COMBINED CYCLOPHOSPHAMIDE, VINCRISTINE, AND PREDNISONE THERAPY OF MALIGNANT LYMPHOMA

JAMES K. LUCE, MD,* JESS F. GAMBLE, MD,* HENRY E. WILSON, MD,† RAYMOND W. MONTO, MD,‡ BERTHA L. ISAACS, MD,§ ROBERT L. PALMER, MD,‖ CHARLES A. COLTMAN, JR., LT. COL., MC, USAF,** JAMES S. HEWLETT, MD,¶ EDMUND A. GEHAN, PHD,* AND EMIL FREI III, MD*

A combination of intravenous cyclophosphamide and vincristine (Oncovin) and oral prednisone (COP) was given every 2 weeks to 262 patients with disseminated Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and follicular lymphoma. A complete remission was produced in 36% of patients with Hodgkin's disease, 50% of patients with lymphosarcoma, and 39% of patients with reticulum cell sarcoma. These remission rates are significantly superior to those produced by single agents. Patients who achieved a complete remission were randomly allocated to monthly COP (maintained remission) or to no treatment (unmaintained remission). The median duration of maintained remission was longer than unmaintained remission for Hodgkin's disease (42 weeks vs. 19 weeks) and lymphosarcoma (49 weeks vs. 21 weeks) but not for reticulum cell sarcoma (24 weeks vs. 25 weeks). The duration of remission for patients with little or no prior therapy was compared to that for patients in a similar study in which single agents were used.[4] For lymphosarcoma and reticulum cell sarcoma, remissions maintained with COP were longer than remissions maintained with cyclophosphamide. For Hodgkin's disease and lymphosarcoma, unmaintained remissions after COP induction were longer than after single agent induction. All parameters of response, that is, complete remission rate, duration of remission, and survival were adversely affected by major prior treatment with radiotherapy and chemotherapy. The initial response to treatment correlated positively with survival. The survival of patients with lymphosarcoma or reticulum cell sarcoma receiving COP treatment was significantly superior to a comparable group of patients treated sequentially with single agents.

SINGLE CHEMOTHERAPEUTIC AGENTS PRODUCE tumor regression in 50 to 70% of patients with malignant lymphoma; however, only 10 to 20% of patients achieve a complete remission.[4,20] If treatment is stopped after complete remission is achieved, the median time to relapse is 12 weeks. If treatment is continued during complete remission the remission lasts from 15 to 54 weeks.[4] It is not known whether chemotherapy prolongs survival in patients with lymphoma.

Chemotherapeutic agents with qualitatively different types of dose-limiting toxicity may often be given simutlaneously at the same doses tolerated when the drugs are used alone. This rationale for combination chemotherapy has proved successful in the treatment of patients with acute leukemia,[8] various solid tu-

Study undertaken by the Southwest Cancer Chemotherapy Study Group (Chairman, Emil Frei III), CA-03753.

Supported by Public Health Service Research Grants from the National Cancer Institute.

* University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Tex. (CA-10379, CA-06444).

† Ohio State University School of Medicine, Columbus, Ohio (CA-04920).

‡ Henry Ford Hospital, Detroit, Mich. (CA-04915).

§ Northwestern University School of Medicine, Chicago, Ill. (CA-06746).

‖ Scott and White Clinic, Temple, Tex. (CA-10187).

** Wilford Hall USAF Hospital, Lackland Air Force Base, San Antonio, Tex.

¶ Cleveland Clinic, Cleveland, Ohio (CA-04919).

Other participating institutions were: Baylor University College of Medicine, Houston, Tex. (Montague Lane, MD), CA-03392: Louisiana State University School of Medicine, New Orleans, La. (John N. Bickers, MD), CA-08002, CA-10455; Tulane University School of Medicine, New Orleans, La. (William J. Stuckey, Jr., MD), CA-03389; University of Arkansas Medical Center, Little Rock. Ark. (Arthur Haut, MD), CA-03400.

Address for reprints: James K. Luce, MD, Department of Developmental Therapeutics, the University of Texas M.D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Ave., Houston, Tex. 77025.

Received for publication February 12, 1971.

mors of childhood,[29] multiple myeloma,[1] and malignant lymphoma.[6,7,15,17] Preliminary studies performed by the Southwest Cancer Chemotherapy Study Group (SWCCSG) using a combination of cyclophosphamide (Cytoxan, Mead Johnson) vincristine (Oncovin, Eli Lilly), and prednisone (COP) demonstrated that these drugs can be given together at the same maximum doses tolerated when each is given alone.

Experimental and clinical trials indicate that for most rapidly growing tumors, intermittent drug treatment is superior to continuous daily drug administration.[2,14,18,25,26] Therefore, in this study, COP was given as pulse treatment at 2-week intervals in patients with Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma.

The objectives of this clinical trial were as follows:

1. To determine whether COP treatment could increase the response rate, particularly the complete remission rate, over that reported in the literature for single agents.

