdominal disease died early during induction therapy. The incidence of hospitalization for sepsis was low. The apparently lower risk of disabling mucositis in the regi-

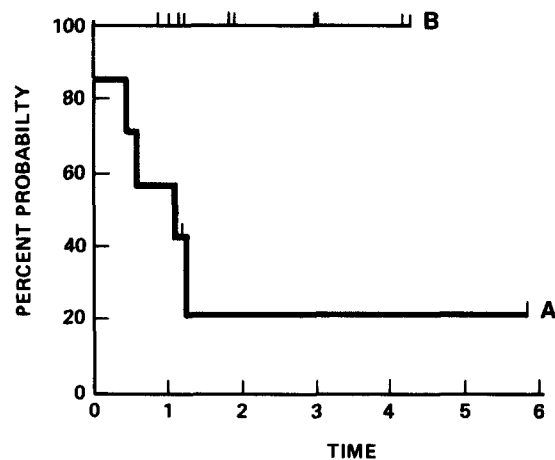


Fig 7. Survival, stage C or D, and high LDH (> 500 IU/L) v all others. (A) Stage C or D patients with high LDH; (B) all others.

men compared with that of Magrath et al may be due to the shorter duration of methotrexate infusion,¹¹ but direct comparisons of toxicity cannot be made outside the setting of a randomized trial. Drug dose delivery is another measure of toxicity; 83% of patients received > 75% of their ideal calculated doses of each cytotoxic agent.

An effective well-tolerated combined modality therapy has been described that can cure a large fraction of adults with SNCL. Furthermore, a subpopulation has been identified that has a significantly worse prognosis (PB stage C or D patients with pretreatment LDH > 500 IU/L, masses measuring > 10 cm, or bone marrow or CNS involvement). A role for hyperfrac-

tionated radiotherapy in the induction of remission has not been demonstrated; radiotherapy is of speculative benefit for adults presenting with bulky unresectable disease. It is justified to continue this protocol for patients with favorable presentations. Consideration will be given to surgical debulking or hyperfractionated radiotherapy for those with residual mass and the use of additional chemotherapy for those patients at higher risk for systemic and meningeal relapse.

