

Opportunistic Infection and Immunologic Function in Patients With Human Immunodeficiency Virus-Associated Non-Hodgkin's Lymphoma Treated With Chemotherapy

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Background: The incidence of systemic non-Hodgkin's lymphoma (NHL) is higher in the population infected with human immunodeficiency virus (HIV) than in the uninfected population. Standard treatment for this cancer involves the administration of systemic chemotherapy. **Purpose:** Our objective was to determine the relative risk (RR) of opportunistic infection and the relative change in immunologic function in a cohort of patients who had HIV-associated NHL and who were treated with combination chemotherapy and to compare them with those in a matched cohort of control subjects who had advanced HIV infection but no signs of NHL. **Methods:** We performed a case-control study in which the clinical course of each patient with HIV-associated NHL (n = 43; case subjects) treated with infusional cyclophosphamide, doxorubicin, and etoposide was compared with that of two patients with HIV infection but without lymphoma who were matched for CD4 lymphocyte count and prior opportunistic infection (n = 86; control subjects). The patients' medical records were reviewed for all information related to acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections, survival, cause of death, and lymphocyte subset analyses. Univariate and multivariate analyses were performed to determine whether any of a number of confounding factors (e.g., age, sex, CD4 count, prior opportunistic infection, and prior antiretroviral therapy) could have influenced the risk of developing a first infectious event (defined as opportunistic infection or nonlymphoma death). All *P* values resulted from two-sided statistical tests. **Results:** In the univariate analysis, a significantly greater risk for a first event was associated with being a case subject (RR = 1.8; 95% confidence intervals [CI] = 1.1-3.0; *P* < .05), having a low CD4 count (<100/ μ L) (RR = 3.1; 95% CI = 1.8-5.4; *P* < .0001), being female (RR = 1.7; 95% CI = 1.1-3.3; *P* < .05), having prior *Pneumocystis carinii* pneumonia (RR = 3.5; 95% CI = 1.9-6.3; *P* < .0001), having any prior opportunistic infection (RR = 3.6; 95% CI = 2.1-6.4; *P* < .0001), and having prior antiretroviral therapy (RR = 1.9; 95% CI = 1.1-3.3; *P* < .05). In the multivariate analysis, however, being a case subject (RR = 2.1; 95% CI = 1.2-3.6; *P* < .01), having a low CD4 count (RR = 2.1; 95% CI = 1.2-3.9; *P* < .05), and being female (RR = 3.0; 95% CI = 1.8-5.6; *P* < .001) were the only characteristics associated with an increased risk of a first event. When the mean CD4 lymphocyte count at approximately 1 year was compared with that at baseline, there was a significantly greater decrease in the CD4 count among case subjects than

among control subjects (mean decrease \pm standard deviation [SD] = 99/ μ L \pm 138/ μ L versus 29/ μ L \pm 100/ μ L; *P* = .03). **Conclusions:** Treatment of patients who have HIV-associated NHL with a non-steroid-containing chemotherapy regimen was associated with a significant and sustained reduction in the CD4 lymphocyte count and a twofold increase in the risk of developing opportunistic infection. **Implications:** Oncologists and other physicians who treat patients with HIV-associated NHL should be familiar with the prophylaxis, recognition, and management of opportunistic infection. In addition, there is a need to identify effective strategies for the amelioration of chemotherapy-induced immunosuppression in this population. [J Natl Cancer Inst 1997;89:301-7]

The incidence of non-Hodgkin's lymphoma (NHL) in patients with the human immunodeficiency virus (HIV) infection is increasing; approximately 5000 of such cases were diagnosed in the United States in 1992, or approximately one in nine patients with NHL (1). The improved prophylaxis and management of opportunistic infections as well as the use of improved antiretroviral therapies have undoubtedly contributed to this phenomenon, primarily because these treatment advances have prolonged the period that patients survive with profound immunodeficiency. For example, in one series of patients, NHL occurred in 19% and 29% of patients who had survived 3 years and who had been treated with didanosine or zidovudine, respectively (2). With continued improvement in supportive care and time of survival, the incidence of HIV-associated NHL may very likely continue to increase (1).