2. To compare the durations of complete remission in patients maintained on COP treatment with those not maintained on treatment.

3. To compare the durations of complete remission in patients maintained on COP treatment with those maintained by single agents.

4. To compare the durations of unmaintained complete remission in patients whose remissions were induced by COP treatment with those whose remissions were induced by single agents.

5. To compare survival of patients treated with COP to that of patients treated sequentially with single agents.

MATERIAL AND METHODS

Patients with disseminated histologically verified Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma were selected for treatment. Patients with a blood urea nitrogen level greater than 25 mg/100 ml or with a life expectancy estimated at less than one month were excluded. Prior radiotherapy or chemotherapy, including treatment with one or more of the drugs used in this study, did not exclude patients. *Major prior chemotherapy* was defined as at least 6 weeks of treatment with an alkylating agent or a periwinkle alkaloid (vincristine or vinblastine). *Major prior radiotherapy* consisted of greater than 2,500 rads to the mediastinum, abdomen and/or pelvis.

Patients were divided into two groups according to bone marrow reserve: *adequate bone marrow reserve* or *partially impaired bone marrow reserve.* Patients with *adequate bone marrow reserve* had white blood cell counts of 5,000/mm^3 or greater, and platelet counts of 150,000/mm^3 or greater, were less than 65 years of age, and had no history of previous mediastinal, abdominal, or pelvic radiotherapy. Patients with a *partially impaired bone marrow reserve* had one or more of the following: persistent white blood cell count between 3,000 and 5,000/mm^3 or platelet count between 100,000 and 150,000/mm^3, history of previous mediastinal, abdominal, or pelvic radiotherapy; were 65 years of age or older; or had a hypocellular marrow or marrow infiltrated with lymphoma cells. Patients with severely compromised bone marrow reserve such as those with persistent white blood cell counts of less than 3,000/mm^3, or platelet counts of less than 100,000/mm^3, were excluded from the study.

Each course of treatment consisted of a single intravenous injection of cyclophosphamide and vincristine on day 1 and of prednisone by mouth on days 1 through 5 followed by 3 days of decreasing doses. Courses were administered every 2 weeks. A schematic outline of the protocol is presented in Fig. 1.

The initial doses of drugs for patients with adequate bone marrow reserve were: cyclophosphamide, 800 mg/m^2, vincristine, 2 mg total dose; and prednisone, 60 mg/m^2 daily for 5 days followed by 3 days of decreasing doses (usually 40, 20, and 10 mg/day, respectively). Patients with moderately impaired bone marrow reserve received 400 mg/m^2 of cyclophosphamide with the same doses of vincristine and prednisone. Patients 65 years of age or older received a maximum of 1 mg of vincristine per course of treatment. The dosage of cyclophosphamide was increased or decreased with each course to produce minimal to moderate myelosuppression. The dosages of vincristine and prednisone were lowered if more than moderate toxicity developed.

Treatment designed to produce a complete remission (remission induction treatment) consisted of 6 courses of COP at 14-day intervals. When complete remission was achieved, 4 additional courses were given at 14-day intervals. Complete remission was defined as the absence of any clinical evidence of disease. Pa-

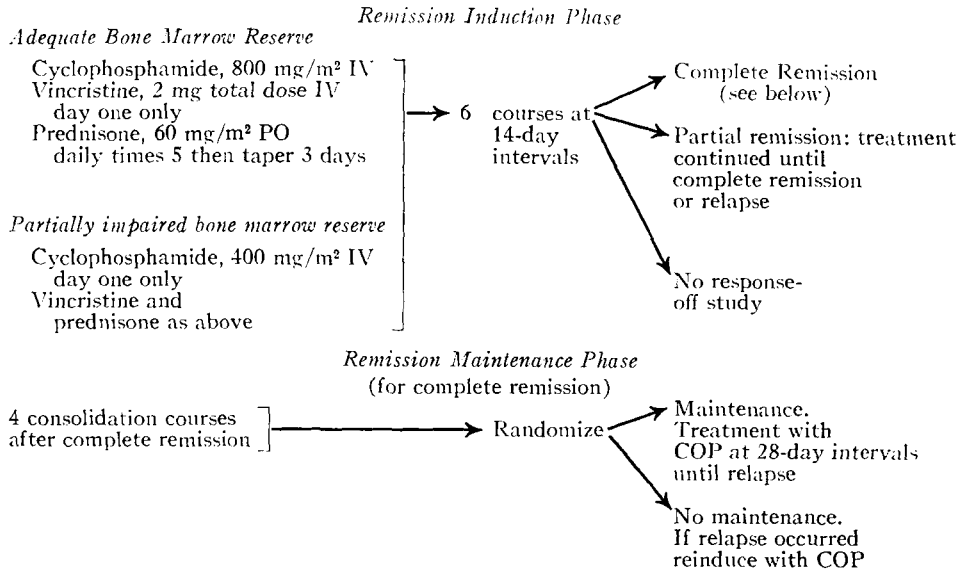

FIG. 1. Outline of study.

tients in complete remission after 10 courses of treatment were randomly allocated to either no further treatment (unmaintained remission) or continued treatment with COP administered at 4-week intervals (maintained remission). Relapse was defined as unequivocal evidence of recurrent tumor. Patients who relapsed during unmaintained remission received reinduction treatment with COP. Patients who attained a partial remission (greater than 50% reduction in the product of 2 diameters of all tumors but less than complete disappearance of tumors) were continued on COP treatment until complete remission or relapse occurred. If complete remission occurred, 4 additional courses were given and the patient was randomly allocated to maintenance therapy or to no maintenance therapy. Patients who did not respond to remission induction treatment were removed from the study.

