Incidence and Management of AIDS-Related Lymphoma

By Jamie Hayden Von Roenn, MD

Advances in antiretroviral therapy have dramatically improved human immunodeficiency virus (HIV)-associated morbidity and mortality. The use of highly active antiretroviral therapy (HAART) has led to a decrease in the incidence of opportunistic diseases, including some malignancies. Moreover, increased use of effective antiretroviral therapy may alter the incidence, presentation, prognosis, and therapeutic recommendations for patients with acquired immunodeficiency syndrome (AIDS)-related non-Hodgkin’s lymphoma.

In developed countries, systemic non-Hodgkin’s lymphoma accounts for approximately 3% of all AIDS-defining illnesses.[1] Systemic non-Hodgkin’s lymphoma occurs as a secondary condition in another 5% of HIV-seropositive patients after a preceding AIDS-defining illness.[1] Data from multiple case control studies and international databases of HIV and cancer suggest that the incidence of systemic non-Hodgkin’s lymphoma has stabilized; however, as outlined by Dr. Levine et al, a number of investigations, including the international collaborative study and other large series, have reported a meaningful decline in the incidence of AIDS-related non-Hodgkin’s lymphoma.[2-8] Whether the incidence of systemic non-Hodgkin’s lymphoma has declined subtly or not, its relative importance as a cause of HIV-associated morbidity and mortality has increased with the coincident HAART-related reduction in other complications of AIDS.

Risk Factors and HAART Therapy

In people with HIV infection, the relative risk of lymphoma increases as immune function decreases. In a report by Grulich and colleagues, independent predictors of non-Hodgkin’s lymphoma risk included duration of immunodeficiency, as measured by time from seroconversion and CD4 cell count 1 year prior to non-Hodgkin’s lymphoma diagnosis, and B-cell stimulation, as indicated by higher serum globulin levels.[9]

The impact of HAART on the incidence of lymphoma continues to be evaluated. Dr. Levine and colleagues suggest that there has been a steady drop in the median CD4 count of non-Hodgkin’s lymphoma patients. The median CD4 count of patients with AIDS-associated non-Hodgkin’s lymphoma decreased over the course of the AIDS epidemic, particularly in the early 1990s, prior to the widespread use of HAART therapy. However, more recent studies suggest a possible reversal in this trend. As noted by Dr. Levine, patients enrolled between 1987 and 1989 in the AIDS Clinical Trials Group (ACTG) phase II study of low-dose m-BACOD (methotrexate, bleomycin [Blenoxane], doxorubicin [Adriamycin], cyclophosphamide [Cytosan, Neosar], vincristine [Oncovin], dexamethasone) had a median CD4 count of 150 cells/mm$^3$.[10] The subsequent ACTG trial, a randomized phase III trial of low-dose vs standard-dose m-BACOD, noted a median CD4 count of approximately 100 cells/mm$^3$.[11]

Dose-Escalation Study

The AIDS Malignancy Consortium (AMC) enrolled patients between 1996 and 1997 into a dose-escalation study of CHOP chemotherapy (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) with HAART. The median CD4 count of enrolled patients was approximately 130 cells/mm$^3$. [personal communication, J. Lee, 2001] Similarly, the ongoing AMC trial, a
randomized study of CHOP with or without rituximab (Rituxan), has enrolled patients with a median CD4 count of approximately 120 cells/mm³.

In a large phase II Eastern Cooperative Oncology Group (ECOG) trial of infusional CDE (cyclophosphamide, doxorubicin, and etoposide), patients were treated either with or without concurrent HAART therapy. Patients enrolled before the widespread availability of HAART had a median CD4 count of 78 cells/mm³, whereas those who received HAART therapy had a median CD4 count of 227 cells/mm³.[12] The increased CD4 cell count associated with effective antiretroviral therapy but without complete reversal of the underlying immunosuppression may lead to a rising incidence of AIDS-related non-Hodgkin’s lymphoma over the coming decade.

Will HAART therapy have an impact on the clinical presentation and prognosis of systemic AIDS-related lymphoma? The single most important prognostic factor for patients with systemic AIDS-related lymphoma is a CD4 count of less than 100 cells/mm³. With HAART therapy improving the CD4 count, the prognosis of these patients may significantly improve. Indeed, the high death rate from opportunistic infection reported in earlier trials in AIDS-related non-Hodgkin’s lymphoma patients, and the marked decline in opportunistic infection-related deaths in more recent studies suggest a potential improvement in outcome for this patient population.

Further Prognostic Improvements

Clinically, AIDS-related lymphoma is characterized as a systemic, aggressive, B-cell lymphoma with frequent extranodal sites of involvement. The most common extranodal sites are the central nervous system (CNS), bone marrow, liver, and gastrointestinal tract. Central nervous system involvement, primarily meningeal disease, has been reported in anywhere from 20% to 42% of patients at diagnosis. Although this varies from center to center, it appears that the incidence of CNS involvement at presentation is declining.

In 1994, Ziegler et al reported CNS involvement in 42% of patients,[13] while the ACTG randomized study of m-BACOD (1991 to 1994) reported that only 3 of 198 patients had meningeal involvement.[11] Similarly, in the ECOG trial of infusional CDE, only 4 of 108 patients presented with meningeal disease.[12]

In addition to the improvements in CD4 count with HAART therapy, one would anticipate that better control of HIV infection and a decreased viral load would result in a more favorable cytokine milieu. The local cytokine environment of HIV-associated NHL is T-helper type 2-like in character, favors B-cell proliferation, and provides little immunologic support for antitumor response.[14]

Recently Evaluated Chemotherapy Regimens

The substantially improved outcome for patients with HIV infection as a result of HAART underscores the need to identify the most effective treatment for AIDS-related lymphoma and justifies the use of aggressive, cure-oriented therapy. Levine and colleagues have provided an excellent review of recent therapeutic trials. Although the ACTG trial that compared low- vs standard-dose m-BACOD found no impact on survival but less toxicity with the low-dose regimen, it is inappropriate to conclude that low-dose therapy is an acceptable standard for patients with AIDS-related lymphoma.[11]

Standard CHOP therapy has proven to be more effective than dose-reduced CHOP therapy for AIDS-related lymphoma.[15] Because standard CHOP is equally as effective and less toxic than standard m-BACOD in immunocompetent patients with advanced systemic lymphoma, CHOP might be considered a “reasonable” treatment standard for AIDS-related non-Hodgkin’s lymphoma.[16] More recently, two infusional regimens[CDE and risk-adjusted EPOCH (etoposide, prednisone, vincristine [Oncovin], cyclophosphamide, doxorubicin HCl)] have produced improved median survivals, compared with all prior therapeutic trials.[12,17]

It is unclear whether patient selection, use of antiretroviral therapy, or an improvement in treatment efficacy accounts for the observed differences in outcome. These issues present important avenues for future research. As reviewed by Dr. Levine and colleagues, HAART has not had a negative impact
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on non-Hodgkin’s lymphoma treatment or outcome. Aggressive antineoplastic therapies, like those being evaluated in immunocompetent patients with systemic lymphoma, should be the standard of care as we work toward integrating the best HIV treatment with the best lymphoma therapy.

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