HIV-associated NHL typically presents as an intermediate- or high-grade lymphoma of B-cell phenotype and frequently involves one or more extranodal sites, such as the bone marrow, gastrointestinal tract, central nervous system, or other sites. Treatment consists of combination chemotherapy regimens that are potentially curative for lymphomas that arise in patients who

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See "Notes" following "References."

are not infected with HIV. These treatment regimens typically involve administration of cyclophosphamide, doxorubicin, and vincristine as an intravenous bolus injection together with oral prednisone (CHOP) or these drugs plus cytotoxic agents such as methotrexate and bleomycin (3). Patients who are administered these regimens typically experience complete remission rates of 30%-50% and median survival times of 6-9 months (3). Administration of cyclophosphamide (800 mg/m²), doxorubicin (50 mg/m²), and etoposide (240 mg/m²) as a 96-hour continuous intravenous infusion every 28 days (CDE) for four to six cycles together with granulocyte colony-stimulating factor (5 µg/kg given subcutaneously daily beginning on day 6 until neutrophil recovery of >10 000/µL) represents an alternative approach that has resulted in an encouraging complete response rate (57%) and median survival (18 months) in preliminary studies involving 46 patients (4-7).

Opportunistic infections are frequently a complication of the administration of combination chemotherapy to patients with HIV-associated NHL, and they occur in anywhere from 10% to 78% of the patients (4-16). The incidence of these infections is dependent on the intensity of the chemotherapy regimen (11) and the severity of the patient's underlying immunodeficiency (15).

To determine the effect of combination chemotherapy on immunologic function and the risk of opportunistic infection, we performed a case-control study in which we compared the clinical course of 43 patients who had HIV-associated NHL that was treated with infusional CDE (case subjects) with that of a group of 86 patients who had advanced HIV infection that was unassociated with NHL (control subjects). The primary objectives of our study were to determine the relative risk (RR) of developing opportunistic infection or death due to causes other than non-Hodgkin's lymphoma and to determine the long-term effects of chemotherapy on CD4 and CD8 T-lymphocyte number as well as total T lymphocytes.

Subjects and Methods

Patients

Case subjects. Forty-six patients with HIV-associated NHL were treated in two sequential trials performed at the Albert Einstein Cancer Center of the Montefiore Medical Center (n = 44) and the Graduate Hospital (n = 2) from August 1990 through February 1995. Patients received CDE used either alone (n = 21) in the first trial (4,5) or in combination with didanosine (n = 25) in the second trial (6,7). Forty-three patients served as the case subjects; three patients (of the 21 treated with CDE alone) were excluded either because of inadequate follow-up data (n = 2) or because of concomitant infection with human T-cell leukemia/lymphoma virus (n = 1), which may also produce immunosuppression (17). The excluded patients survived 28, 31, and 3 months, respectively, with the former two being alive at the last follow-up. Details regarding selection criteria, systemic chemotherapy, and central nervous system prophylaxis for patients treated with CDE were reported previously (4-7). Supportive care included *Pneumocystis carinii* pneumonia prophylaxis (160 mg trimethoprim plus 800 mg sulfamethoxazole once or twice daily) for all patients or alternative measures for patients with sulfa intolerance (e.g., oral dapsone and inhaled pentamidine). After oral and/or esophageal candidiasis was noted to commonly complicate therapy, oral fluconazole (100 mg daily) was used prophylactically in all subsequent patients (n = 33). Granulocyte colony-stimulating factor was given as primary prophylaxis after it became commercially available (n = 35). Antiretroviral therapy was not given concomitantly with chemotherapy in the initial study (n = 18), but didanosine was given at recommended doses concomitantly with chemotherapy in alternating cycles as previously described (n = 25) (6,7). All patients were advised to resume (or continue) standard antiretroviral therapy and supportive care at the conclusion of chemotherapy according to guidelines that

were considered standard at that time, which in general included monotherapy with the nucleoside analogues zidovudine or didanosine or combination therapy with zidovudine plus zalcitabine (18).

Control subjects. Each patient with HIV-associated NHL for whom adequate follow-up data were available (n = 43) was matched with two control subjects followed in the acquired immunodeficiency syndrome (AIDS) clinic at Montefiore Medical Center (n = 86), a New York state-designated AIDS center. Case subjects were matched with control subjects for prior AIDS-defining opportunistic infection (yes or no) and were also matched as closely as possible for CD4 count and date of initiation of chemotherapy or first visit to the AIDS clinic. Control subjects were selected from the AIDS center database without knowledge of their clinical course or survival status. All patients in the AIDS clinic were treated by physicians experienced in the care of HIV-infected individuals, and standard guidelines were employed regarding infection prophylaxis and antiretroviral therapy (18). Control subjects were treated during the period from August 1990 through September 1995.