STATISTICAL METHODS

The statistical methods used included: chi-square tests for testing differences in remission rates, a generalized Wilcoxon test[12] to test differences between remission or survival curves, and remission and survival curves calculated according to the method of Kaplan and Meier.[16] For significance tests, when the probability of the observed difference in response rates, survival curves, etc., was less than .05 or less than .01, the evidence against the null hypothesis was interpreted as significant or highly significant, respectively.

DESCRIPTION OF PATIENT SAMPLE

A total of 287 patients with malignant lymphoma who qualified for the study was entered between June 7, 1966 and April 28, 1968. Sixteen (6%) of the 287 cases were not used because of major deviations from the protocol, and 9 (3%) were not included for other reasons. Therefore, 262 (91%) patients were considered valid for analysis; these were entered from 11 institutions* in the SWCCSG. The number of patients by disease was: Hodgkin's disease 107, lymphosarcoma 74, reticulum cell sarcoma 66, and follicular lymphoma 15. Because of the small number entered, patients with follicular lymphoma are excluded from the remainder of the analysis. The age, sex, and stage of disease of patients in this study are shown in Table 1.

The ALB-EST study[4] is used as a single-drug control for this study. In that study, remissions were induced with either cyclophosphamide or a vinca alkaloid (vinblastine for

* The number of patients analyzed by institution was: Baylor College of Medicine, 8; Cleveland Clinic, 10; Henry Ford Hospital, 60; Louisiana State University School of Medicine, 3; Northwestern University School of Medicine, 28; Ohio State University School of Medicine, 55; Scott and White Clinic, 16; Tulane University School of Medicine, 10; University of Arkansas School of Medicine, 10; University of Texas M. D. Anderson Hospital and Tumor Intitute, 47; Wilford Hall USAF Medical Center, 15.

TABLE 1. Distribution of Patients by Disease Category* and Factors Which May Influence Response, Length of Remission, and Survival

Pretreatment factors		Hodgkin's disease		Lympho-sarcoma		Ret. cell sarcoma	
Total Patients		No.† 107	Per cent† (100)	No. 74	Per cent (100)	No. 66	Per cent (100)
Age (yrs.)							
3–29		35	(33)	6	(8)	6	(9)
30–49		45	(42)	24	(32)	20	(30)
over 50		27	(25)	44	(59)	40	(61)
Sex							
Male		76	(71)	53	(72)	41	(62)
Female		31	(29)	21	(28)	25	(38)
Stage							
III-No symptoms		6	(6)	11	(17)	7	(13)
With symptoms		23	(23)	7	(11)	6	(11)
IV-No symptoms		13	(13)	14	(22)	5	(9)
With symptoms		56	(57)	31	(49)	36	(67)
Prior Treatment							
Radiotherapy	*Chemotherapy*						
None or minor	None or minor	38	(36)	35	(47)	40	(61)
Major	None or minor	24	(22)	16	(22)	17	(26)
None or minor	Major	21	(20)	15	(20)	3	(4)
Major	Major	24	(22)	8	(11)	6	(9)
Bone Marrow Reserve							
Adequate		55	(52)	42	(58)	37	(57)
Partially impaired		51	(48)	30	(42)	28	(43)

* Excluding 15 patients with follicular lymphoma.
† Number in parentheses is percentage of patients. When numbers in a category do not add to total, status was unknown for remaining patients. Percentages were calculated using total patients with known status as a base.

Hodgkin's disease and vincristine for lymphosarcoma and reticulum cell sarcoma). Patients who achieved complete remission were randomly allocated to either maintenance treatment with cyclophosphamide or no maintenance treatment.

All patients in the ALB-EST study had Stage III or IV disease. However, patients having received major prior chemotherapy or those with moderately impaired bone marrow reserve (as defined in this study) were excluded from their study. Thus, in terms of prior treatment and bone marrow reserve, two major prognostic determinants, our patients in the *none or minor* prior treatment category are comparable to the ALB-EST patients. The percentage of males in the ALB-EST study with Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma, were, respectively, 68%, 66%, and 68%. In the same order, the percentages of patients below age 30 in the ALB-EST study were 38%, 11%, and 8%. All these figures are similar to those given in Table 1 for our study. Hence, when adjustment is made for prior therapy, it is concluded that the patients in the ALB-EST study constitute an adequate literature control group for the patients in this study.

