

Chemotherapy for Diffuse Large-Cell Lymphoma—Rapidly Responding Patients Have More Durable Remissions

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Fifty-one patients with diffuse large-cell lymphoma (DLCL) were treated with a six-drug combination chemotherapy regimen including cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine, and prednisone. The patients were restaged after three cycles of therapy, and restaging was repeated at 2-month intervals in patients who had persistent disease. Responding patients received two cycles of therapy after documentation of complete remission (CR). With all patients considered evaluable, 73% of the patients achieved a CR. Twenty-six of the 37 CRs

(70%) achieved remission in the first three treatment cycles. The durability of remission in the rapidly responding patients was significantly better than in patients who required five cycles to achieve CR (80% v 40% at 2 years, $P = .02$) despite the latter patients having received two more cycles of therapy. Rapidly responding patients with DLCL do not require prolonged therapy and have a better prognosis than patients achieving a CR more slowly. *J Clin Oncol* 4:160-164. © 1986 by American Society of Clinical Oncology.

ONE OF THE exciting achievements of the treatment of cancer with drugs has been the demonstration that some patients with diffuse large-cell lymphomas (DLCL) can be cured. Following the original report by DeVita et al using C-MOPP/MOPP,¹ several other groups have reported a variety of treatment regimens capable of producing complete remissions (CRs) and long-term, disease-free survival.²⁻¹² Most of these treatment regimens have been administered for six to nine cycles, sometimes followed by maintenance chemotherapy, regardless of the rate of tumor response. It has become generally accepted that maintenance therapy is of no value in this disease and may do harm by increasing the chance of subsequent second malignancies. Recently, two very intensive regimens have been reported in which the amount of treatment was varied according to tumor response,^{13,14} and another regimen has been described where treatment was administered for only 12 weeks.¹⁵ It appears that durable remissions can be achieved

with very short treatment durations. We report here the results with a new six-drug regimen in which we adjusted treatment duration according to the rapidity of tumor response with patients receiving five, seven, or nine cycles of treatment depending on the speed at which they achieved CR.

PATIENTS AND METHODS

This report includes all the patients with stage II-IV de novo DLCL, who had not received previous chemotherapy, treated with this regimen by members of the Nebraska Lymphoma Study Group between September 1982 and August 1984. There were 51 patients initially treated by group members during that time period and all of these patients are considered evaluable. Their clinical characteristics are presented in Table 1. The patients' median age was 61 years with a range from 15 to 80 years. Serum lactic dehydrogenase (LDH) levels are given in relation to maximum normal values, since not all measurements were made using the same methods and normals. Four patients did not have pretreatment LDH levels measured. The median time of observation for patients alive at the time of this report was 21 months.

Anatomic stage and symptom status were assigned using the Ann Arbor rules for Hodgkin's disease.¹⁶ Patients with DLCL entirely confined to one extranodal site, excluding liver and bone marrow, were designated stage IE and those with one extranodal site plus involved regional lymph nodes but no other disease were designated stage IIE. Laparotomy for staging purposes was not done in these patients. The patients undergoing laparotomy were those who had the operation done for diagnostic reasons. A positive biopsy was considered necessary to prove liver involvement, which undoubtedly led to the underdiagnosis of liver metastasis. Staging in all patients included, in addition to history, physical and routine laboratory and x-ray studies.

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Table 1. Clinical Characteristics of the 51 Treated Patients

