

LOW-DOSE COMPARED WITH STANDARD-DOSE m-BACOD CHEMOTHERAPY  
FOR NON-HODGKIN'S LYMPHOMA ASSOCIATED WITH HUMAN  
IMMUNODEFICIENCY VIRUS INFECTION

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**ABSTRACT**

**Background** Reduced doses of cytotoxic chemotherapy or standard-dose therapy plus a myeloid colony-stimulating factor decreases hematologic toxicity and its complications in patients with non-Hodgkin's lymphoma associated with infection with the human immunodeficiency virus (HIV). However, the effect of reducing the doses of cytotoxic chemotherapeutic agents on clinical outcome is not known.

**Methods** We randomly assigned 198 HIV-seropositive patients with previously untreated, aggressive non-Hodgkin's lymphoma to receive standard-dose therapy with methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) along with granulocyte-macrophage colony-stimulating factor (GM-CSF; n=94) or reduced-dose m-BACOD with GM-CSF administered only as indicated (n=98).

**Results** A complete response was achieved in 39 of the 94 assessable patients assigned to low-dose therapy (41 percent) and in 42 of the 81 assessable patients assigned to standard-dose therapy (52 percent, P=0.56). There were no significant differences in overall or disease-free survival; median survival times were 35 weeks for patients receiving low-dose therapy and 31 weeks for those receiving standard-dose therapy (risk ratio for death in the standard-dose group, 1.17; 95 percent confidence interval, 0.84 to 1.63; P=0.25). Toxic effects of chemotherapy rated grade 3 or higher occurred in 66 of 94 patients assigned to standard-dose therapy (70 percent) and 50 of 98 patients assigned to low-dose treatment (51 percent, P=0.008). Hematologic toxicity accounted for the difference.

**Conclusions** As compared with treatment with standard doses of cytotoxic chemotherapy (m-BACOD), reduced doses caused significantly fewer hematologic toxic effects yet had similar efficacy in patients with HIV-related lymphoma. Dose-modified chemotherapy should be considered for most HIV-infected patients with lymphoma. (N Engl J Med 1997;336:1641-8.)

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THE human immunodeficiency virus (HIV) increases the risk of aggressive B-cell lymphoma,<sup>1,2</sup> which often presents at an advanced stage and frequently involves extranodal sites, such as the central nervous system and bone marrow.<sup>3-7</sup> In HIV-infected patients, the rate of complete response to the treatment of lymphoma with combination chemotherapy is approximately 50 percent, and the median survival is only five to six months.<sup>4-6,8</sup> Factors that favor longer survival include a higher number of CD4+ lymphocytes,<sup>4,9</sup> the absence of a prior diagnosis indicating progression to the acquired immunodeficiency syndrome (AIDS),<sup>4,9</sup> a Karnofsky performance score of 70 or more,<sup>4,9</sup> the absence of extranodal disease,<sup>4</sup> an early disease stage (I or II),<sup>10,11</sup> a nonimmunoblastic subtype,<sup>5,10</sup> polyclonality,<sup>12</sup> the absence of bone marrow involvement,<sup>9</sup> an age of less than 35 years,<sup>11</sup> and a low serum lactate dehydrogenase concentration.<sup>11</sup>

Treatment of HIV-related lymphoma with myelotoxic drugs frequently causes prolonged neutropenia. The poor bone marrow reserve in patients with HIV-related lymphoma makes the administration of standard doses of chemotherapy difficult. Previous clinical trials have demonstrated that hematologic toxic effects and their sequelae can be lessened by reducing the dose of chemotherapy<sup>13</sup> or using colony-stimulating factor as support during standard-dose therapy.<sup>8,14</sup> However, the effect of a reduction in the dose of chemotherapeutic agents on outcome

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is not known. In this trial, we evaluated the response rates, survival, and toxic effects in HIV-infected patients with non-Hodgkin's lymphoma who were treated with reduced-dose chemotherapy or a standard-dose therapy with granulocyte-macrophage colony-stimulating factor (GM-CSF) as support.