RESULTS

Remission Induction

The response to remission induction treatment with COP in this study compared to single drug treatment and other drug combinations is presented in Table 2. In this study, 36% of patients with Hodgkin's disease, 50% with lymphosarcoma, and 39% with reticulum cell sarcoma achieved complete remission.

In comparative studies, cyclophosphamide was found to be as effective as other alkylating agents in producing remissions in patients with Hodgkin's disease.[13,19,27] In the ALB-EST study,[4] 53% of patients who received cyclophosphamide had at least partial remission, but only 14% had complete remission. In a collected series[20] of patients treated with cyclophosphamide, the partial plus complete and the complete objective remission rates were essentially the same as those in the ALB-EST

TABLE 2. Remission Rate by Disease Category in This Study and Others Reported in the Literature

Treatment	Hodgkin's disease			Lymphosarcoma			Ret. cell sarcoma			Reference
	No. of patients	Rem. Rate (%) Total§	CR‖	No. of patients	Rem. Rate (%) Total§	CR‖	No. of patients	Rem. Rate (%) Total§	CR‖	
Single Agents										
Cyclophosphamide										
ALB-EST*	86	53	14	56	68	11	33	52	12	4
Collected Series	389	56	11	234	62	20	197	57	13	13, 19, 20, 28
Vinblastine										
ALB-EST	88	65	20							4
Vincristine										
ALB-EST				47	38	6	32	38	12	4
Combination Chemotherapy										
COP (Ctx, Vcr, Pred)	107	77	36	74	88	50	66	78	39	This study
Ctx, Vcr, Pred(ALB)				37	95	35	26	69	31	15
MOPP (HN_2, Vcr Procarb, Pred)										
NCI†	43		81							6
SWCCSG‡	110	89	72							21

* Leukemia B-Eastern Solid Tumor Group.
† National Cancer Institute.
‡ Southwest Cancer Chemotherapy Study Group.
§ Total remission rate equals complete plus partial remissions.
‖ CR = complete remission.

study.[4] Vinblastine and the alkylating agents are about equally effective in Hodgkin's disease.[4,28] Of patients with Hodgkin's disease in this study, 36% had a complete remission with COP; this is significantly better than the complete remission rate for cyclophosphamide or vinblastine alone ($P < .01$ for both comparisons). The COP treatment, however, resulted in a lower percentage of complete remissions than that produced by the MOPP program reported in studies conducted by the National Cancer Institute[6] and by the SWCCSG.[21]

The complete remission rate in the COP study for patients with lymphosarcoma was 50%, which is significantly greater than the complete remission rate for cyclophosphamide (11%) or for vincristine alone, 6% ($P < .01$ for both comparisons). The complete remission rate after COP treatment was similar to that reported by the ALB group for a somewhat different program[15] using a combination of the same 3 drugs: cyclophosphamide, vincristine, and prednisone.

Patients with reticulum cell sarcoma had a complete remission rate of 39% which was significantly better than that reported[4,20] for cyclophosphamide (12%) or for vincristine alone, 12% ($P < .01$ for both comparisons). Again, the results with COP compared favorably to those reported by the ALB group[15] in which their combination resulted in a 31% complete remission rate.

Because the number of patients in many of the treatment and disease categories was small, the results for all 3 disease categories were grouped together for the analysis of the relationship of major prior radiotherapy and chemotherapy to response (Table 3). Major prior therapy, particularly with both modalities, adversely affected response and survival.

Of the patients in whom a complete remission was induced, 25% achieved a complete remission within 7 weeks from the beginning of treatment, 50% within 10 weeks, 75% within 18 weeks, and 95% within 25 weeks. The median time from beginning of treatment to complete remission was approximately the same for each disease.

Duration of Complete Remission

Patients who achieved complete remission received a total of 10 or more courses (at least 4 courses after achieving complete remission) and then were randomly allocated to maintenance treatment or to no maintenance treatment. Duration of complete remission was measured from the time of random allocation unless otherwise indicated in the text or the tables.

Maintenance vs. no maintenance during

TABLE 3. Relationship of Prior Treatment to Response

Prior treatment*		No. of patients	Percent complete remission	Median length complete remission (wks).	Median survival† (wks.)
Chemotherapy	Radiotherapy				
None or minor	None or minor	113	50	48	113
None or minor	Major	57	39	25	34
Major	None or minor	39	33	20	84
Major	Major	38	26	43	55

* See text for definitions of prior therapy.
† Survival include all patients, regardless of response.

remission: Patients with Hodgkin's disease had a 42-week median duration of complete remission if maintained on COP treatment compared to 19 weeks not maintained (P = 0.05). Patients with lymphosarcoma had a median duration of 48 weeks if maintained on COP treatment compared to 21 weeks for non-maintained patients (P = 0.06). Maintenance treatment did not prolong the duration of complete remission in patients with reticulum cell sarcoma (Table 4).