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REFERENCES

1. 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* 49:2112-2135, 1982
2. Rappaport H: Tumors of the hematopoietic system, in *Atlas of Tumor Pathology*, section 3, fascicle 8. Washington, DC, Armed Forces Institute of Pathology, 1966, pp 98-99
3. Berard CW, O'Connor GT, Thomas LB, et al: Histopathological definition of Burkitt's tumor. *Bull WHO* 40: 601-607, 1969
4. Lukes RJ, Collins RD: Immunologic characterization of human malignant lymphomas. *Cancer* 34:1488-1503, 1974
5. Miliauskas MB, Berard CW, Young RC, et al: Undifferentiated non-Hodgkin's lymphomas (Burkitt's and non-Burkitt's types). The relevance of making this histologic distinction. *Cancer* 50:2115-2121, 1982
6. Levine AM, Pavlova Z, Pockros AW: Small noncleaved follicular center cell (FCC) lymphoma: Burkitt's and non-Burkitt's variants in the United States. I. Clinical features. *Cancer* 52:1073-1079, 1983
7. Grogan TM, Warnke RA, Kaplan HS: A comparative study of Burkitt's and non-Burkitt's "undifferentiated" malignant lymphoma: Immunologic, cytochemical, ultrastructural, cytologic, histopathologic, clinical and cell culture features. *Cancer* 49:1817-1828, 1982
8. Ramirez I, Sullivan MP, Wang YM, et al: Effective therapy for Burkitt's lymphoma: High-dose cyclophosphamide and high-dose methotrexate with coordinated intrathecal therapy. *Cancer Chemother Pharmacol* 3:103-109, 1979
9. Ziegler JL, Magrath IT, Deisseroth AB, et al: Combined modality treatment of Burkitt's lymphoma. *Cancer Treat Rep* 62:2031-2034, 1978
10. Jenkin DT, 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* 2:88-97, 1984
11. 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* 63:1102-1111, 1984
12. Anderson JR, Wilson JF, Jenkin DT: Childhood non-Hodgkin's lymphoma. The results of a randomized therapeutic trial comparing a 4-drug regimen (COMP) with a 10-drug regimen (LSA2-L2). *N Engl J Med* 308:559-565, 1983
13. Skarin AT, Canellos GP, Rosenthal DS, et al: Improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high dose methotrexate alternating with standard agents (M-BACOD). *J Clin Oncol* 1:91-98, 1983
14. Banks PM, Arsenau JC, Gralnick HR, et al: American Burkitt's lymphoma: A clinicopathologic study of 30 cases. II: Pathologic correlations. *Am J Med* 58:322-329, 1975
15. Berard CW, Dorfman RF: Histopathology of malignant lymphomas. *Clin Haematol* 3:39-76, 1974
16. Pavlova Z, Levine AM, Feinstein DI, et al: Small noncleaved follicular center cell lymphoma, Burkitt's vs. non-Burkitt's variants: Pathologic definition. *Lab Invest* 46:64A, 1982 (abstr)
17. Ziegler JL, Magrath IT: Burkitt's lymphoma. *Pathobiol Annu* 4:129-142, 1974
18. Magrath IT, Lwanga S, Carswell W, et al: Surgical reduction of tumor bulk in the management of abdominal Burkitt's lymphoma. *Br Med J* 2:308, 1974
19. Carbone PP, Kaplan HS, Mushoff K, et al: Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 31:1860-1861, 1971
20. Cohen LF, Balow JE, Magrath IT, et al: Acute tumor lysis syndrome. A review of 37 patients with Burkitt's lymphoma. *Am J Med* 68:486-491, 1980
21. Bleyer WA: The clinical pharmacology of methotrexate. New applications of an old drug. *Cancer* 41:36-51, 1978
22. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
23. Gehan EA: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrika* 52:203-223, 1965
24. Ziegler JL: Burkitt's Lymphoma. *N Engl J Med* 305:735-745, 1981

25. Ziegler JL, DeVita VT, Graw RG, et al: Combined modality treatment of American Burkitt's lymphoma. *Cancer* 38:2225-2231, 1976
26. Ziegler JL, Magrath IT, Olweny CL: Cure of Burkitt's lymphoma: Ten-year follow-up of 157 Ugandan patients. *Lancet* 2:936-938, 1979
27. Murphy SB, Hustu O, Rivera, et al: End results of treating children with localized non-Hodgkin's lymphomas with a combined modality approach of lessened intensity. *J Clin Oncol* 1:326-330, 1983
28. Murphy SB, Hustu HO: A randomized trial of combined modality therapy of childhood non-Hodgkin's lymphoma. *Cancer* 45:630-637, 1980
29. Kemeny MM, Magrath IT, Brennan MF: The role of surgery in the management of American Burkitt's lymphoma and its treatment. *Ann Surg* 196:82-86, 1982
30. Magrath IT, Lee YJ, Anderson T, et al: Prognostic factors in Burkitt's lymphoma. Importance of total tumor burden. *Cancer* 45:1507-1515, 1980
31. Janus C, Edwards BK, Sariuban E, et al: Surgical resection and limited chemotherapy for abdominal undifferentiated lymphomas. *Cancer Treat Rep* 68:599-605, 1984
32. Ziegler JL: Treatment results of 54 American patients with Burkitt's lymphoma are similar to the African experience. *N Engl J Med* 297:75-80, 1977
33. Norin T, Onyango J: Radiotherapy in Burkitt's lymphoma: Conventional or superfractionated regime—Early results. *Int J Radiat Oncol Biol Phys* 2:399-406, 1977
34. Sariban E, Edwards B, Janus C, et al: Central nervous system involvement in American Burkitt's lymphoma. *J Clin Oncol* 1:677-681, 1983