## METHODS

### Eligibility and Pretreatment Evaluation

HIV-seropositive patients over 12 years of age were eligible if they had previously untreated intermediate- or high-grade lymphoma, confirmed by biopsy or cytologic study, at any stage and had no acute opportunistic infection. Determination of disease stage included chest radiography; computed tomographic or magnetic resonance scanning of the chest, abdomen, pelvis, and brain; bilateral iliac-crest bone marrow biopsy; and lumbar puncture with routine studies and cytologic examination.

### Treatment

After stratification according to the presence or absence of a prior AIDS-defining diagnosis and according to the Karnofsky performance score ( $\geq 70$  or  $< 70$ ), patients were randomly assigned to receive standard-dose chemotherapy with methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) with GM-CSF support, beginning with the first cycle of chemotherapy, or reduced-dose m-BACOD chemotherapy without routine GM-CSF (Table 1).

GM-CSF (molgramostim, Leucomax, Schering-Plough, Kenilworth, N.J.), in a dose of 5  $\mu\text{g}$  per kilogram of body weight per day, was administered subcutaneously on days 4 through 13 of each chemotherapy cycle to all patients randomly assigned to standard-dose chemotherapy. The duration of GM-CSF administration was extended beyond day 13 during episodes of febrile neutropenia. Administration of GM-CSF to patients in the low-dose group was not allowed until September 1991, when the administration of GM-CSF during subsequent cycles of low-dose chemotherapy was allowed if the absolute neutrophil count was below 1000 per cubic millimeter on day 22 of any chemotherapy cycle or below 500 per cubic millimeter at any time during a chemotherapy cycle.

Antiretroviral therapy was optional, but zidovudine was specifically excluded because of its potential for myelosuppression.

In both groups, cycles of chemotherapy were initiated after the neutrophil count recovered to at least 1000 per cubic millimeter, but not earlier than day 22 of the previous cycle. Chemotherapy was administered for two cycles after a complete remission was achieved and for a minimum of four cycles.

Meningeal lymphoma was treated with whole-brain radiotherapy at a rate of 200 cGy per day, for a total dose of 2400 cGy. Cytarabine (50 mg) was administered intrathecally three times per week until the cerebrospinal fluid was cleared of malignant cells, and then monthly for one year.

Clinical and laboratory assessments were performed at the start of each treatment cycle, and a complete blood count was obtained weekly. Complete restaging was performed for all previously identified sites of disease after every other cycle and at the conclusion of chemotherapy.

### Assessment of Quality of Life and Central Pathological Review

Patients completed a quality-of-life questionnaire at base line, after cycles 1 and 3, and four weeks after the completion of chemotherapy. The questionnaire was based on an earlier version of the General Health Assessment Questionnaire currently used in several AIDS Clinical Trials Group (ACTG) trials.<sup>15</sup>

Histologic and cytologic diagnoses were reviewed retrospectively by a single pathologist.

### End Points

The primary end point was survival from the time of initiation of chemotherapy. Secondary end points included the rate of complete response, the duration of antitumor response, the development of opportunistic infection, and toxic effects of treatment. The longest tumor dimension and the length of the perpendicular dimension were measured. Antitumor responses were graded according to standard oncologic criteria. A complete response was defined as the absence of clinically detectable disease and normal radiographic studies at any previously abnormal sites for at least four weeks. A partial response was defined as a decrease of at least 50 percent in the measurable tumor burden lasting for at least one month. Stable disease was defined as a reduction of less

**TABLE 1. LOW-DOSE AND STANDARD-DOSE m-BACOD CHEMOTHERAPY REGIMENS.\***

AGENT	STANDARD-DOSE THERAPY	LOW-DOSE THERAPY
Methotrexate (IV)	200 mg/m <sup>2</sup> , day 15	200 mg/m <sup>2</sup> , day 15
Bleomycin (IV)	4 U/m <sup>2</sup> , day 1	4 U/m <sup>2</sup> , day 1
Doxorubicin (IV)	45 mg/m <sup>2</sup> , day 1	25 mg/m <sup>2</sup> , day 1
Cyclophosphamide (IV)	600 mg/m <sup>2</sup> , day 1	300 mg/m <sup>2</sup> , day 1
Vincristine (IV)	1.4 mg/m <sup>2</sup> , day 1	1.4 mg/m <sup>2</sup> , day 1
Dexamethasone (oral)	6 mg/m <sup>2</sup> , days 1–5	3 mg/m <sup>2</sup> , days 1–5
GM-CSF (SC)	5 $\mu\text{g}$ /kg, days 4–13	5 $\mu\text{g}$ /kg, days 4–13, as needed
Meningeal lymphoma prophylaxis†	Cytarabine (50 mg, IT), days 1, 8, 15, and 22	
Pneumocystis prophylaxis	Trimethoprim-sulfamethoxazole, dapsone, or inhaled pentamidine	

