Lymphoma in the Setting of HIV Disease

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LYMPHOMAS HAVE LONG BEEN SOME OF THE most devastating and complex opportunistic diseases of HIV infection. Their epidemiologies, both before and after the widespread use of HAART, have not been fully elucidated, and their various treatments, both in the setting of underlying immune suppression and used concurrently with antiretroviral therapy, have not been officially standardized. As for their etiologies and pathogeneses, there is still much to understand, including the role of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) and the Epstein-Barr virus (EBV) in the transformation of B-cells into lymphomas in the setting of HIV disease (as reflected in our cover art). But this much is clear: Lymphomas remain the most lethal complications of HIV disease (Chaisson, 1998). Yet it is also true that the incidence of HIV-related lymphoma has decreased in recent years. What's more, the immune recovery associated with antiretroviral treatment has enabled many more patients to better tolerate chemotherapy and to live longer, healthier, and cancer-free lives after receiving what is potentially a grim diagnosis.

Epidemiology

IT IS WELL ESTABLISHED THAT THE RISK OF lymphomas in HIV disease appears to increase with progressive immunodeficiency. As discussed by Dr. Scadden, the incidence in symptomatic HIV-positive patients is estimated to be 1.6% to 6.0% per year. He also noted that the magnitude of increased risk, compared with that of the general population, has been estimated at 60- to 110-fold and includes systemic lymphoma, primary CNS lymphoma, primary effusion lymphoma, and Hodgkin's disease. And according to a paper published by the Imperial Cancer Research Fund (ICRF) at the Radcliffe Infirmary in Oxford, England, which involved an analysis of AIDS-related lymphoma cases reported to the U.S. Centers for Disease Control through June 1989, these types of lymphoma are twice as common in Caucasians as in people of African or Caribbean descent and in men as in women. Lymphomas were most common in patients with clotting disorders, such as hemophilia, and least common in those born in the Caribbean or Africa who had acquired HIV by heterosexual contact (Beral, 1991).

What might explain these varying levels of risk among different racial groups of HIV-positive patients? According to one team at the National Cancer Institute (NCI), genetic polymorphisms in chemokines and chemokine receptors may provide possible answers (Rabkin, 1999). Stromal cell-derived factor 1 (SDF-1), for example, is a potent mitogen and chemoattractant for B-cells and plays a significant role in normal B-cell proliferation and maturation. In this study, the SDF-1-3'A chemokine variant—which is carried by 37% of Caucasians and 11% of people of African and Caribbean descent—was associated with approximate doubling of the non-Hodgkin's lymphoma (NHL) risk in individuals with a heterozygous variant and roughly a fourfold increase in individuals with a homozygous variant. After a median follow-up of 11.7 years, NHL developed in 6/30 (19%) homozygous and 22/202 (10%) heterozygous patients, respectively, compared with 24/514 (5%) patients with wild-type SDF-1. The study authors thus concluded that racial differences in SDF-1-3'A frequency may contribute to the lower risk of HIV-associated NHL in people of African and Caribbean descent compared with Caucasians.

With respect to the impact of highly active antiretroviral therapy (HAART), a spate of recent studies suggests that lymphoma incidence rates have declined over the past few years (Kirk, 2001; Besson, 2001; Grulich, 2001)—good news in light of earlier concerns that prolonged survival associated with HAART might increase the risk of lymphomas in HIV-positive patients. In a study conducted by the ICRF and highlighted by Dr. Scadden, cancer incidence data from 23 prospective studies that included 47,936 HIV-positive patients from North America, Europe, and Australia were collated, checked, and analyzed (International Collaboration on HIV and Cancer, 2000). Adjusted incidence rates—expressed as the number of cancers per 1000 person-years—for Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, cervical cancer, and 20 other cancer types or sites were calculated. Rate ratios were estimated, comparing incidence rates from 1997 through 1999 with rates from 1992 through 1996, after adjustment for study, age, sex, and HIV risk group.