Follow-up information was available for all case subjects and control subjects for at least 6 months or until death in all of the case subjects and in 80 of 83 control subjects (96%). Three control subjects were followed for 4, 4, and 5.5 months, and AIDS-defining events occurred in one of three of these control subjects. The mean and median periods of follow-up were 14.6 and 10.3 months, respectively, for case subjects and 21.1 and 17.5 months, respectively, for control subjects.

Data

The medical records for all case subjects and control subjects were reviewed for survival, cause of death, lymphocyte subset analyses (including CD4, CD8, and CD3 [T] lymphocytes), AIDS-defining opportunistic infections, and noninfectious AIDS-defining events. AIDS-defining events were defined using standard criteria (19), including opportunistic infections (e.g., *P. carinii* pneumonia, toxoplasmosis, cryptococcosis, *Mycobacterium avium*-intracellulare infection, or cytomegalovirus retinitis or disease) and noninfectious events (e.g., Kaposi's sarcoma and dementia). *P. carinii* pneumonia was considered "documented" if the diagnosis was confirmed by use of tests involving collection and analysis of induced sputum, bronchoalveolar lavage, or transbronchial biopsy and was considered "suspected" if the treating physician documented that he or she believed that the clinical and radiographic features were suggestive of *P. carinii* pneumonia and if appropriate therapy for *P. carinii* pneumonia was administered. Other infections were diagnosed by use of standard microbiologic and/or clinical criteria specific for each infection. Only opportunistic infections serious enough to require hospitalization were considered events for this analysis, although there were no documented patients with infections found in our review who were treated as out-patients. There was a bias in both the case and control subject groups to admit patients with known or suspected opportunistic infections, since the patient population consisted predominantly of injection drug users or those who had limited education or limited support in their homes. For analysis of the lymphocyte subsets, data regarding the CD4, CD8, and total T-lymphocyte counts were available at baseline and after approximately 1 year of follow-up for 15 case subjects and 30 control subjects. All case subjects were treated in studies that were approved by the institutional review boards at Montefiore Medical Center and the Graduate Hospital, and all gave written informed consent. Retrospective chart review of the control subjects was approved by the Institutional Review Board at Montefiore Medical Center.

Statistical Analysis

The study was designed to have 80% power to detect at least a 1.5-fold difference in the RR of opportunistic infection and nonlymphoma death, with an α level of .05. Patients who died of lymphoma were censored from the analysis at the time of their death. In addition, two of the control subjects died of causes other than systemic lymphoma (lung carcinoma and central nervous system lymphoma) and were censored from the analysis at the time of their death. The rate of all opportunistic infections and nonlymphoma deaths (i.e., events) was calculated in person-years (number of events/100 person-years of follow-up). The RRs of these events were calculated for the case subjects versus the control subjects, and their 95% confidence intervals (CIs) were estimated under the assumption of Poisson distribution. The RR of a first event was estimated by use of Cox's proportional hazards model (20,21). The product limit method of Kaplan and Meier (22) was used to estimate the proportion of patients who developed a first event. The logrank test was used in conjunction with the

univariate survival analysis (23). For the multiple survival analysis, all the baseline clinical features that were significantly associated with a first event in the univariate analysis were controlled for in the proportional hazards model (20). Wald's test was used in conjunction with the multiple survival analysis. The mean difference in CD4, CD8, and total T lymphocytes between case and control subjects was compared by the analysis of variance method for the matched data. All *P* values shown resulted from the application of two-sided statistical tests.

Results

Patient Population

The characteristics of the case subject and control subject populations are shown in Table 1. The groups are well matched with regard to age, sex, risk factors for HIV infection, prior antiretroviral therapy, prior opportunistic infection, and the CD4 lymphocyte count.