\*IV denotes intravenous, GM-CSF granulocyte-macrophage colony-stimulating factor, SC subcutaneous, and IT intrathecal. Doses are given per square meter of body-surface area or per kilogram of body weight.

†Prophylaxis was administered in cycle 1 only.

than 50 percent in measurable disease in the absence of progression. Progressive disease was defined as a 25 percent or greater increase in measurable disease, or the appearance of disease at a new site. The length of time to disease progression was measured from the initiation of chemotherapy until progression was documented. The standard criteria of the World Health Organization were used to grade toxic effects.

The relative dose intensity (the ratio of the actual dose to the expected dose per unit of time) was calculated for each agent as  $100 \times D \div T$ , where  $D$  = the sum of doses received in each cycle  $\div$  (the initial dose prescribed  $\times$  the number of cycles administered) and  $T$  = drug-exposure time  $\div$  (21 days  $\times$  the number of cycles received).

**Statistical Analysis**

We used an intention-to-treat approach that included all observations even when therapy was discontinued prematurely. Differences in survival between the treatment groups were evaluated with the Wilcoxon log-rank test and Cox regression analysis. The sample size gave the study 80 percent power to detect an increase in survival from six to nine months. Quality-of-life data were analyzed by analysis of variance, in which scores after randomization were compared, with adjustment for base-line levels.

**RESULTS**

**Characteristics of Patients**

Between February 1991 and October 1994, we randomly assigned 198 patients at 27 ACTG sites to treatment groups. Six of these patients were never actually treated — one who was discovered not to have lymphoma, one who had an acute opportunistic infection, one who was lost to follow-up after randomization, and three because of violations of the entry criteria. After these 6 patients were excluded, the sample consisted of 98 patients assigned to low-dose treatment and 94 assigned to standard-dose therapy.

Forty patients (20 percent of the total enrollment) underwent randomization before the protocol was modified to allow GM-CSF to be administered to patients receiving low-dose therapy if they had neutropenia. Of these 40 patients, 1 never received the study treatment, 19 were assigned to receive low-dose treatment, and 20 were assigned to receive standard-dose therapy.

The two groups did not differ significantly with respect to established predictive factors, including the Karnofsky performance score; the CD4+ lymphocyte count; the presence or absence of a previous AIDS-defining opportunistic illness, extranodal involvement, or bone marrow involvement; the lactate dehydrogenase concentration; the disease stage; and age (Table 2). The most common extranodal sites of disease were the liver (in 26 percent of the patients), the gastrointestinal tract (24 percent), the bone marrow (15 percent), and the lung (14 percent). Only three patients in each treatment group had lymphomatous meningitis at entry.

Patients assigned to low-dose therapy received a mean ( $\pm$ SE) of  $3.8 \pm 1.8$  cycles of chemotherapy, whereas those assigned to standard-dose therapy received a mean of  $3.2 \pm 1.7$  cycles. Patients in each

treatment group received therapy at 90 to 100 percent of the planned dose intensity for each cytotoxic agent, except for methotrexate. For that drug the relative dose intensity was significantly lower for patients assigned to standard-dose therapy (74 percent) than for those assigned to low-dose therapy (84 percent,  $P = 0.005$ ). Of the patients assigned to low-dose therapy after the protocol was modified to allow GM-CSF prophylaxis in this group, 36 of 79 (46 percent) received GM-CSF at some time during therapy.