In this study, 108 patients achieved partial remission only. All such patients were maintained on COP treatment during remission. The median duration of partial remissions was 18 weeks; only 25% of these patients had remissions which lasted longer than 30 weeks. The median duration of maintained complete remission for the 3 diseases in this study was 43 weeks which is significantly longer than the maintained partial remissions.

Duration of maintained complete remission: The median duration of COP-maintained complete remission as influenced by prior treatment and as compared to single agent induction and maintenance treatment is presented in Table 5. In this table, the duration of COP remission is measured from the time complete remission is achieved in order to compare remission duration with single agent remission induction. All patients who achieved complete remission and received maintenance treatment are listed, including those patients relapsing prior to randomization or those not randomized to maintenance treatment but who nevertheless received maintenance treatment for various reasons. In papatients who had not received major prior treatment the duration of COP-maintained remission was substantially longer than those with major prior treatment in Hodgkin's dis-

TABLE 4. Duration of Complete Remission from Time of Randomization

Disease and treatment during remission	No. of patients*	Median length of complete remission
Hodgkin's disease	31	20
Maintenance	11	42
No maintenance	20	19
Lymphosarcoma	32	37
Maintenance	17	48
No maintenance	15	21
Reticulum cell sarcoma	19	24
Maintenance	11	24
No maintenance	8	25

* Patients were randomized to maintenance or no maintenance without respect to type of disease. This explains the excess of patients on maintenance treatment for Hodgkin's disease. Overall, 43 patients were on no maintenance compared with 39 on maintenance.

TABLE 5. Duration of Maintained Complete Remission

	No. of patients	Median duration of complete remission (wks.)†
Hodgkin's Disease		
COP		
No major prior therapy	12	42
Major prior therapy	6	14
Cyclophosphamide*	23	55
Lymphosarcoma		
COP		
No major prior therapy	10	49
Major prior therapy	12	45
Cyclophosphamide*	11	22
Reticulum Cell Sarcoma		
COP		
No major prior therapy	12	28
Major prior therapy	6	10
Cyclophosphamide*	10	14

* Single agent (cyclophosphamide) treatment during remission (ALB-EST study[1]).
† From onset of complete remission to relapse.

ease (42 weeks vs. 14 weeks) and in reticulum cell sarcoma (28 weeks vs. 10 weeks) but not in lymphosarcoma (49 weeks vs. 45 weeks). Possibly because of the small numbers of patients, none of these differences was near statistical significance at the 5% level.

Patients in the single drug study (ALB-EST) had not received major prior treatment and are comparable to the COP patients without prior treatment. The median durations of maintained remission were similar in the COP and the single agent study for Hodgkin's disease but were longer for COP treatment in lymphosarcoma (49 weeks vs. 22 weeks) and reticulum cell sarcoma (28 weeks vs. 14 weeks), although the differences were not statistically significant.

Duration of unmaintained complete remission: The median duration of unmaintained complete remission following COP remission induction according to prior treatment status and as compared to single agent (cyclophosphamide) remission induction is presented in Table 6. The duration of remission is measured from the time of randomization to no maintenance treatment. In Hodgkin's disease, the median duration of unmaintained remission following COP induction treatment was longer in patients without prior treatment (19 weeks) than in patients with prior major chemotherapy or radiotherapy (11 weeks). The number of patients in the other disease categories was too small for valid comparison.

TABLE 6. Duration of Unmaintained Complete Remission*

	No. of patients	Median duration of complete remission (wks.)
Hodgkin's Disease		
COP Induction		
No major prior therapy	10	19
Major prior therapy	10	11
Single agent induction†	12	11
Lymphosarcoma		
COP Induction		
No major prior therapy	12	21
Major prior therapy	3	—
Single agent induction‡	6	11
Reticulum Cell Sarcoma		
COP Induction		
No major prior therapy	7	17
Major prior therapy	1	—
Single agent induction‡	5	24

* From end of treatment (time of randomization) to relapse.
† Cyclophosphamide or vinblastine.
‡ Cyclophosphamide or vincristine.

The median duration of unmaintained remission was longer following COP induction than cyclophosphamide induction in patients with Hodgkin's disease (19 weeks vs. 11 weeks) and lymphosarcoma (21 weeks vs. 11 weeks).

None of these differences in unmaintained remission duration between the COP and the ALB-EST studies (Table 6) are statistically significant perhaps because of the small number of cases in most categories.

Survival

The comparative effects of COP treatment and single-agent sequential treatment (ALB-EST study[4]) on survival are presented in Fig. 2. Survival curves for the COP program are given for all patients and for those who did not receive major prior therapy. The latter group is comparable to the ALB-EST single-agent control.

Generally, the survival curves in Fig. 2 follow a straight-line pattern, indicating exponential distribution and a constant death rate per unit time. If a constant death rate is confirmed to be characteristic in patients with lymphoma treated with chemotherapy, it may be possible to extrapolate survival early during the course of therapeutic trials and add the important parameter of survival to an evaluation of the efficacy of the trial.

