

CHEMOTHERAPY ALONE COMPARED WITH CHEMOTHERAPY PLUS RADIOTHERAPY FOR LOCALIZED INTERMEDIATE- AND HIGH-GRADE NON-HODGKIN'S LYMPHOMA

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ABSTRACT

Background Patients with clinically localized, intermediate- or high-grade non-Hodgkin's lymphoma usually receive initial treatment with a doxorubicin-containing regimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Pilot studies suggest that eight cycles of CHOP alone or three cycles of CHOP followed by involved-field radiotherapy are effective in such patients.

Methods We compared these two approaches in a prospective, randomized, multi-institutional study. The end points were progression-free survival, overall survival, and life-threatening or fatal toxic effects. Two hundred eligible patients were randomly assigned to receive CHOP plus radiotherapy, and 201 received CHOP alone.

Results Patients treated with three cycles of CHOP plus radiotherapy had significantly better progression-free survival ($P=0.03$) and overall survival ($P=0.02$) than patients treated with CHOP alone. The five-year estimates of progression-free survival for patients receiving CHOP plus radiotherapy and for patients receiving CHOP alone were 77 percent and 64 percent, respectively. The five-year estimates of overall survival for patients receiving CHOP plus radiotherapy and for patients receiving CHOP alone were 82 percent and 72 percent, respectively. The adverse effects included one death in each treatment group. Life-threatening toxic effects of any type were seen in 61 of 200 patients treated with CHOP plus radiotherapy and in 80 of 201 patients treated with CHOP alone ($P=0.06$). The left ventricular function was decreased in seven patients who received CHOP alone, whereas no cardiac events were recorded in the group receiving CHOP plus radiotherapy ($P=0.02$).

Conclusions Three cycles of CHOP followed by involved-field radiotherapy are superior to eight cycles of CHOP alone for the treatment of localized intermediate- and high-grade non-Hodgkin's lymphoma. (N Engl J Med 1998;339:21-6.)

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PATIENTS with intermediate- or high-grade non-Hodgkin's lymphoma can be cured with doxorubicin-containing combination chemotherapy.¹ The cure rate varies according to several pretreatment prognostic variables, including the stage of disease.² Chemotherapy cures most patients with localized disease (stage I or II), but only

about 30 to 40 percent of patients with advanced disease (stage III or IV).^{1,3}

Two strategies for treating localized intermediate- and high-grade histologic subtypes of lymphoma have emerged in the past 15 years: chemotherapy alone with a doxorubicin-containing combination regimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), administered for six to eight cycles, or a short course of chemotherapy (usually three cycles of CHOP) followed by involved-field radiotherapy.⁴ The presumed advantages of chemotherapy alone are the avoidance of long-term complications of radiotherapy and the higher total doses of systemic therapy, which increase the potential for eliminating microscopic sites of disease. The possible benefits of a short course of chemotherapy followed by radiotherapy are the reduction in the risk of cardiac toxicity due to the lower total dose of doxorubicin administered, the use of two mainly non-cross-resistant treatments, and the administration of radiotherapy directly to sites of detectable disease. There is no convincing evidence in favor of either strategy.³ Consequently, in 1988 the Southwest Oncology Group began a prospective, randomized trial to compare these two widely used treatments.

METHODS

Patient Selection

This study (Southwest Oncology Group Study 8736) enrolled patients with biopsy-proved intermediate- or high-grade non-Hodgkin's lymphoma (working-formulation groups D through J), excluding patients with lymphoblastic lymphoma.⁵ Histologic specimens were evaluated by independent expert reviewers. All patients had stage I, stage IE (including bulky disease), nonbulky stage II, or nonbulky stage IIE disease. Bulky disease was defined as a mediastinal mass with a maximal diameter exceeding one third the maximal chest diameter or any other mass 10 cm or more in maximal diameter. For staging of their disease, all patients underwent a physical examination, chest radiography, computed tomography of the abdomen and pelvis, and bone marrow biopsy; measurement of serum aspartate aminotransferase, total

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bilirubin, alkaline phosphatase, and lactate dehydrogenase; and peripheral-blood counts. Assignment of the Ann Arbor stage was based on clinical findings and tumor measurements obtained before excisional biopsy.⁶

All the patients were ambulatory, and no patient had a history of congestive heart disease or another cancer, symptoms or findings compatible with central nervous system involvement with lymphoma, or any prior treatment for lymphoma. At the time of randomization, patients were stratified according to age (≥ 65 years vs. < 65 years), stage (I vs. II), and histologic subtypes (diffuse large-cell [working-formulation groups G and H] vs. all other eligible histologic subtypes, including follicular large-cell, diffuse small-cleaved-cell, diffuse mixed small- and large-cell, and diffuse small-noncleaved-cell [working-formulation groups D, E, F, and J, respectively]), site of disease involvement (gastrointestinal tract vs. all other sites), and whether all visible and measurable tumors were resected. All patients gave written informed consent according to institutional guidelines.