**Therapeutic Response**

The mean lengths of follow-up in the low-dose group ( $10.6 \pm 1.05$  months) and the standard-dose group ( $9.1 \pm 0.94$  months) did not differ significantly. Data on responses to chemotherapy were available for 175 patients (91 percent) — 94 assigned to low-dose therapy and 81 assigned to standard-dose therapy (Table 3). There were no significant differences in response rates between the two treatment

**TABLE 2.** PRETREATMENT CHARACTERISTICS OF PATIENTS ASSIGNED TO LOW-DOSE AND STANDARD-DOSE m-BACOD.

CHARACTERISTIC	LOW-DOSE THERAPY (N=98)	STANDARD-DOSE THERAPY (N=94)
Sex — no. (%)		
Male	96 (98)	90 (96)
Female	2 (2)	4 (4)
Race or ethnic group — no. (%)		
White	73 (74)	59 (63)
Black	9 (9)	12 (13)
Hispanic	15 (15)	21 (22)
Other	1 (1)	2 (2)
Risk group — no. (%)		
Homosexual or bisexual	86 (88)	69 (73)
Injection-drug user	14 (14)	29 (31)
Heterosexual	6 (6)	12 (13)
Transfusion recipient	2 (2)	2 (2)
Other	7 (7)	4 (4)
Prior opportunistic infection — no. (%)	52 (53)	45 (48)
Disease stage — no. (%)*		
I or II	28 (29)	33 (36)
III or IV	70 (71)	59 (64)
Histologic type — no. (%)†		
Large cell	42 (62)	43 (62)
Small noncleaved cell	16 (24)	19 (28)
High grade, not otherwise specified	10 (15)	7 (10)
Extranodal disease	77 (79)	74 (79)
Karnofsky performance score >70 — no. (%)	80 (82)	78 (83)
Lactate dehydrogenase — U/liter		
Median	392	367
Range	87–3782	141–8000
CD4+ (cells/mm <sup>3</sup> )		
Median	100	107
Range	0–1148	0–484
CD4+ >200 cells/mm <sup>3</sup> — no. (%)	30 (31)	25 (27)
Age — yr		
Median	38	39
Range	22–64	24–68

\*Data were not available for two patients in the standard-dose group.

†Data include only centrally reviewed histologic specimens.

groups (Table 3). The median length of time to complete remission was eight weeks for both groups.

Nine patients in the low-dose group had recurrence of disease after a complete response (23 percent), as did 17 (40 percent) in the standard-dose group ( $P=0.08$ ). The median time to recurrence after a complete response was 106 weeks in the standard-dose group and had not been reached at 190 weeks in the low-dose group ( $P=0.06$ ). The overall length of time to disease progression was similar in the two groups — a median of 39 weeks for the low-dose group and 30 weeks for the standard-dose group. Meningeal relapse occurred in three patients in each treatment group.

No significant differences were noted in overall or disease-free survival (Fig. 1A and 1B). The median survival time was 35 weeks (95 percent confidence interval, 30 to 45) for patients receiving low-dose therapy and 31 weeks (95 percent confidence interval, 22 to 42) for those receiving standard-dose therapy. The risk ratio for death was 1.17 in the standard-dose group as compared with the low-dose group (95 percent confidence interval, 0.84 to 1.63;  $P=0.25$ ). The median length of disease-free survival was 56 weeks in the low-dose group and 38 weeks in the standard-dose group (risk ratio for death or recurrent disease in the standard-dose group, 1.22; 95 percent confidence interval, 0.71 to 2.09;  $P=0.28$ ). Twenty-six patients receiving low-dose therapy (27 percent) and 23 receiving standard-dose therapy (24 percent) survived for more than one year. Eleven patients receiving low-dose therapy (11 percent) and seven receiving standard-dose therapy (7 percent) survived for more than two years.

Patients with CD4+ lymphocyte counts above 100 per cubic millimeter survived longer, on average, than those with counts of 100 or fewer, but there were no significant differences in survival between the treatment groups after we controlled for the absolute CD4+ count ( $P=0.23$ ) (Fig. 2). Among patients with CD4+ lymphocyte counts above 200 per cubic millimeter, the median survival times were 66 weeks for the low-dose group and 73 weeks for the standard-dose group ( $P=0.89$ ).

There was no significant difference in survival between the two groups in a multivariate analysis in which we controlled for disease stage (I or II vs. III or IV), the presence or absence of extranodal involvement, the presence or absence of bone marrow involvement, the histologic type of tumor (large cell vs. small noncleaved cell), the lactate dehydrogenase concentration, the Karnofsky performance score ( $\leq 70$  vs.  $>70$ ), risk group, and age.