The median survival time in Hodgkin's disease has not been reached in any of the treatment groups, although it will be approximately 100 weeks for all patients in the COP study. Hodgkin's disease patients with little or no prior treatment have an estimated median survival time of 140 weeks. The median length of survival for the ALB-EST single agent sequential treatment group was 93 weeks. The patients in the ALB-EST group are comparable to those with no prior treatment in the COP study, and the results suggest that survival may be increased by COP treatment. However, the difference is not statistically significant ($P > .20$).

For patients with lymphosarcoma, the percentage surviving one year was 71% for all patients treated with COP and 81% for COP-treated patients who had not received major prior treatment. In the ALB-EST study, 53% of lymphosarcoma patients survived one year.

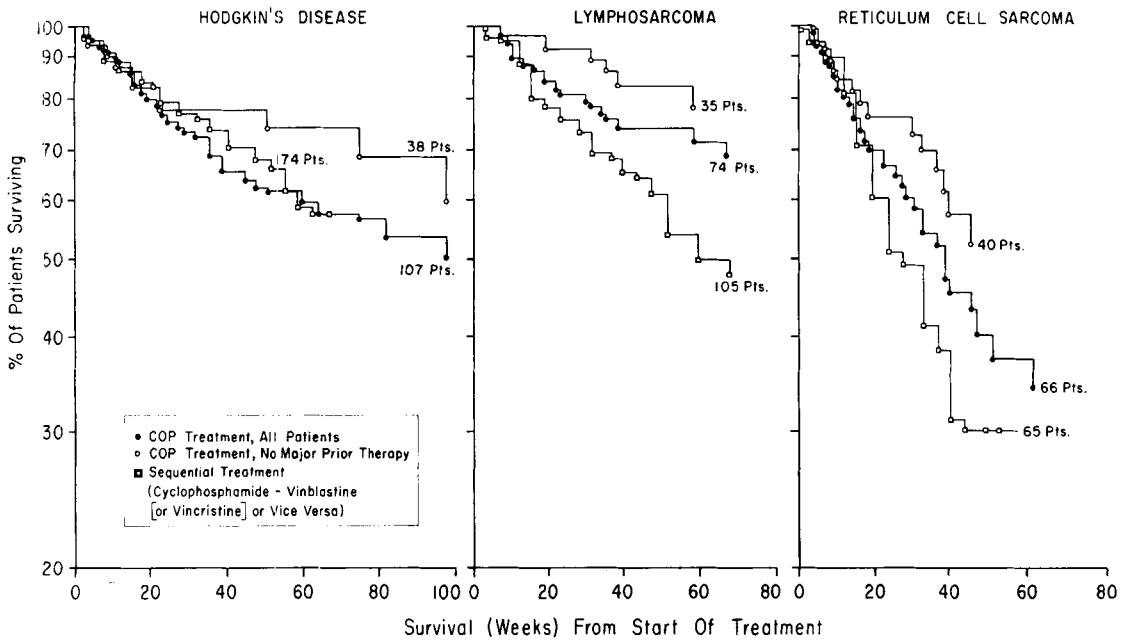

FIG. 2. Survival time: comparison of combined and sequential single agent treatment.

The survival curve for COP patients not having received major prior therapy was significantly superior ($P < .01$) while that for all patients was suggestively better ($P = .10$) than that for patients in the ALB-EST study.

The one-year survival rate for reticulum cell sarcoma patients in the ALB-EST study was 31%. The one-year survival rate was 37% for all COP patients and 45% for COP patients with no major prior treatment. The difference between survival rates for all COP reticulum cell sarcoma patients and the ALB-EST patients was nearly significant ($P = .09$), and the difference between survival rates for the COP reticulum cell sarcoma patients without major prior treatment and the ALB-EST patients was highly significant ($P = .01$).

The relationship of initial response to COP treatment and survival is shown in Fig. 3. Clearly, patients achieving complete remission had a substantially longer survival than those who did not respond (whether adjustment is