Opportunistic Infection and Nonlymphoma Deaths

The number, rate, and causes of opportunistic infections and deaths due to causes other than lymphoma (hereafter referred to as "event") are shown in Table 2. When evaluating the event rate, the RR for any event was 2.0-fold greater in case subjects than in control subjects (95% CI = 1.4-3.0; *P* < .001) if all events were included in the analysis. This result was due to a significant increase in the risk of opportunistic infection (RR = 2.0; 95% CI = 1.3-3.2; *P* < .01). There was a trend for an increased risk of death due to causes other than lymphoma (RR = 2.0; 95% CI = 0.9-4.5; *P* = .07). Most of the nonlymphoma deaths (*n* = 24) that occurred among the case subjects (*n* = 10) and control

subjects (*n* = 14) were due to opportunistic infection (*n* = 11) or unspecified pneumonia (*n* = 4), but some patients died of Kaposi's sarcoma (*n* = 1) or of wasting, dementia, or unspecified causes (*n* = 8). Although the study was not designed to assess the RR of specific infections, we found that cytomegalovirus infection (RR = 4.3; 95% CI = 1.6-11.6; *P* < .01) and herpes simplex infection (RR = 7.2; 95% CI = 1.6-32.1; *P* < .01) occurred significantly more often in the case subjects.

The Kaplan-Meier analysis indicated that case subjects were significantly more likely to develop a first event than control subjects (*P* = .03) (Fig. 1). The median time to a first event was 13.6 months for the case subjects (95% CI = 9.0-25.7 months) and 27.9 months for the control subjects (95% CI = 21.1 to more than 55 months).

Univariate and Multivariate Analyses

Univariate and multivariate analyses were performed to determine whether any of a number of confounding factors could have influenced the risk of developing a first event (Table 3). In the univariate analysis, a significantly greater risk for a first event was associated with being a case subject, having a low CD4 lymphocyte count (<100/μL), being female, having prior *P. carinii* pneumonia, having any prior opportunistic infection, and having prior antiretroviral therapy. Age and risk factor for HIV infection were not found to be associated with development of a first event. In the multivariate analysis, only being a case subject, having a low CD4 lymphocyte count, and being female were associated with an increased risk of developing a first event.

Noninfectious AIDS-Defining Events

We also evaluated the risk of noninfectious events that were AIDS related. Among the case and control subjects, there were a total of eight and seven events, respectively (including three and two events of Kaposi's sarcoma, respectively; five and four events of dementia, respectively; and zero and one event of multifocal leukoencephalopathy, respectively). The risk of dementia was significantly increased in the case subjects (RR = 3.6; 95% CI = 1.1-12.4; *P* < .05). Three of the five case subjects with dementia, however, received whole-brain irradiation for the treatment of lymphomatous meningitis, which may have contributed to the development of this complication (24).

Survival and Cause-Specific Survival

The estimated median survival was 18.2 months for case subjects (95% CI = 7.0-50.1 months) compared with 57.8 months for control subjects (95% CI could not be estimated) (*P* = .0001). This difference was attributable to the 37% tumor-related mortality among the case subjects. If deaths due to lymphoma were censored from the analysis, there was no significant difference in the cause-specific survival for case subjects (50.1 months) compared with control subjects (57.8 months).

Lymphocyte Subsets

After approximately 1 year of follow-up, there was a significantly greater decrease in CD4 lymphocytes in the case subjects than in the control subjects (mean decrease ± standard deviation [SD] = 99/μL ± 138/μL versus 29/μL ± 100/μL; *P* = .03), but not CD8 lymphocytes (mean decrease ± SD = 266/μL ± 713/

Table 1. Patient characteristics*

	Subjects†	
	Case	Control
Total No. of subjects	43	86
Age, y		
Median	38	35
Range	28-59	22-63
Sex		
Male	34 (79)	62 (72)
Female	9 (21)	24 (28)
Risk factors		
Intravenous drug use	21 (49)	38 (44)
Homosexual	10 (23)	15 (17)
Other	12 (28)	33 (38)
Prior antiretroviral therapy	25 (58)	49 (57)
Prior opportunistic infection	11 (26)	22 (26)
Prior AIDS-defining infections		
<i>Pneumocystis carinii</i> pneumonia	6 (14)	18 (21)
<i>Mycobacterium avium</i> -intracellular	3 (7)	2 (2)
Cytomegalovirus	1 (2)	2 (2)
Toxoplasmosis	0	5 (6)
Cryptococcosis	3 (7)	0
Esophageal <i>Candida</i>	2 (5)	1 (1)
CD4 lymphocyte count, per μL		
Median	94	88
Mean	165	161
Range	3-724	5-797

*Data were derived from the clinical history and CD4 counts at the time that the patients began therapy for the lymphoma (for the case subjects) or the first visit to the acquired immunodeficiency syndrome (AIDS) clinic (for the control subjects).