#### Causes of Death

The three treatment-associated deaths were due to respiratory failure caused by ascending paralysis resulting from cytarabine toxicity, hepatic failure, and sepsis

**TABLE 3.** RATES OF RESPONSE TO LOW-DOSE AND STANDARD-DOSE m-BACOD THERAPY.\*

OUTCOME	LOW-DOSE THERAPY (N=94)	STANDARD-DOSE THERAPY (N=81)
	no. (%)	
Complete response	39 (41)	42 (52)
Partial response	26 (28)	21 (26)
Stable disease	11 (12)	8 (10)
Progression of disease	18 (19)	10 (12)
	no./total no. (%)	
Recurrence after complete response	9/39 (23)	17/42 (40)†

\*Only patients who could be assessed for the response to chemotherapy are included.

† $P=0.08$  for the comparison with the low-dose group.

with neutropenia. Of the 140 patients who died during follow-up, the cause of death was lymphoma, progression of HIV, or a combination of both in 128 (91 percent). Forty-nine (70 percent) of the patients in the low-dose group who died and 40 (57 percent) of the patients in the standard-dose group who died had active lymphoma at the time of death ( $P=0.50$ ). Among the patients who died, progression of HIV alone was the primary cause of death for 18 patients receiving low-dose therapy (26 percent) and 21 receiving standard-dose therapy (30 percent).

#### Toxic Effects

Grade 3 or higher-grade toxic effects of chemotherapy occurred in 66 patients assigned to standard-dose therapy (70 percent) and 50 patients assigned to low-dose therapy (51 percent) ( $P=0.008$ ). Grade 4 neutropenia (absolute neutrophil count,  $<500$  per cubic millimeter) developed in 49 patients who received low-dose therapy (50 percent), as compared with 65 assigned to standard-dose therapy (69 percent) ( $P=0.007$ ). Similarly, 89 of 373 chemotherapy cycles in the low-dose group (24 percent) and 117 of 299 cycles in the standard-dose group (39 percent) were associated with grade 4 neutropenia. Episodes of febrile neutropenia complicated 6 percent of the cycles (22 of 373) in patients assigned to low-dose therapy and 8 percent of the cycles (24 of 299) in the standard-dose group. Grade 3 or higher-grade thrombocytopenia was observed in 11 of the patients assigned to low-dose therapy (11 percent) and 32 of those assigned to standard-dose treatment (34 percent) ( $P<0.001$ ). Grade 3 or higher-grade anemia occurred in 31 of the patients given low-dose therapy (32 percent) and 49 of those assigned to standard-dose therapy (52 percent) ( $P<0.001$ ).

The only significant differences in nonhematolog-

ic toxic effects between the treatment groups were that shortness of breath was more common in the standard-dose group and elevations in aspartate aminotransferase concentrations were more common in the low-dose group (Table 4).