Characteristic	No. of Patients (%)
Age	
< 54	15 (29)
55-69	22 (43)
≥ 70	14 (28)
Sex	
Male	33 (65)
Female	18 (35)
Stage	
I	10 (20)
II	10 (20)
IV	31 (60)
Symptoms	
A	33 (65)
B	18 (35)
Karnofsky performance score	
≥ 80	43 (84)
60-70	6 (12)
≤ 50	2 (4)
Histology	
Diffuse large cell	29 (57)
Immunoblastic	22 (43)
Maximum tumor diameter	
≤ 2 cm	9 (18)
2-10 cm	27 (53)
≥ 10 cm	15 (29)
LDH	
Less than twice normal	35 (74)
Greater than twice normal	12 (26)
Number of extranodal sites of DLCL	
0	14 (27)
1	20 (39)
≥ 2	17 (33)
Extranodal sites of involvement	
Bone marrow	9 (18)
Gastrointestinal	8 (16)
Testis	7 (14)
Soft tissue	4 (8)
Other	4 (8)
None	2 (4)
Relapsed at 3- or 4-week intervals	
Yes	12 (24)
No	39 (76)

marrow biopsy, and evaluation for abdominal involvement by computed tomography (CT) with or without lymphangiography, ultrasonography, and radionuclide studies. Restaging included reevaluation, including rebiopsy, whenever possible, of sites known previously to contain disease.

The treatment regimen used is presented in Table 2. As noted, patients were restaged after three cycles of therapy. If active disease was still present, patients were treated for two more cycles and then restaged again. This process was repeated one or more times in patients who still had not achieved a CR after five cycles of therapy. Two cycles of the regimen were planned to be

given after documentation of CR. However, one 81-year-old patient who achieved CR after three cycles and one 48-year-old patient who achieved CR after seven cycles did not receive the planned two further cycles of treatment. The former patient relapsed after 2 months of remission and the latter patient remains in remission at 9+ months. Neither is included in calculations of remission duration since they did not complete the planned treatment regimen, but both are included in survival analysis. Two patients were felt to have abnormal imaging studies after three cycles of therapy (ie, abdominal CT in one case and abdominal ultrasound in one case), and after two additional cycles of treatment the findings were unchanged. Laparotomy was then performed in both patients and histologic examination showed scarring only. Both patients received no further treatment and are considered to have achieved remission in three cycles. Although treatment at 3- or 4-week intervals was acceptable, it became apparent early in the study that many patients could not receive full doses of myelosuppressive agents at 3-week treatment intervals.

Although almost all patients had some objective tumor response, only CRs, which required the disappearance of all previously known disease documented at restaging evaluation, were considered clinically useful and are reported here. The diagnosis of DLCL includes all patients in the diffuse, large-cell, and immunoblastic categories of the Working Formulation.¹⁷ All other lymphomas and composite lymphomas were excluded from this report. All the slides were reviewed by a single, experienced hematopathologist (D.D.W.). Survival and CR duration were calculated using the life-table method. Significance of differences between groups was determined using the chi-squared test with the Yates correction and significance of differences between survival curves was determined using the log-rank test.

RESULTS

The treatment outcome is presented in Table 3. Thirty-seven of the 51 patients (73%) achieved CR. Three patients failed to achieve a CR for reasons other than treatment toxicity or resistance of the tumor to the regimen. Two patients died in the first treatment cycle from an acute myocardial infarction and a cerebral vascular accident, respectively, and one patient discontinued therapy after one cycle and elected not to pursue further treatment. If these latter three patients were excluded, the CR rate would be 77%. Patients with bulky (ie, largest diameter, ≥ 10 cm) tumors at the time of initiation of treatment had lower CR rates than patients with smaller masses (47% v 83%; $P = .02$). Patients with tumor confined to lymph nodes had a slightly higher CR rate than those with any site of extranodal disease (93% v 65%; $P = .10$), as did patients whose pretreatment LDH level did not exceed twice the maximum normal value (80% v 50%; $P = .10$).

Table 2. Treatment Regimen

Drug	Dose*	Route	Schedule†
Cyclophosphamide	650 mg/m ²	IV	Day 1
Doxorubicin	50 mg/m ²	IV	Day 1
Procarbazine	100 mg/m ²	Orally	Days 1-7
Bleomycin	10 mg/m ²	Subcutaneous	Day 15
Vincristine	1.4 mg/m ²	IV	Day 15
Prednisone	100 mg	Orally	Days 15-21

*In patients ≥ 70 years, two-thirds doses of all drugs except prednisone were administered.