Treatment

Patients were randomly assigned to receive eight cycles of CHOP alone or three cycles of CHOP followed by radiotherapy. The CHOP regimen was the standard regimen, consisting of cyclophosphamide (750 mg per square meter of body-surface area, given as a 15-minute intravenous infusion on day 1), doxorubicin (50 mg per square meter, given intravenously in a bolus over a period of 1 to 2 minutes on day 1), vincristine (1.4 mg per square meter [maximal dose, 2.0 mg], given intravenously in a bolus over a period of 1 to 2 minutes on day 1), and prednisone (100 mg daily, given orally on days 1 to 5).¹ The CHOP cycles were repeated at 21-day intervals. Involved-field radiotherapy began three weeks after the third cycle of CHOP for the patients assigned to receive three cycles of CHOP plus radiotherapy. The radiotherapy doses ranged from 4000 to 5500 cGy. The total dose was determined by the treating radiotherapist; patients receiving higher doses generally had clinical evidence of residual disease after having received 4000 cGy (the majority of patients received 4500 to 5000 cGy). The daily dose varied from 180 to 200 cGy. The radiotherapy ports included all visible sites of disease determined before biopsy and treatment with CHOP. The treatment plans were reviewed by an independent radiotherapist before treatment was initiated.

Statistical Analysis

All eligible patients were included in comparisons of treatment. Life-table estimates of outcome used the Kaplan–Meier method.⁷ Progression-free survival was measured from the time of randomization until progression of disease, relapse, or death from any cause. Overall survival was measured from the time of randomization until death from any cause. Comparisons were adjusted for stratification factors by Cox regression, and all tests were two-sided.^{8,9} The hazard ratios for progression-free survival and overall survival were estimated by Cox regression.⁹ Patient characteristics and toxic effects were compared between groups by the chi-square test. Toxic effects and responses to therapy were coded according to standard Southwest Oncology Group guidelines.

RESULTS

Patient Characteristics

Between March 1988 and June 1995, 442 patients were registered for the study. Of these, 41 were not eligible, mainly because their biopsies showed low-grade histologic features (24 patients). All 401 patients who were eligible for the study were included in all analyses; 201 patients were assigned to receive eight cycles of CHOP alone, and 200 patients were assigned to receive three cycles of CHOP

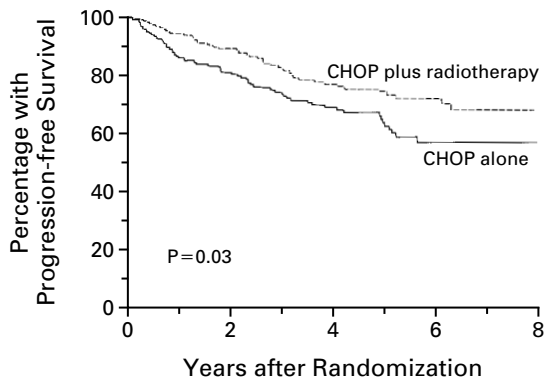
TABLE 1. CLINICAL CHARACTERISTICS OF 401 PATIENTS TREATED WITH EIGHT CYCLES OF CHOP OR THREE CYCLES OF CHOP PLUS RADIOTHERAPY.

CLINICAL VARIABLE	8 CYCLES OF CHOP (N=201)	3 CYCLES OF CHOP PLUS RADIOTHERAPY (N=200)
	number (percent)	
Age		
≤ 60 yr	103 (51)	101 (50)
> 60 yr	98 (49)	99 (50)
Stage		
I	135 (67)	136 (68)
II	66 (33)	64 (32)
Serum lactate dehydrogenase		
Normal	159 (79)	159 (80)
Increased	42 (21)	41 (20)
Performance status		
0 or 1	193 (96)	194 (97)
2	8 (4)	6 (3)
No. of risk factors*		
0 or 1	142 (71)	147 (74)
2	44 (22)	38 (19)
3	14 (7)	14 (7)
4	1 (<1)	1 (<1)

*Adverse risk factors were defined as an age > 60 years, stage II disease, increased serum lactate dehydrogenase, and a performance status of 2.

plus radiotherapy. The clinical characteristics of the patients are summarized in Table 1. These characteristics correspond to those of the international prognostic index, except that patients with stage I disease and those with stage II disease were classified separately.² There were no patients with more than one extranodal site of disease, a variable used in the international prognostic index, because patients were selected for stage I or II disease. The modified international prognostic index used in this study tabulated the total number of high-risk features applicable to each patient, including age greater than 60 years, stage II disease, increased serum lactate dehydrogenase concentration, and decreased performance status. Risk was assigned according to the number of adverse prognostic features. Table 1 also shows patients categorized according to risk group with the international prognostic index modified for stage.