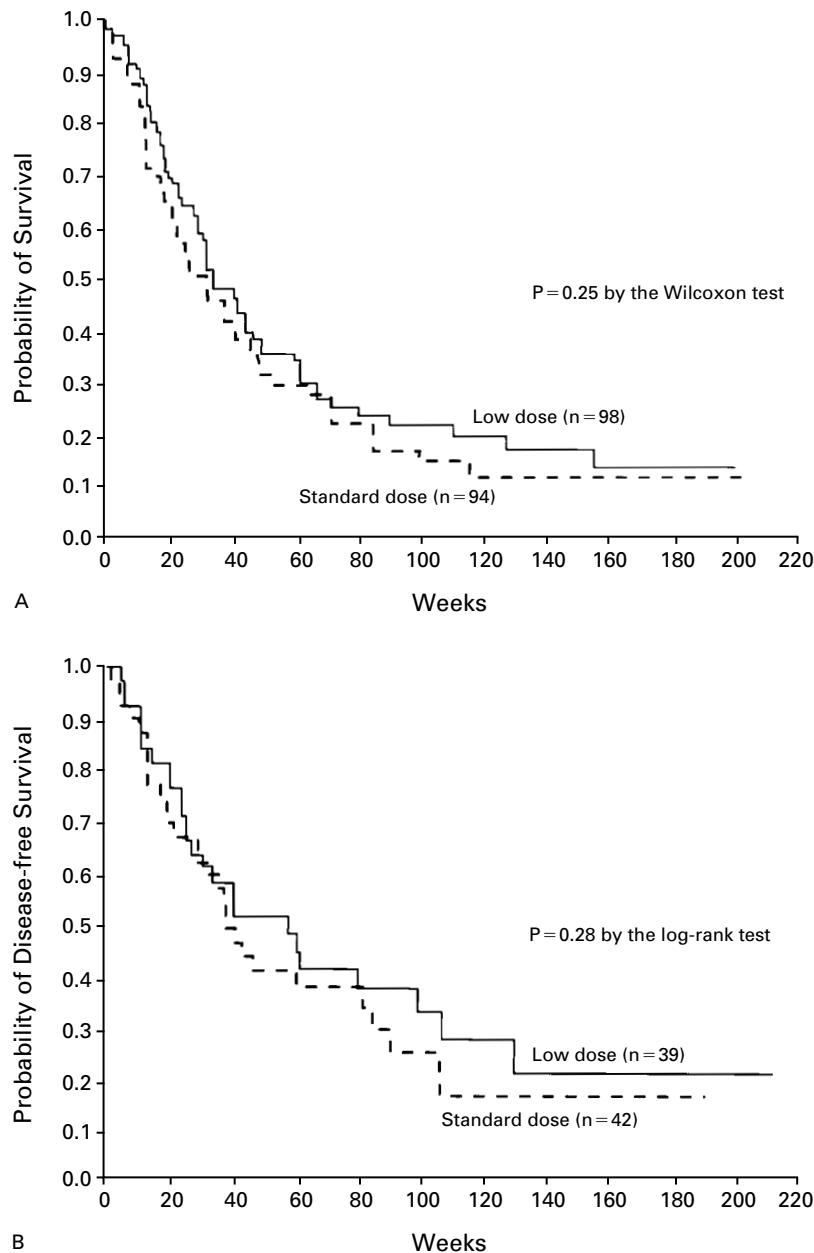
**Opportunistic Illness**

An AIDS-defining opportunistic illness complicated treatment in 22 of the patients receiving low-

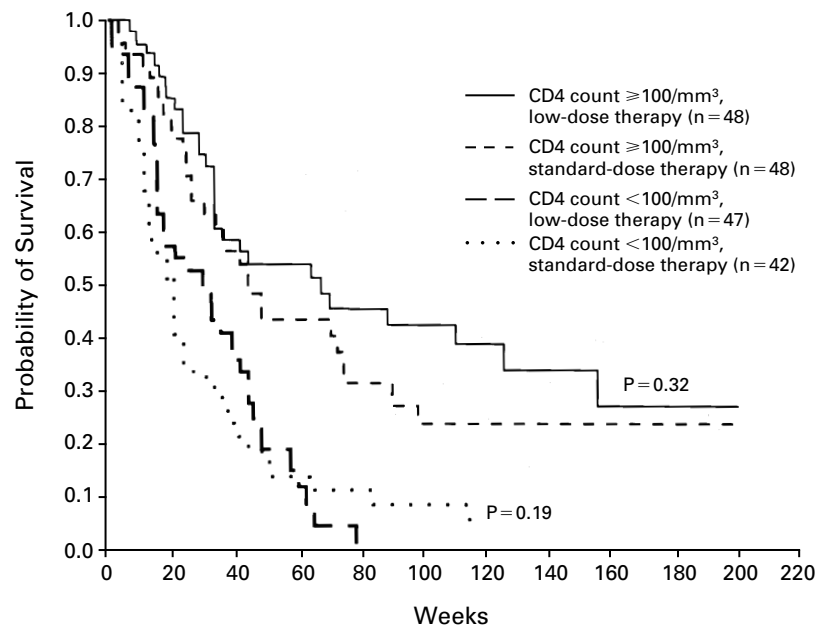
dose chemotherapy (22 percent) and 22 of those receiving standard-dose chemotherapy (23 percent) ( $P = 1.0$ ).

**Central Pathological Review**

Among the 192 patients in the study, histologic or cytologic specimens were submitted for review for 137 (71 percent). This audit confirmed the diagnosis of non-Hodgkin's lymphoma in all but one case.