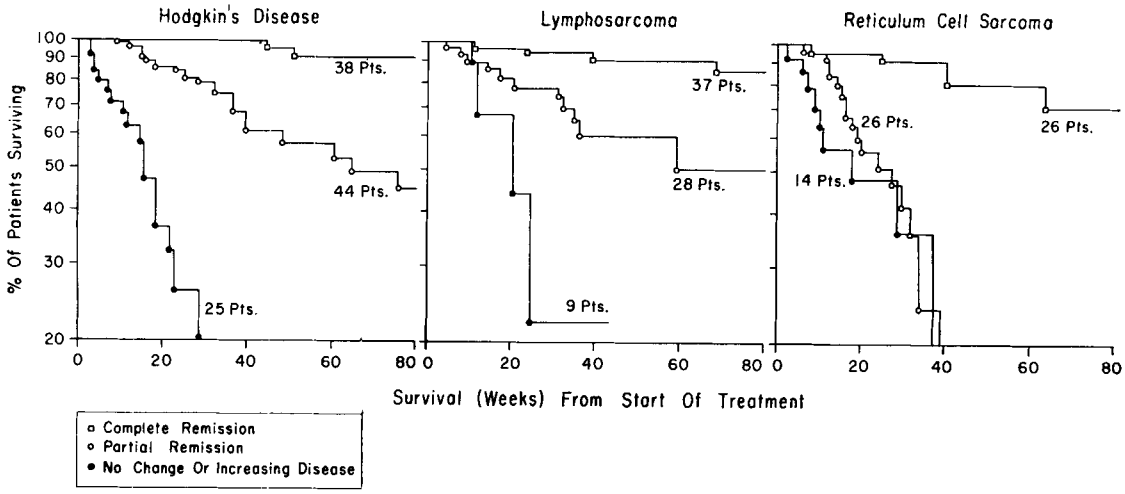

FIG. 3. Effect of response to chemotherapy on survival.

made for the 10-week median time to complete remission or not). With the exception of patients with reticulum cell sarcoma, the survival curves for patients achieving partial remission were intermediate between those for complete responders and non-responders.

Toxicity

Types of toxicity encountered in the COP program are outlined in Table 7. More than one type of toxicity usually developed in patients.

The most common toxic effect was bone marrow depression caused by cyclophosphamide. This was intrinsic to the design of the study and occurred in 88% of the patients. Myelosuppression was considered severe in 9% of patients and fatal in 1%.

Paresthesias caused by vincristine were the second most frequent toxicity, with 20% of patients having moderate and 6% having severe paresthesias. In addition, 10% of patients had moderate or severe gastrointestinal toxicity (abdominal pain and constipation) and 12% had moderate or severe motor weakness. Vincristine toxicity was severe enough to require permanent cessation of vincristine therapy in 35 patients (13%).

Some degree of hair loss occurred in 37% of patients; severe alopecia was recorded in 7%. Patients treated with the COP regimen should be forwarned of the possibility of hair loss which is reversible.

Severe infections occurred in 4% of the patients. One per cent of patients died from infections which were associated with severe leukopenia resulting from the chemotherapy.

In general, prednisone was well tolerated. Only 29% of the patients had Cushingoid manifestations and these were usually mild. The possibility that prednisone increased the patients' susceptibility to infections cannot be excluded.

Fatal drug toxicity occurred in 4 patients. Three patients died from cyclophosphamide-induced leukopenia and resulting septicemia and one from a bleeding peptic ulcer presumably caused by prednisone.

TABLE 7. Toxicity

Type of toxicity	No. of patients*	Degree of toxicity				
		None	Mild	Moderate	Severe	Fatal
General						
Infection†	250	207 (82)	12 (5)	17 (7)	11 (4)	3 (1)†
Hemorrhage	253	244 (96)	4 (2)	2 (1)	2 (1)	2 (1)‡
Hair loss	253	160 (63)	39 (15)	37 (15)	17 (7)	0 (0)
Cyclophosphamide						
Bone marrow	258	30 (12)	104 (40)	97 (38)	24 (9)	3 (1)
Hem. cystitis	252	239 (95)	3 (1)	9 (4)	1 (0)	0 (0)
Vincristine						
G. I. (constipation, abdominal cramps)	252	200 (79)	27 (11)	20 (8)	5 (2)	0 (0)
Motor weakness	249	192 (77)	26 (10)	25 (10)	6 (2)	0 (0)
Paresthesias	255	96 (38)	92 (36)	52 (20)	15 (6)	0 (0)
Prednisone						
Cushingoid (moonface, striae, acne)	253	177 (70)	44 (17)	31 (12)	1 (0)	0 (0)
G. I. (gastritis, peptic ulcer)	252	208 (82)	22 (9)	15 (6)	6 (2)	1 (0)†
Anxiety	251	222 (88)	18 (7)	7 (3)	4 (2)	0 (0)
Insomnia	251	237 (94)	9 (4)	3 (1)	2 (1)	0 (0)
Psychosis	251	245 (98)	1 (0)	1 (0)	4 (2)	0 (0)
Other	255	232 (91)	7 (3)	14 (6)	2 (1)	0 (0)

* Number of patients who had a report for the particular type of toxicity.
† Infection presumed related to chemotherapy.
‡ 3 patients died from infection while myelosuppressed; one patient also had a massive G. I. hemorrhage. The 4th patient died of G. I. hemorrhage from a peptic ulcer.
Numbers in parentheses are percentage of patients.