For the period from 1992 through 1999, 2,702 cancers were reported in 138,148 person-years of observation, and more than 90% of them were either Kaposi's sarcoma or non-Hodgkin's lymphoma. The incidence rates for NHL declined, from 6.2 to 3.6, based on 623 cases from 1992 through 1996 and 134 cases from 1997 through 1999, respectively (P<.0001). Among the lymphoma subtypes, there were marked reductions in the incidence of primary CNS lymphoma and immunoblastic lymphoma when comparing the two timeframes. However, there were no statistically significant changes in the incidence rates for Burkitt's lymphoma and Hodgkin's disease. "In other words," Dr. Scadden added, "among the systemic lymphomas in the era of HAART, immunoblastic histology is diminished while Burkitt's lymphoma and Hodgkin's disease remain unaffected."

TABLE 1. Comparison of HIV-Associated Lymphomas

Feature	Histologic Lymphoma Subtypes		
	Burkitt/Burkitt-like	Immunoblastic	Primary Effusion Lymphoma
Presentation	Systemic	CNS/extranodal	Effusions
Prior AIDS	<30%	>75%	>75%
CD4+ cell count	Usually normal	Decreased	Decreased
Epstein-Barr virus	50%	>90%	>90%
HHV-8	Negative	Negative	Positive
C-myc oncogene	>65%	Negative	Negative

Source: Little, 2001. Reprinted with permission of the *Journal of the American Medical Association* and the American Medical Association.

Clinical Presentations

THERE ARE GENERALLY THREE SUBTYPES OF HIV-related lymphomas: large-cell immunoblastic, small noncleaved-cell (Burkitt's or Burkitt's-like lymphoma), and diffuse large cell. Large-cell immunoblastic and small noncleaved-cell histologies are considered to be high-grade B-cell tumors that, according to Dr. Scadden, make up the vast majority (greater than 80%) of HIV-related lymphoma cases being reported today. This is compared to a much smaller percentage (between 30% and 40%) typically found in populations of non-HIV-infected patients with lymphoma (Levine, 1992).

Extranodal disease in HIV-related lymphoma is more often the rule than the exception. In fact, several early reports described stage IV lymphomas—a stage that embodies significant extranodal involvement—in 60% to 70% of HIV-positive patients at the time of diagnosis (Levine, 1991; Kaplan, 1989; Knowles, 1988; Ziegler, 1984). As explained by Dr. Scadden, lymphomas can appear at almost any site in the body, with a noted tendency toward the bone marrow (approximately 23% of cases), the central nervous system (22%), the GI tract (21%), the liver (13%), and soft tissue (7%). There have also been data indicating that, in 30% to more than 50% of HIV-related lymphoma cases, disease can be exclusively extranodal with no involvement of the lymph nodes (Kaplan, 1989; Raphael, 1991).

Dr. Scadden also pointed out that specific sites of extranodal disease are roughly linked to histologic types. For example, large-cell immunoblastic tumors preferentially involve the CNS and GI tract, whereas small noncleaved histologies often involve the bone marrow.

Constitutional "B" symptoms—fever, night sweats, and/or weight loss in excess of 10% of normal body weight—are another hallmark of HIV-related lymphomas. It has been estimated that 82% of patients with systemic lymphoma and 91% with primary CNS lymphoma present with these "B" symptoms (Levine, 1991). However, Dr. Scadden also warned that symptoms can be remarkably diverse, given that extranodal disease is common in HIV-related lymphoma and, thus, can give rise to additional symptoms associated with disease of a particular organ system. In addition, "B" symptoms should not be assumed to be of tumor origin in a patient with confirmed lymphoma. "A thorough microbiologic assessment is needed to exclude secondary infections that may significantly complicate lymphoma therapy," Dr. Scadden warned.

All patients with lymphoma are staged according to the Ann Arbor classification system originally proposed for Hodgkin's disease. Most HIV-related lymphomas are stage III or IV (III: involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by direct extension to extralymphatic organ or site or by involvement of the spleen or both; IV: diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement).

With respect to primary CNS lymphoma, the incidence has been estimated to be as high as 20%, although most epidemiology-based studies in the era of HAART suggest a dramatic decrease in recent years. Still, HIV-positive patients who present with systemic lymphoma—even those who are still responding sufficiently to HAART—should undergo careful assessment of the CNS (e.g., MRI/PET scanning and CSF evaluation). Dr. Scadden stressed that particular vigilance is needed for those in whom Epstein-Barr virus (EBV) is documented in the primary tumor. According to a report published by Dr. Antonella Cingolani and her colleagues at the Catholic University of Rome, the risk for primary CNS lymphoma relapse was highly associated with the presence of EBV in primary tumors (Cingolani, 2000). These data have, in turn, provided the rationale for using prophylactic intrathecal Ara-C chemotherapy, not only in patients with extranodal involvement of high-risk sites (e.g., bone marrow and paranasal sinus), but also in those with EBV in tumor tissues found anywhere in the body.