**Figure 1.** Overall Survival (Panel A) and Disease-free Survival (Panel B) among Patients Treated with Low-Dose m-BACOD Therapy or Standard-Dose m-BACOD Therapy.



**Figure 2.** Overall Survival among Patients with CD4+ Cell Counts below and Those with CD4+ Counts at or above 100 per Cubic Millimeter Who Were Treated with Low-Dose or Standard-Dose m-BACOD Therapy.

Data are based on available CD4+ counts. P values are for the comparison between treatment groups for each of the CD4-count cohorts.

On the basis of these specimens, 85 patients (62 percent) were classified as having large-cell lymphoma (intermediate-grade, diffuse large-cell, and high-grade immunoblastic types), 35 (26 percent) were classified as having small-noncleaved-cell lymphomas, and 17 (12 percent) were classified as having high-grade lymphomas, not otherwise specified. The median survival times were  $36 \pm 3.5$  weeks for the patients with large-cell lymphomas,  $41 \pm 12.8$  weeks for those with small-noncleaved-cell lymphomas, and  $29.6 \pm 9.4$  weeks for those with nonspecific high-grade lymphomas. These times are not significantly different. Among 84 specimens reviewed by both the central study pathologist and an outside pathologist, there was disagreement regarding the histologic subtype in 29 percent of the cases.

#### Quality of Life

The number of hospital days for patients in the standard-dose group was 76 percent higher than that for the low-dose group ( $P=0.03$ ). The scores on 11 of the remaining 12 quality-of-life measures indicated a worse quality of life for the group given standard-dose therapy, although not significantly so.

#### DISCUSSION

We did not find that standard-dose m-BACOD chemotherapy was superior to low-dose chemother-

apy in patients with HIV-related lymphoma. However, we did find that patients treated with low-dose m-BACOD had significantly fewer hematologic toxic effects and spent fewer days in the hospital than patients treated with conventional doses of m-BACOD. These findings were independent of the absolute CD4+ lymphocyte count, although the number of participants with counts above 200 per cubic millimeter was too low for us to determine whether some of them might have benefited from more aggressive therapy. Nevertheless, the data justify the treatment of most patients who have HIV-associated lymphoma with reduced doses of cytotoxic chemotherapy.

Previous clinical trials have demonstrated that the use of a myeloid colony-stimulating factor<sup>8,14</sup> or a low-dose regimen of m-BACOD reduces hematologic toxicity.<sup>13</sup> More aggressive regimens, on the other hand, have generally been associated with a poor clinical outcome and a high incidence of fatal opportunistic infection.<sup>4,16</sup> The relatively favorable outcome with the aggressive LNH84 chemotherapy regimen may have been related to the median CD4+ count of more than 200 per cubic millimeter in the study population.<sup>10</sup>

Our results indicate that the absolute CD4+ cell count is a more important predictor of survival than the dose intensity of chemotherapy. When patients were grouped according to the CD4+ count, longer survival was linked to higher CD4+ counts but not

**TABLE 4.** ADVERSE EVENTS DURING TREATMENT WITH LOW-DOSE OR STANDARD-DOSE m-BACOD.

ADVERSE EVENT (GRADE 1-4)	LOW-DOSE THERAPY (N=98)	STANDARD-DOSE THERAPY (N=94)
	no. of patients	
Elevation in aspartate aminotransferase	43	29
Elevation in alanine aminotransferase	40	22*
Elevation in alkaline phosphatase	29	19
Diarrhea	40	36
Constipation	32	19
Anorexia	35	41
Hyponatremia	29	25
Hyperglycemia	26	31
Bone pain	16	20
Peripheral neuropathy	21	16
Vertigo or disequilibrium	21	30
Cough	30	26
Shortness of breath	21	32†
Rash	17	13
Fever	67	73
Headache	58	45
Abdominal pain	14	22
Allergic reaction	14	13
Nausea	59	48
Vomiting	45	37
Stomatitis	39	46

\*P=0.01 for the comparison with the low-dose group.

†P=0.05 for the comparison with the low-dose group.

to the type of treatment (Fig. 2). Although this analysis is limited by the small number of patients with CD4+ T-cell counts above 200 per cubic millimeter, the survival curves for the two treatment groups appear similar even for patients with more than 200 CD4+ lymphocytes per cubic millimeter, suggesting that our results might apply to patients with relatively intact immune function.