The two treatment groups did not differ in clinical characteristics or risk categories. For all 401 patients, the median age was 59 years, and diffuse large-cell lymphoma (working-formulation groups G and H) was the most common histologic subtype (75 percent of all patients). Other subtypes included follicular large-cell, 10 percent; diffuse small-cleaved-cell, 10 percent; diffuse mixed small- and large-cell, 2 percent; diffuse mixed small- and large-cell, 6 percent; and diffuse small-noncleaved-cell, 6 percent (working formulation groups D, E, F, and J, respectively). Extranodal sites of disease were found in 150 of the 401 patients (37 percent).



No. AT RISK		0	2	4	6	8
CHOP alone		201	172	111	55	14
CHOP plus radiotherapy		200	178	119	70	17

Figure 1. Progression-free Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

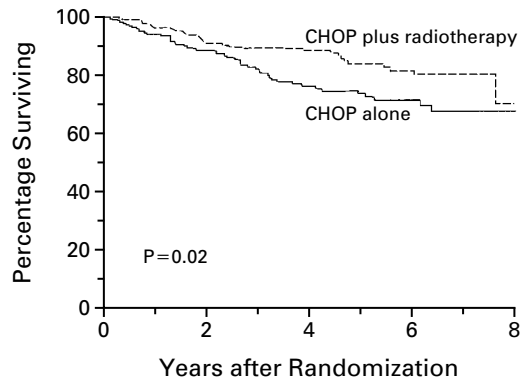
Sixty-five patients in the CHOP-alone group died or had progression of their disease, as compared with 45 patients in the CHOP-plus-radiotherapy group. The estimated rates of progression-free survival at five years were 64 percent and 77 percent, respectively.

Response to Treatment

All visible tumors were resected as a consequence of the diagnostic biopsy before the start of treatment in 116 patients (58 patients in each treatment group). There was a complete response (resolution of all visible tumors) in 210 of 285 patients with residual disease after the biopsy (74 percent). There were 104 complete responses in 143 patients treated with CHOP alone (73 percent) and 106 complete responses in 142 patients treated with CHOP plus radiotherapy (75 percent).

Survival

Patients treated with three cycles of CHOP plus radiotherapy had significantly better progression-free survival than patients treated with eight cycles of CHOP alone ($P=0.03$) (Fig. 1). The estimated hazard ratio for the CHOP-alone group as compared with the CHOP-plus-radiotherapy group was 1.5 (95 percent confidence interval, 1.0 to 2.2). The five-year estimates of progression-free survival for patients treated with CHOP plus radiotherapy and CHOP alone were 77 percent and 64 percent, respectively. Similarly, overall survival was better for patients treated with CHOP plus radiotherapy than for those treated with CHOP alone ($P=0.02$) (Fig. 2). The estimated hazard ratio for the CHOP-alone group as compared with the CHOP-plus-radiotherapy group was 1.7 (95 percent confidence interval, 1.1 to 2.7). The five-year survival estimates for pa-



No. AT RISK		0	2	4	6	8
CHOP alone		201	187	120	61	14
CHOP plus radiotherapy		200	185	128	75	17

Figure 2. Overall Survival of 201 Patients Receiving Eight Cycles of CHOP and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

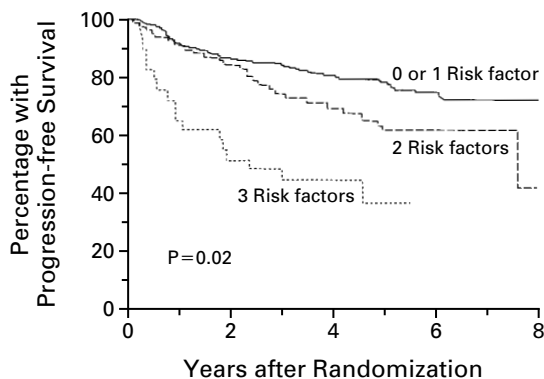
There were 51 deaths in the CHOP-alone group, and 32 in the CHOP-plus-radiotherapy group. The estimated rates of survival at five years were 72 percent and 82 percent, respectively.

tients treated with CHOP plus radiotherapy and CHOP alone were 82 percent and 72 percent, respectively. The median follow-up for patients still alive was 4.4 years for these analyses.