Also discussed by Dr. Scadden was primary effusion lymphoma (PEL), a distinct clinicopathologic entity of particular interest. PEL is a rare tumor—a liquid phase hematologic malignancy—that rarely involves the blood or lymph nodes. It is sometimes referred to as body cavity-based lymphoma, and less frequently, AIDS-related lymphomatous effusion.

PEL presents with effusions in body cavities with large cells appearing to be either anaplastic or immunoblastic, with unusual cell surface phenotypic markings. While surface CD45—a common leukocyte antigen—is generally seen, B (CD20 or CD19) or T (CD3) markers are notably absent. Southern blot analyses have also demonstrated VDJ rearrangement of the immunoglobulin locus, indicating that the cancer is of B-cell origin. And as has been discussed in a previous issue of *The PRN Notebook* (see, "Kaposi's Sarcoma and Multicentric Castleman's Disease: An Update on KSHV/HHV-8 and Targeted Therapies," published in the December 1999 issue), PEL is uniformly associated with the presence of the KSHV genome in tumor tissue, with the EBV genome frequently, but not consistently, also being present.

Diagnostic Considerations

DIAGNOSING LYMPHOMAS IN THE SETTING OF HIV poses something of a challenge, given the significant overlaps that exist between the two diseases. For example, lymphadenopathy is a key feature of lym-

Agent	Standard-Dose Chemotherapy	Low-Dose Chemotherapy
Methotrexate	200 mg/m², day 15	200 mg/m², day 15
Bleomycin	4 U/m², day 1	4 U/m², day 1
Doxorubicin	45 mg/m², day 1	25 mg/m², day 1
Cyclophosphamide	600 mg/m², day 1	300 mg/m², day 1
Vincristine	1.4 mg/m², day 1	1.4 mg/m², day 1
Dexamethasone	6 mg/m², days 1 through 5	3 mg/m², days 1 through 5
Response Rates		
Number of Patients	81	94
Complete Response (CR)	52%	41%
Partial Response	26%	28%
Stable Disease	10%	12%
Progression of Disease	12%	19%
Recurrence After CR	40%*	23%

TABLE 2. Low-Dose and Standard-Dose mBACOD for HIV-Associated Lymphoma

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

Source: Kaplan, 1997

phoma, yet it is also a key feature of HIV infection itself. There are also the constitutional "B" symptoms to consider. Many of these symptoms, particularly fever and weight loss, are relatively common in patients with advanced HIV disease and in patients with hepatitis coinfections, which can delay the diagnosis of lymphoma. Finally, as pointed out by Dr. Scadden, a variety of symptoms can be associated with HIV-related lymphoma, given the high percentage of patients with extranodal or multi-organ involvement.

When, then, should a biopsy be ordered to confirm a suspected case of lymphoma? Focusing specifically on suspect lymph nodes, Dr. Scadden explained that a biopsy should be conducted under the following conditions: 1) a lymph node—or set of nodes—appear asymmetrically large, 2) the adenopathy cannot be explained by another secondary process, 3) there is progressive growth of the lymph nodes over one month and/or greater than two centimeters in diameter, 4) rising LDH is detected in blood samples, and 5) associated systemic symptoms are present with a negative microbiologic evaluation. Generally speaking, a confirmation of lymphoma is made by positive fine-needle aspiration (FNA) or tissue biopsy sampling from any organ believed to be involved. It should be noted, however, that Hodgkin's disease is often missed by FNA. Therefore,

if the index of suspicion is high for malignancy and the FNA is nondiagnostic, an excisional biopsy may be required. Bone marrow sampling may also confirm a diagnosis, despite negative FNA or excisional biopsy results from other sites.