†Repeat at 21- to 28-day intervals. Patients were restaged after three cycles and, if disease was still present, after five and seven cycles. Two cycles were administered after documentation of CR.

The durability of CR and the survival of all treated patients are presented in Figs 1 and 2. The 1- and 2-year survivals for all treated patients are 65% and 54%. Life-table analysis predicts eventual relapse of 33% of the patients with 67% remaining in CR 2 years after ending therapy. CR was achieved in three cycles in 26/37 (70%) of the CRs. Relapse after CR has been seen less often in patients who achieved CR in three cycles than in patients requiring five cycles. At 2 years, 80% of patients achieving CR in three cycles remain in remission in contrast to 40% of patients who required five cycles ($P = .02$) (Fig 2). This same result of more durable CRs in patients achieving remission in three cycles was found when only the 30 CRs without bulky tumor were analyzed (80% v 33% remission durability at 2 years; $P = .02$). Remission duration was not significantly affected by stage, tumor bulk, symptoms, treatment interval, or the presence of extranodal disease.

The toxicity of this treatment regimen was significant with four patients (8%) having treatment-related deaths. Two patients died in the first treatment cycle from neutropenic sepsis. Four patients developed diffuse interstitial pulmonary disease during or after the completion of therapy that was otherwise unexplained and felt to represent bleomycin toxicity. Two patients died from this complication.

DISCUSSION

Beginning with the report by DeVita et al,¹ it has become apparent that DLCL could be cured with combination chemotherapy administered for a relatively short period of time. However, the proportion of patients cured has generally been $< 50\%$ and the treatment has been associat-

Table 3. Treatment Outcome by Clinical Characteristics

Characteristic	No. of Patients	No. of CRs (%)
All patients	51	37 (73)
Age		
≤ 54	15	12 (80)
55-69	22	14 (64)
≥ 70	14	11 (79)
Stage		
II	10	7 (70)
III	10	10 (100)
IV	31	20 (65)
Symptoms		
A	33	26 (79)
B	18	11 (61)
Karnofsky score		
≥ 80	43	33 (77)
60-70	6	4 (67)
≤ 50	2	0 (0)
Histology		
Diffuse large-cell	29	20 (69)
Immunoblastic	22	17 (77)
Maximum tumor diameter		
≤ 2 cm	9	7 (77)
2-10 cm	27	23 (85)
> 10 cm	15	7 (47)
LDH		
Less than twice normal	35	28 (80)
Greater than twice normal	12	6 (50)
Number of extranodal sites of DLCL		
0	14	13 (93)
1	20	12 (60)
≥ 2	17	12 (71)
Sites of involvement		
Marrow	9	6 (67)
Gastrointestinal	8	5 (63)
Lung	7	5 (71)
Skin	4	4 (100)
Bone	4	2 (50)
Liver	2	0 (0)
Treatment at 3- or 4-week intervals		
3 wk	12	9 (75)
4 wk	39	28 (72)

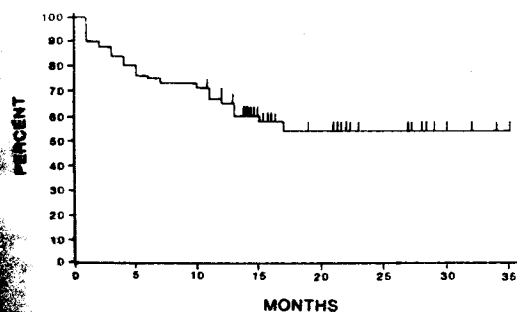


Fig 1. A life-table plot of survival for all 51 patients treated with this regimen. Tic marks indicate patients surviving to that interval.

ed with considerable toxicity. We attempted to shorten treatment duration in rapidly responding patients by early restaging and administering only two cycles of therapy past documentation of CR.