DISCUSSION

The combination chemotherapy program (COP) employed in this study has increased significantly the complete remission rate in patients with lymphoma over that which can be achieved with single-agent treatment. If one assumes independent drug action and if Ca, Cb, and Cc are the chances of achieving a complete remission for the 3 agents the following formula should predict the complete remission rate (C) for a combination of the 3 drugs employed at full doses:

$$C = 1 - [(1 - Ca)\ (1 - Cb)\ (1 - Cc)].$$

Assuming a 0.15 complete remission rate for each agent used alone, the predicted complete remission rate for the combination (COP) is 0.39. This predicted remission rate is consistent with the clinical results of the COP program in which complete remission rates of 35% to 50% were produced. This finding suggests that the 3 drugs acted independently. Similar observations have been made for acute lymphocytic leukemia wherein full doses of combinations of agents with qualitatively different toxicities gave increases in the complete remission rate consistent with a calculated rate assuming independent drug action.[8]

The magnitude of the initial response to COP markedly influenced survival as evidenced in Fig. 3. This correlation of the initial response rate with survival indicates that the frequency and magnitude of initial response may be employed effectively in the rapid evaluation of new treatment programs.

It has been demonstrated in patients with lymphocytic leukemia and in those with lymphoma that drug treatment continued during remission will prolong the duration of remission.[4,10,23] In the present study, this was found to be true also for Hodgkin's disease and lymphosarcoma in which complete remissions maintained on COP lasted more than twice as long as unmaintained remissions (Table 4).

Major prior treatment adversely affected all parameters of response, that is complete remission rate, duration of maintained and unmaintained remissions, and survival (Tables 3, 5, 6, Fig. 2). The few exceptions to this, such as the duration of maintained complete remission in lymphosarcoma (Table 5), may not be significant in view of the small number of patients. The adverse effect of major prior radiotherapy is explained, at least in part, by chronically compromised bone marrow reserve. Thus, the average dose of cyclophosphamide per course of treatment in patients with major prior radiotherapy was 62% of that for patients without major prior treatment.

Except for Hodgkin's disease maintained remissions, the durations of maintained and unmaintained complete remission were longer in the COP program for patients not having received major prior treatment than for patients receiving single-agent remission induction and maintenance programs (Tables 5, 6). This is also true in acute lymphocytic leukemia in which prolonged durations of unmaintained complete remissions were achieved after combined intensive treatment.[8] The duration of unmaintained complete remission has been employed to evaluate the number of neoplastic cells persisting at the end of treatment.[8,26] Assuming comparable lymphoma cell proliferative behavior, longer durations of unmaintained remission indicate that fewer neoplastic cells persist at the end of treatment. In this context, COP treatment is more effective than single agent treatment.

The combination treatment program consisting of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) for Hodgkin's disease[6] is superior to the COP program both in rate of complete remission and in duration of unmaintained complete remission (Table 2). The median duration of unmaintained remission following 6 courses of MOPP treatment is 24 months, compared to only 5 months in the COP program.

There are 3 major differences between the MOPP program and the COP program. 1. The alkylating agent in the MOPP program is mechlorethamine, and in the COP program it is cyclophosphamide. Comparative studies in patients with Hodgkin's disease indicate that the 2 agents have reasonably comparable activity.[13,19,27] Thus, for Hodgkin's disease, there is no evident reason why the alkylating agent should make a difference between the MOPP and COP program. 2. The MOPP program incorporates procarbazine which is not included in the COP program. Procarbazine is probably as effective as the alkylating agents or periwinkle alkaloids for Hodgkin's disease[22] and could be the significant factor is increasing the response rate. Procarbazine, however, is myelosuppressive and both its dose and the dose of mechlorethamine are decreased to about 60% of full doses for the MOPP pro-

gram. 3. It is possible that this difference in schedule is responsible for the difference in response. Clinical and experimental studies of alkylating agents and cell cycle specific antimetabolites indicate that the schedule of administration may substantially influence the therapeutic index.[2,14,18,25,26] Therapeutic trials, with drug schedule as an independent variable, are currently underway in patients with lymphoma.

Toxicity for the COP program (Table 7) was mild to moderate and consisted primarily of bone marrow depression, which was intrinsic to the design of the study. Vincristine toxicity was severe in only 6% of the patients. Three died from infection associated with severe granulocytopenia and one died of gastrointestinal hemorrhage from gastric ulceration presumably caused by prednisone. Cushingoid manifestations occured in only 30% of the patients. Continued daily treatment with prednisone for a 3- to 5-month period will produce Cushingoid manifestations in the majority of patients. Previously, it has been observed that intermittent large doses of corticosteroids produces fewer side effects than continuous administration.[3]

The most effective treatment for disseminated Hodgkin's disease currently appears to the MOPP program.[6,21] For lymphosarcoma and reticulum cell sarcoma, the COP program is more effective than single agent sequential treatment and as effective as any reported combined treatment. It is important, however, to emphasize the rapid evolution and improvement which is occurring in the treatment of patients with disseminated lymphoma. Other forms of combined treatment have produced an increase in the remission rate.[7,15,17] A major advance in the management of acute lymphocytic leukemia was the recognition that combined treatment was capable of greatly increasing the complete remission rate.[8] Following this advance, the improvement of treatment during remission including combined, sequential cyclic, and reinduction therapy greatly prolonged the duration of effective survival in acute leukemia.[5,9–11,24,30] Many of these concepts and approaches now are being employed in the treatment of patients with lymphoma, and it seems probable that a similar and substantial prolongation of effective survival will occur.

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