Progression-free survival and overall survival also varied according to the risk groups established according to the stage-modified international prognostic index, when all patients were considered regardless of treatment ($P=0.02$ and $P=0.01$, respectively) (Fig. 3 and 4). The five-year estimates of progression-free survival were 77 percent (95 percent confidence interval, 72 to 83) for patients with zero or one risk factor, 60 percent (95 percent confidence interval, 48 to 72) for patients with two risk factors, and 34 percent (95 percent confidence interval, 13 to 55) for patients with three risk factors. Only two patients had four risk factors, and both died of recurrent lymphoma. The five-year estimates of overall survival according to the number of risk factors were 82 percent (95 percent confidence interval, 77 to 87) for patients with zero or one risk factor, 71 percent (95 percent confidence interval, 60 to 83) for patients with two risk factors, and 48 percent (95 percent confidence interval, 27 to 69) for patients with three risk factors.

Toxicity

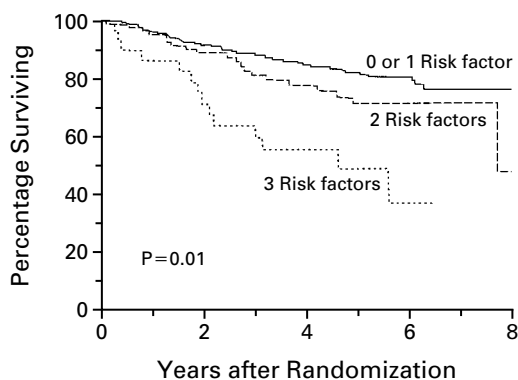
Table 2 summarizes the toxicity of the two treatments. Two patients died as a result of treatment. One patient treated with CHOP alone died of sepsis associated with neutropenia, and one patient treated with three cycles of CHOP plus radiotherapy died



NO. AT RISK						
0 or 1 Risk factor	289	257	172	94	7	
2 Risk factors	82	74	47	26	10	
3 Risk factors	28	18	10	4	0	

Figure 3. Progression-free Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy, According to the Number of Risk Factors.

Sixty-two of 289 patients with zero or one risk factor, 28 of 82 patients with two risk factors, and 18 of 28 patients with three risk factors died or had progression of their disease. The estimated rates of progression-free survival at five years were 77 percent, 60 percent, and 34 percent, respectively.



NO. AT RISK						
0 or 1 Risk factor	289	272	182	99	21	
2 Risk factors	82	77	51	30	19	
3 Risk factors	28	23	14	6	0	

Figure 4. Overall Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy, According to the Number of Risk Factors.

There were 47 deaths among the 289 patients with zero or one risk factor, 20 among the 82 patients with two risk factors, and 14 among the 28 patients with three risk factors. The estimated rates of survival at five years were 82 percent, 71 percent, and 48 percent, respectively.

TABLE 2. NUMBER OF PATIENTS WITH LIFE-THREATENING OR FATAL TOXIC REACTIONS TO EIGHT CYCLES OF CHOP OR THREE CYCLES OF CHOP PLUS RADIOTHERAPY.

TOXIC REACTION	8 CYCLES OF CHOP (N=201)	3 CYCLES OF CHOP PLUS RADIOTHERAPY (N=200)
	no. of patients	
Decreased left ventricular function	7	0
Grade 4 neutropenia*	71	54
Other life-threatening reactions	2	7
Death	1	1

*Grade 4 neutropenia was defined as an absolute neutrophil count below 500 per cubic millimeter.

of liver failure consistent with radiation-induced hepatitis. The incidence of life-threatening toxic effects was higher in the group treated with eight cycles of CHOP alone. Life-threatening toxic effects of any type occurred in 80 of 201 patients treated with CHOP alone (40 percent) and in 61 of 200 patients treated with CHOP plus radiotherapy (30 percent) (P=0.06).

The most common cause of life-threatening toxic effects was myelosuppression from chemotherapy, which caused grade 4 neutropenia (absolute neutrophil count, <500 per cubic millimeter) in 71 patients treated with CHOP alone (35 percent) and 54 patients treated with CHOP plus radiotherapy (27 percent) (P=0.09). Symptoms or signs of congestive heart failure or more than a 20 percent decrease from base line in the left ventricular ejection fraction occurred in seven patients during treatment with CHOP alone but in no patients during treatment with CHOP plus radiotherapy (P=0.02).