†Unless otherwise specified, values = number of subjects (%).

Table 2. Number, rate, and causes of opportunistic infections or deaths due to causes other than lymphoma ("event")

	Subjects		Relative risk*	95% confidence interval	P
	Case	Control			
Total No. of subjects	43	86			
Infections and deaths, total No. (first event)†	44 (24)	62 (39)			
Person-years of follow-up	52.5	151.1			
Rate of infection/death, per 100 person-years	84	41	2.0	1.4-3.0	<.001
Opportunistic infection, total No. (first event)†	34 (21)	48 (30)			
<i>Pneumocystis carinii</i> pneumonia	8 (6)	16 (13)			
Cytomegalovirus retinitis and/or disease	9 (5)	6 (2)	4.3	1.6-11.6	<.01
Herpes simplex‡	5 (4)	2 (0)	7.2	1.6-32.1	<.01
<i>Mycobacterium avium</i> -intracellulare	5 (2)	8 (6)			
Esophageal candidiasis	3 (1)	8 (3)			
Toxoplasmosis	2 (1)	2 (1)			
Cryptococcosis	0	4 (4)			
Cryptosporidiosis	1 (1)	1 (1)			
Tuberculosis	1 (1)	0			
Salmonellosis	0	1 (0)			
Deaths, excluding lymphoma, total No. (first event)†	10 (3)	14 (9)§			

*Relative risk of event rate in case subjects versus control subjects, 95% confidence interval, and P value shown only for event rates that are significantly different.

†Total number of events is shown in each column, and the number of first events is shown in parentheses.

‡Includes only severe herpes simplex infections that required hospitalization and intravenous acyclovir.

§Not including one death due to lung cancer and one death due to primary central nervous system lymphoma.

μL versus $33/\mu\text{L} \pm 405/\mu\text{L}$; $P = .18$) or total T (CD3) lymphocytes (mean decrease \pm SD = $335/\mu\text{L} \pm 803/\mu\text{L}$ versus $63/\mu\text{L} \pm 447/\mu\text{L}$; $P = .17$). There was no significant difference between the case subjects and control subjects in the median interval (11.5 and 12.1 months, respectively; median score test $P = .83$) or in the mean interval (11.9 and 12.5 months, respectively; Student's t test $P = .66$) between the baseline and follow-up lymphocyte count.

Discussion

Opportunistic infections and other serious noninfectious events (such as wasting, dementia, Kaposi's sarcoma, and lymphoma) are recognized complications of advanced HIV infection. Opportunistic infections are particularly common in patients with systemic HIV-associated lymphoma treated with combination chemotherapy, although it is unclear whether such