Once a biopsy result has confirmed a diagnosis of lymphoma, the next step is to consult an oncologist or hematologist. From there, CT and/or PET scans of the chest, abdomen, and pelvis should be scheduled, along with either a CT or MRI of the brain. CD4+ cell counts and viral load should also be assessed, along with LDH, uric acid, renal and hepatic function. If the patient presents with fever, an aggressive microbiologic workup should be conducted. And finally, the patient should be started on prophylaxis to prevent the onset of *Pneumocystis carinii* pneumonia (PCP).

Treatment of HIV-Related Lymphomas

TREATMENT OPTIONS FOR HIV-RELATED LYMphomas are beginning to expand as the impact of HAART has made aggressive therapies used in other patient groups now tolerable—and testable—in HIV-positive patients. Previously, cytotoxic therapies were evaluated with an emphasis on minimizing toxicity due to the overall poor tolerance of medications and the limited prog-

nosis of patients with advanced HIV infection. Today, however, the prognosis for patients with HIV-related lymphoma has dramatically improved. According to one report involving the Multicenter AIDS Cohort Study, published in the *International Journal of Cancer*, the mortality risk since the introduction of HAART has dropped by approximately 84% in HIV-positive patients with lymphoma (Tam, 2002).

Unfortunately, not all patients can expect to benefit from the wonders of HAART at the time of a lymphoma diagnosis. A growing number of HIV-positive patients have exhausted many of the antiretroviral options currently available and will be diagnosed with lymphoma in the throes of late-stage HIV disease. For these patients, modified regimens of standard chemotherapeutics remain an important option. According to one study published in the *New England Journal of Medicine*, half-standard dose m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) provided a comparable overall lymphoma-free survival and response rate when compared with full-dose therapy—with reduced toxicity—in a series of HIV-positive patients (Kaplan, 1997) (see Table 2). However, additional data involving a modified regimen of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) proved to be inferior. Thus, much focus has now been placed on using full-dose chemotherapeutic regimens in the context of HAART to maintain efficacy, reduce side effects, and prolong survival.

Encouraging data have emerged from studies employing continuous infusions of chemotherapeutic agents. In one study, CDE (cyclophosphamide, doxorubicin, and etoposide) was administered as a continuous infusion over 96 hours every 28 days for up to six cycles in 21 patients (Sparano, 1996) (see Table 3). Patients were followed for a median of 21 months. Thirteen (62%) achieved a complete response, and five (24%) achieved a partial response. The median survival was 18 months.

There was also the National Cancer Institute (NCI)-sponsored study using EPOCH (96-hours continuous infusion of etoposide, vincristine, doxorubicin, followed by a bo-

TABLE 3. CDE for HIV-Associated Lymphoma	
Agent	**Dose**
Cyclophosphamide	800 mg/m^2 (96-hour continuous infusion)
Doxorubicin	50 mg/m^2 (96-hour continuous infusion)
Etoposide	240 mg/m^2 (96-hour continuous infusion)
	Response Rates
Number of Patients	21
Complete Response (CR)	58%
Median Length of CR	>18 months
Tumor-Related Mortality	20%
Median Survival	18.4 months
Source: Sparano, 1996	

lus infusion of cyclophosphamide and oral prednisone) (Gutierrez, 2000). The doses used in this study were individually adjusted to reduce toxicity, and antiretroviral therapy was temporarily stopped during chemotherapy to avoid potential drug interactions and overlapping toxicities. Of 30 evaluable patients, 23 (77%) achieved complete response and no patients progressed. After a median follow-up of 29.9 months, progression-free survival was 80.9% and overall survival was 73.5%. HIV control was achieved within three months of reinstituting antiretroviral therapy, and CD4+ cell counts in most patients had returned to prechemotherapy levels within 12 months.

Recent data outside the context of HIV also suggest that the combination of chemotherapy with rituximab, a monoclonal antibody directed against the CD20 antigen found on most high-grade lymphomas, is more effective than treatment with chemotherapy alone. In a phase I/II study involving HIV-positive patients, CDE was combined with rituximab for five to six cycles (Tirelli, 2002) (see Table 4). Of 29 evaluable patients, complete remission was achieved in 86% of the patients, and partial responses to therapy were seen in 4%. After a median follow-up of nine months, the two-year actuarial survival was 80%, and progression-free survival was 79%.

A phase III randomized trial of CHOP, either with or without rituximab, is currently under way through the NIH AIDS Malignancy Consortium (AMC). Approximately 120 patients were enrolled and data analysis is to begin in October 2002.