Severe neutropenia was most frequent among patients who received standard-dose therapy, despite the use of GM-CSF. This growth factor has been shown to reduce the severity, duration, and frequency of complications of neutropenia in patients receiving chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for HIV-related non-Hodgkin's lymphoma.<sup>8</sup> Febrile neutropenia was an infrequent complication in this trial, perhaps because GM-CSF shortened the duration of severe neutropenia.

Calculations of relative dose intensity demonstrated that for the most part patients in each of the treatment groups did receive cyclophosphamide and doxorubicin at the planned dose intensity; the patients assigned to the standard-dose group received

therapy at approximately twice the dose intensity of those assigned to low-dose therapy. However, patients assigned to standard-dose therapy received methotrexate at less than the planned dose intensity. In some of these cases, the physicians may have chosen to drop methotrexate from a cycle rather than delay the beginning of the next cycle. It is unlikely that this difference affected the outcome, because randomized trials in patients with lymphoma who do not have HIV infection have not demonstrated differences in outcome between CHOP and similar regimens to which methotrexate has been added.<sup>17,18</sup>

Whether the lymphoma was of the large-cell or small-noncleaved-cell type did not appear to have an effect on survival; this finding confirms those of previous studies in patients with HIV-associated lymphoma.<sup>4-6,8</sup> However, the classification of non-Hodgkin's lymphoma in patients with HIV infection is difficult even for experienced pathologists, as illustrated by the pathological review for this study, in which the frequency of disagreement about the subtype of disease between the report of the initial pathologist and that of the central study pathologist was 29 percent.

Our results confirm the impression of many physicians that the use of relatively low doses of chemotherapy does not adversely affect the outcome in patients with HIV-related lymphoma.<sup>13</sup> In our experience, low-dose m-BACOD therapy is associated with significantly fewer days of hospitalization than standard-dose therapy. For these reasons, we recommend that low-dose chemotherapy be considered for most patients with HIV infection and non-Hodgkin's lymphoma.

Supported by the National Institute of Allergy and Infectious Diseases ACTG and in part by grants from the National Institutes of Health to Dr. Herndier (CFAR-P30 AI 27763), Dr. Levine (U01-AI-27573), Dr. Cooley (GCRC-RR00533-28), and Dr. Testa (NIH N01-AAI95030).

*We are indebted to Ms. Jessica Ainsworth for her assistance in the preparation of the manuscript.*

#### APPENDIX

The ACTG Protocol 142 investigators who worked on this study included members of the Protocol 142 team, investigators at the National Institute of Allergy and Infectious Diseases (NIAID) AIDS Clinical Trials Units, and investigators at the NIAID Division of AIDS. Additional members of the Protocol 142 team were as follows: M. Niu and G. Galetto, Medical Branch, NIAID, Bethesda, Md.; P. Kasdan, ACTG Operations Center, Bethesda, Md.; M.A. Rice and C.W. Suckow, Frontier Science and Technology Research Foundation, Amherst, N.Y.; C. Caffie, Schering-Plough Corporation, Kenilworth, N.J.; H. Hochster, Department of Medicine, New York University Medical Center, N.Y.; S.G. McCarthy, University of California at Los Angeles Clinical AIDS Research and Education Center, Los Angeles; and I. Fishman, Division of AIDS, NIAID, Bethesda, Md. Additional investigators at NIAID ACTG Units were J. Russell, University of California, San Francisco, and San Francisco General Hospital; D.J. Scadden and B. Chapman, Beth Israel Deaconess Medical Center, Boston; S. Murphy, Northwestern University, Chicago; S. Canmann and S.C. Johnson, University of Colorado, Denver; R. Ambinder and C. Raines, Johns Hopkins University, Baltimore; L. Ratner and M. Gould, Washington University, St. Louis; W.J. Fessel and G. VanRaalte, Stanford University, Stanford, Calif.; P.L. Trizzo and M.F. Para, Ohio State University College of Medicine, Columbus; S.A. Miles and R. Mitsuyasu, University of California at Los Angeles, Los Angeles; A. Greist and J. Craft, Indiana University, Indianapolis; T. Cheung and

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