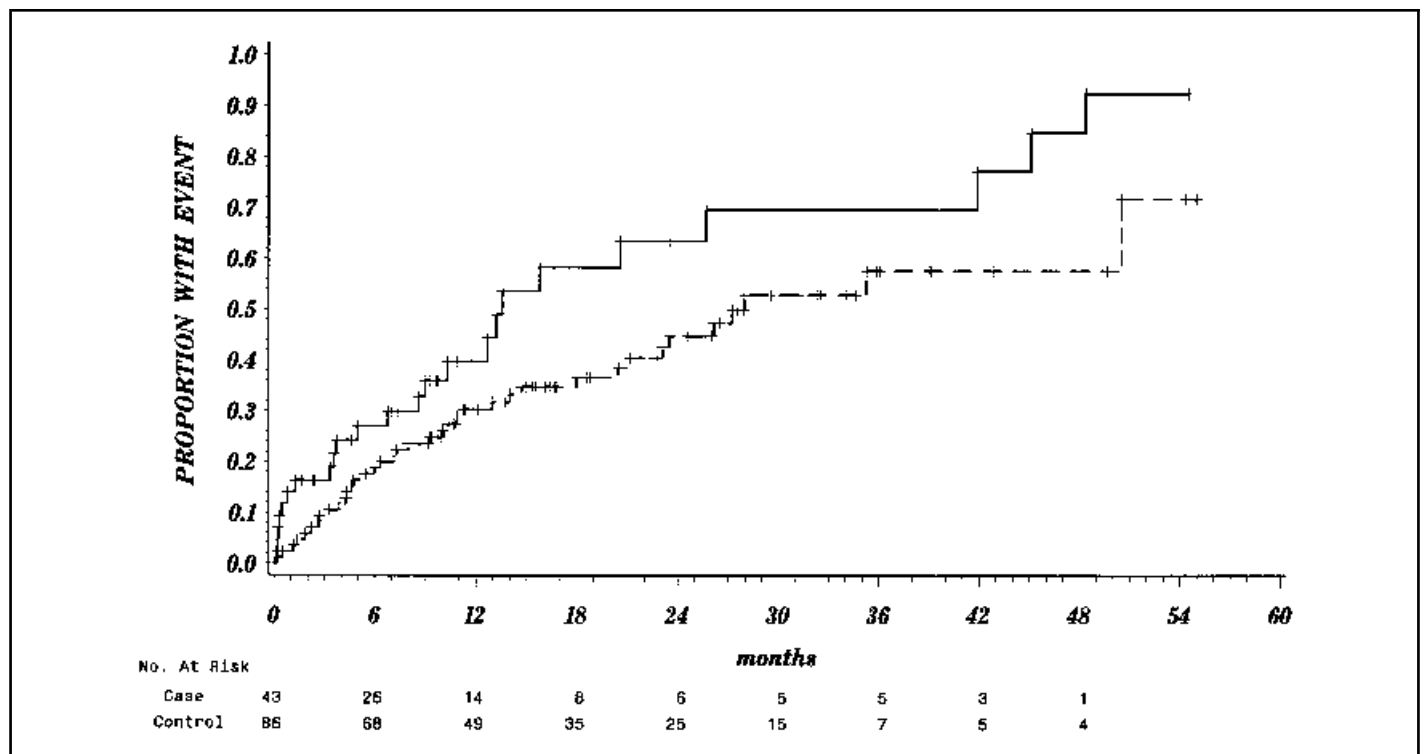


Fig. 1. Kaplan-Meier estimates of the time to the first event (i.e., opportunistic infection or death due to causes other than lymphoma) in case subjects (solid line) and control subjects (dashed line).

Table 3. Effect of confounding factors on risk for a first event (i.e., opportunistic infection or death due to causes other than lymphoma)

Variable	Univariate analysis			Multivariate analysis		
	Relative risk	95% confidence interval	P*	Relative risk	95% confidence interval	P*
Case subjects	1.8	1.1-3.0	<.05	2.1	1.2-3.6	<.01
CD4 lymphocyte count <100/ μ L	3.1	1.8-5.4	<.0001	2.1	1.2-3.9	<.05
Female	1.7	1.1-3.3	<.05	3.0	1.8-5.6	<.001
Prior <i>Pneumocystis carinii</i> pneumonia	3.5	1.9-6.3	<.0001	—	—	NS
Prior opportunistic infection	3.6	2.1-6.4	<.0001	—	—	NS
Prior antiretroviral therapy	1.9	1.1-3.3	<.05	—	—	NS
Age	—	—	NS	—	—	NS
Risk factor	—	—	NS	—	—	NS

*NS = not significant.

infections are attributable to chemotherapy, to the patient's underlying immunosuppression, or to both factors. To investigate this question further, we compared the number and rate of serious or fatal AIDS-defining opportunistic infections in a group of patients (case subjects) treated with a uniform, non-steroid-containing chemotherapy regimen (CDE) (4-7) with those in a group of matched patients with advanced HIV infection (control subjects). We found that CDE therapy was associated with a twofold increase in the RR of developing a serious or fatal opportunistic infection. This observation held true whether we included all infections or just the first infection in the analyses. A significantly higher RR for a first infection was also associated with having a low CD4 count (<100/ μ L), being female, having any prior opportunistic infection, having prior *P. carinii* pneumonia, and having prior antiretroviral therapy but was not influenced by age or risk factor for HIV infection. In the multivariate analysis that adjusted for these factors, however, only the case subjects, patients with low CD4 count, and women had a significantly higher risk of developing a first infection. Low CD4 count is a known risk factor for opportunistic infection (25), and some (26) but not all (25) reports have indicated a higher risk of opportunistic infection in women. Our findings provide strong evidence, therefore, that chemotherapy in patients with HIV-associated lymphoma is associated with a significantly increased risk of developing a serious or fatal opportunistic infection.