A lingering question discussed by Dr. Scadden has been the safety of either initiating or continuing HAART during chemotherapy for HIV-related lymphomas. As was determined by the investigators involved with the NCI EPOCH study reviewed above, there are drug interactions and overlapping toxicities to be concerned about. To evaluate these concerns, the AMC evaluated concurrent HAART (indinavir, stavudine, and lamivudine) in combination with CHOP in 65 patients (40 were treated with modified CHOP and 25 with standard doses of CHOP). The overall response was 60% with modified CHOP and 53% with standard CHOP. There were no unexpected or unusual toxicities. Pharmacokinetics were unperturbed for doxorubicin or indinavir, but an approximate 40% reduction in the clearance of cyclophosphamide was reported. However, this change in pharmacokinetics was not associated with any clinical complications.

"Where does this leave us?" Dr. Scadden asked. "In the EPOCH trial, viral load increases and CD4+ cell count declines were seen, as would be expected. But both parameters returned to baseline levels following reintroduction of HAART at the end of chemotherapy. It's important for every clinician to weigh the relative tolerance of antiretrovirals, especially when other toxic chemotherapeutics are being used, and the potential for drug interaction in deciding whether or not to move forward with antiretroviral treatment during chemotherapy. But it's all or nothing. HAART must either be stopped completely or continued. There are no modified doses of antiretroviral therapy, given the risk of drug resistance and the presently ill-defined nature of the interactions."

With respect to refractory HIV-related lymphoma, Dr. Scadden pointed out that patients who experience a lymphoma relapse are less likely to respond to subsequent therapy. However, the improved tolerance of chemotherapy in patients receiving HAART has encouraged some researchers and clinicians to experiment with high-dose chemotherapeutic regimens with autologous stem cell transplants (ASCT). A report of nine patients from City of Hope Medical Center in Duarte, California, indicated that ASCT was reasonably well tolerated, with return of CD4+ cell counts to pre-chemotherapy levels and control of HIV viral load in those compliant with their HAART regimen (Krishnan, 2001). Patients with both Hodgkin's and non-Hodgkin's lymphoma were included, and disease-free survival was observed in 7/9 (78%) with a median follow-up of 19 months.

As promising as these data are, Dr. Scadden reminded PRN members that ASCT—and possibly non-myeloablative allogenic transplants—are best performed in the context of clinical trials. "Immunologic tumor control, virus control, and graft-versus-host disease demand intensive evaluation to gain some understanding of the proper balance of interventions in HIV-positive patients. With stem cell transplant approaches, one of the things we're now looking at is the possibility of gene modification of the transferred cells." Stem cells, it turns out, are resistant to HIV infection, despite the fact that HIV receptors and coreceptors are expressed on a broad range of hematopoietic progenitors (Shen, 1999). The goal now, Dr. Scadden explained, is to engineer these cells such that they could express HIV inhibitory genes decreasing…their differentiation into various cells types, all of which would putatively resist HIV infection.

Conclusions

BY WAY OF A TAKE-HOME MESSAGE, Dr. Scadden reiterated what clinicians—and HIV-positive patients—can expect from chemotherapy for lymphoma. There is still an increased risk of PCP, hence the importance of initiating PCP prophylaxis after a diagnosis has been established. There is also neutropenia to be concerned about, requiring growth factor support in the vast majority of patients undergoing chemotherapy. While 48% to 75% of patients will respond positively to chemotherapy, Dr. Scad-

TABLE 4. CDE Plus Rituximab for HIV-Associated Lymphoma

Agent	Dose
Cyclophosphamide	800 mg/m² (96-hour continuous infusion)
Doxorubicin	50 mg/m² (96-hour continuous infusion)
Etoposide	240 mg/m² (96-hour continuous infusion)
Rituximab	375 mg/m², day 1 of each cycle
Response Rates	
Number of Patients	29
Complete Response (CR)	86%
Partial Response	4%
Two-Year Actuarial Survival	80%
Two-Year Progression-Free Survival	79%

Source: Sparano, 1996

den reckons that roughly 75% of HIV-positive patients diagnosed with lymphoma will ultimately die of the disease. However, a cure is possible and ASCT appears to be an evolving option for those who fail their first-line regimen. *prn*

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