Thirty-one patients did not complete the assigned regimen; 28 of these patients were assigned to CHOP alone and 3 to CHOP plus radiotherapy (P<0.01). These patients were removed from the protocol at the discretion of the treating physician (20 patients) or at their own request (11 patients). For 29 of these 31 patients, the initiating event was a toxic reaction. The most common and serious toxic effects were sepsis (nine patients) and decreased left ventricular function (seven patients). The 28 patients assigned to CHOP alone received from one to seven cycles of chemotherapy (median, four), and nine received subsequent radiotherapy.

DISCUSSION

Our results indicate that three cycles of CHOP followed by involved-field radiotherapy are superior to eight cycles of CHOP alone as treatment for localized stages of intermediate- and high-grade non-

Hodgkin's lymphoma. The design of the study derives from a long history of exploratory trials. Before 1980, patients with clinically localized non-Hodgkin's lymphoma were treated with radiotherapy; the five-year survival rates were 56 to 100 percent for patients with stage I disease and 0 to 55 percent for patients with stage II disease.¹⁰⁻¹⁵ The wide ranges are probably due to the selection of patients, with higher five-year survival rates in series that used aggressive staging techniques, including surgery.^{12,13}

Since 1980, localized non-Hodgkin's lymphoma has usually been treated initially with doxorubicin-containing chemotherapy, because Miller and Jones¹⁶ found that CHOP not only was effective but also obviated the need for surgical staging. Subsequent single-institution and cooperative-group series, in which chemotherapy was used for localized disease, with or without consolidation radiotherapy, reported five-year rates of relapse-free survival of 94 to 100 percent for stage I disease¹⁷⁻²⁰ and 72 to 78 percent for stage II disease.^{17,18,20} Current practice is to treat patients with localized intermediate- and high-grade non-Hodgkin's lymphomas initially with doxorubicin-containing chemotherapy, but the role of consolidation radiotherapy is unknown.²¹

Radiotherapy is effective for disease confined to treatment fields and can cure some patients. Connors et al.¹⁸ have argued that radiotherapy is an effective consolidation treatment and permits a reduction in the total dose of chemotherapy required, a potential advantage for elderly patients with reduced myocardial reserve. Our study shows that radiotherapy is valuable not only in reducing the number of courses of chemotherapy, but also in producing superior overall survival and progression-free survival. These results, combined with the preliminary report by Glick et al.²² (who studied a group that included patients with bulky stage II disease), suggest that radiotherapy is an important component of treatment for clinically localized lymphomas.

We selected patients for treatment using criteria previously thought to assure a homogeneous population. Of our 401 patients, 350 (87 percent) were considered at low risk according to the criteria of the international prognostic index.² Furthermore, 395 of the 401 eligible patients (99 percent) were in the two lowest risk groups of the international prognostic index. However, we found considerable heterogeneity in outcome among prognostic groups when patients were separated into those with stage I and those with stage II disease. This modification of the international prognostic index results in five-year estimates of progression-free survival of 77 percent for patients with zero or one risk factor and only 34 percent for patients with three risk factors (Fig. 3). It is apparent that outcome analyses of patients with "localized" lymphoma who are lumped without regard to important prognostic features are inadequate,

and that future studies will have to account for extreme heterogeneity among patients with localized lymphoma by using a stage-modified international prognostic index.

The patients in this trial had more frequent and more severe toxic reactions than the patients in phase 2 trials of the same regimens.^{17,18,20} Although only two patients died while receiving treatment (one in each treatment group), life-threatening toxic effects were common, occurring in 40 percent of the patients treated with eight cycles of CHOP and in 30 percent of the patients treated with three cycles of CHOP plus radiotherapy. The most frequent toxic effect, neutropenia, followed treatment with CHOP in both treatment groups.

Our study was conducted during the years when granulocyte growth factors came into clinical use, and the complications of neutropenia may be mitigated in future trials with the use of these factors. Even so, there remains the disconcerting finding of myocardial toxicity associated with eight cycles of CHOP chemotherapy. Left ventricular function, usually associated with clinical symptoms of congestive heart failure, decreased substantially in seven patients who received eight cycles of CHOP chemotherapy. The finding is underscored by the fact that seven patients treated with eight cycles of CHOP but only two treated with three cycles of CHOP plus radiotherapy subsequently died of apparent heart disease. The apparent excess mortality from heart disease among patients receiving eight cycles of CHOP may be due to the older age of the patients we treated and the relatively high survival rate, which allows time for cardiac complications to become manifest. Longer follow-up may also reveal serious, and frequently fatal, complications of radiotherapy.²³⁻²⁵

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