The study was not designed to have sufficient statistical power to detect differences in the rate for specific AIDS-defining infections. Nevertheless, we found that cytomegalovirus retinitis and/or disease and severe herpes simplex infection occurred significantly more often in the case subjects than in the control subjects. The rate of AIDS-defining infection or death in our control subject population (41 per 100 person-years) was comparable to the rate reported in a similar patient population treated with zidovudine (53 per 100 person-years) and didanosine (37 per 100 person-years) (27).

We have previously reported (4-7) that CDE results in a significant decrease in CD4 lymphocytes that becomes evident after two cycles of therapy and that this effect cannot be ameliorated by concomitant didanosine monotherapy. This lymphopenia is associated with increased HIV burden, a finding that may be attributable to release of trapped virus from lymphocytes and dendritic cells or perhaps other mechanisms (7). The current study now indicates that this chemotherapy-induced lymphopenia may persist for at least 1 year. Persistent lymphopenia also

occurs in immunocompetent patients treated with intensive chemotherapy, especially adults who lack residual thymic function (28).

Our trial has a number of potential limitations. However, we believe that none of these limitations would likely have influenced our findings.

First, we have made the assumption that the lymphoma does not confer some additional immune suppression. Although immune suppression accompanies Hodgkin's disease, it has not been reported consistently for patients with NHL (i.e., who are not known to be HIV infected) (29,30).

Second, although the groups were well balanced with regard to surrogate markers of immune function (i.e., CD4 count and prior infection), it is now well recognized that these are incomplete markers (31). Quantitation of HIV burden may be more accurate in predicting outcome, for example, but it was not routinely available during the course of our study (32). Nevertheless, multivariate analysis that included several recognized prognostic variables demonstrated a significantly greater risk of first infection in the case subjects.

Third, we included in our analysis only opportunistic infections that were serious enough to require hospitalization or resulted in death. We limited our analysis to these events because we were primarily interested in whether chemotherapy increased the risk of developing serious infections that would significantly impair the patient's quality of life (or duration of life), rather than mild or moderate infections that were nondebilitating and more likely to be difficult to define precisely.

Fourth, it is possible that the differing rates of infection could be attributable to closer follow-up given to the lymphoma patients than to the control subjects. This is unlikely, since we included only events that were serious enough to require hospitalization. Furthermore, patients in the control subject group were followed for nearly threefold more person-years than patients in the case subject group because of the greater longevity of the control subjects.

Fifth, it is possible that the differences in the rates of infection could be attributable to different patterns of antiretroviral use, infection prophylaxis, or physician experience (33). This hypothesis is highly unlikely for several reasons. All patients with lymphoma treated with CDE were managed not only by medical oncologists who were familiar with the care of HIV-infected individuals but also by AIDS specialists. Supportive care measures were prescribed as a part of the lymphoma treatment protocol, including *P. carinii* pneumonia prophylaxis in all patients

and fungal prophylaxis in most patients. With regard to antiretroviral therapy, these drugs were prescribed to both groups either during or after the completion of chemotherapy according to guidelines that were considered to be standard practice at the time (18). The only agents that were available at the time of this study (zidovudine, didanosine, and zalcitabine) have marginal clinical efficacy, especially if they are used as monotherapy (as was the practice at that time) (27,34). Furthermore, we have reported previously (4-7) that concomitant administration of didanosine with CDE did not reduce opportunistic infection or ameliorate chemotherapy-induced lymphopenia.

Our findings have important implications for the management of patients with AIDS-related cancers. Combination chemotherapy was associated with a sustained impairment of immunologic function and was also associated with a statistically significant increase in the risk of opportunistic infection. Just as combination antiretroviral therapy is becoming standard practice for patients with advanced and perhaps even early HIV infection (35), our findings provide support for the investigation of combination antiretroviral therapy in conjunction with chemotherapy in order to ameliorate the chemotherapy-induced deterioration in immunologic function. Such investigations need to proceed cautiously, however, because of the potential for serious adverse drug-drug interactions. Finally, medical oncologists who treat patients with AIDS-related cancers should become familiar with antiretroviral agents, drug-drug interactions, and the prophylaxis, recognition, and management of opportunistic infections. Oncologists lacking such familiarity should work closely with AIDS specialists in caring for such patients.

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Notes

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