It does not appear that shortening the duration of treatment to five cycles increased the risk of relapse. In fact, patients who achieved CR within three cycles of initiating therapy had more durable remissions than patients who required five cycles to achieve remission and thus received two more total treatment cycles. This suggests that rapidity of response might be a prognostic factor in DLCL with more rapidly responding patients having a better prognosis. Amadori et al have reported a higher CR durability in rapidly responding patients with a mixture of diffuse, aggressive non-Hodgkin's lymphomas treated with the F-MACHOP regimen.¹⁸ Similar data suggesting a better outcome associated with a rapid response to chemotherapy have also been reported for patients with testicular cancer.¹⁹ A recently described treatment regimen, MACOP-B, was administered for only 3 months to patients with DLCL with a high CR rate and durable remissions.¹⁵ Thus, durable CRs can be produced with therapy of brief duration in DLCL. Previous regimens have probably treated rapidly responding patients longer than necessary, and thus exposed them to unnecessary treatment-related toxicity. Two other intensive regimens^{13,14} have individualized treatment duration. Both used possibly non-cross-resistant combinations given sequentially and demonstrated high CR rates.

Previous treatment studies for DLCL have used a variety of clinical and pathologic varia-

bles to significantly predict for the chance to achieve CR and for CR durability.²⁰⁻²⁵ However, the same characteristics have not been uniformly found to be important from one study to another. This might reflect the patient mix in the various studies, the characteristics of the treatment regimen, or statistical variation. As treatment results improve, previously important prognostic variables might lose their significance for predicting outcome. For example, we found no impact on outcome based on the histologic subtypes diffuse, large-cell, and immunoblastic.¹⁷ The only variable significantly associated with a decreased chance to achieve CR in our study was tumor bulk. Patients with a high LDH level, the presence of extranodal tumor, and B symptoms had lower, but not significantly different, CR rates. Stage was not an important predictor of the chance to achieve CR. In fact, patients with stage II disease had approximately the same chance to achieve CR as those with stage IV disease. This comparability of outcome with stage II and stage IV was also found in a recent study using MACOP-B.¹⁵ It appears that when intensive regimens are used for DLCL, tumor bulk as reflected by tumor size, LDH level, and the presence of extranodal tumor (whether or not the tumor is located above and below the diaphragm), are important prognostic factors predicting chances to achieve CR. The duration of CR might be most significantly affected by the sensitivity of the tumor to the chemotherapy as reflected by the rapidity of tumor regression and time to CR. However, the small number of patients with bulky disease in this study who achieved a CR

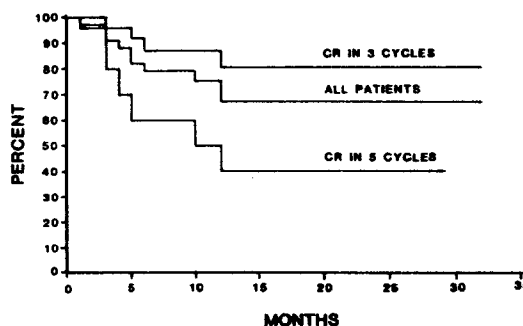


Fig 2. Life-table plots of CR duration for all 37 CRs, those having CR documented after three cycles of therapy, and those patients requiring five cycles to achieve CR. Remissions were significantly more durable for patients achieving CR in three cycles ($P = .02$).

makes it difficult to be certain about the effect of tumor bulk on remission duration.

In summary, we treated 51 patients with DLCL using an intensive, six-drug combination chemotherapy regimen. We varied the duration of treatment depending on the rapidity of tumor response. The CR rate was similar to other, previously reported, intensive regimens. Approximately two-thirds of patients destined to achieve CR did so in the first three cycles of therapy.

Although patients received only two cycles of treatment past documentation of CR, patients who responded rapidly and thus received less total drugs had more durable remissions. It appears that rapidly responding patients with DLCL do not require prolonged therapy and that patients with slow tumor regression have a poor outlook and should be considered for alternate, consolidative therapy.

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