AIDS-related lymphoproliferative disease

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Not long after the recognition of HIV as the causative agent of AIDS, it was evident that individuals infected with HIV developed lymphoma at a greater rate than the population at large. Approximately two thirds of AIDS-related lymphoma (ARL) cases are categorized as diffuse large B-cell type, with Burkitt lymphomas comprising 25% and other histologies a much smaller proportion. Typically, these individuals have presented with advanced extranodal disease and CD4+ lymphocyte counts of less than 200/mm². Recent clinical trials have demonstrated a better outcome with chemotherapy for ARL since the introduction of combination antiretroviral treatment, termed highly active antiretroviral therapy (HAART). For patients with relapses, solid evidence points to the safety and utility of hematopoietic-cell transplantation as a salvage modality. Coinfection with other viruses such as Epstein-Barr virus and Kaposi sarcoma–associated herpesvirus have led to the genesis of previously rare or unrecognized lymphoma subtypes such as plasmablastic and primary effusion lymphomas. The immunosuppressive impact of treatment for patients with ARL receiving chemotherapy with HAART appears transient and opportunistic infections have become less problematic than prior to HAART. Significant progress has been made in the understanding and management of ARL but outcomes still remain inferior compared to those achieved in HIV- individuals. (Blood. 2006;107:13-20)

Introduction

Since the inclusion of non-Hodgkin lymphoma (NHL) as an AIDS-defining illness in 1985, much has changed in the HIV pandemic. The predominance of new cases has shifted to the developing world and the advent of highly active antiretroviral therapy (HAART) has dramatically altered the prognosis for HIV-infected individuals when HAART is available. Furthermore, the beneficial impact of HAART on the incidence and outcomes in AIDS-related lymphoma (ARL) has become clearer. The involvement of viruses such as EBV and HIV-8 in the genesis of ARL is being explored. With HAART-associated improvements in the outlook for HIV-infected patients firmly established, efforts are now underway to optimize lymphoma therapy to reap gains in lymphoma-free and overall survival. This review describes uncommon lymphomas occurring in HIV- individuals, outlines the evidence for recent progress in outcomes for ARL, and discusses the data regarding immunologic effects of antilymphoma therapy in the setting of HIV infection.

HIV-associated NHL prior to HAART

In the pre-HAART era, treatment for ARL mandated risk assessment, comparing the chance of successful lymphoma therapy against the possibility of worsening severe immunodeficiency leading to mortality. A variety of treatment approaches were evaluated including standard-dose, reduced-dose, and even escalated-dose chemotherapy.1-4 Outcomes were poor regardless of treatment choice with complete response rates of about 50% and median survivals in the 5- to 8-month range.1-3 Studies of prognostic factors in this patient population demonstrated that variables associated with the underlying immunodeficiency disease such as CD4 count, prior AIDS diagnosis, and performance score were more important predictors of clinical outcome than were features associated with lymphoma such as stage, lactic dehydrogenase (LDH) concentration, bone marrow or central nervous system (CNS) involvement.1 In 1997, a phase 3 clinical trial, AIDS Clinical Trials Group Study 142, assessed the utility of standard-dose versus low-dose methotrexate, bleomycin, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), and dexamethasone (m-BACOD).4 In that trial, the dose-reduced arm proved equivalently dismal to standard-dose therapy in median survival (35 versus 31 weeks, respectively; P = .25). Those receiving reduced-intensity therapy were more likely to have recurrences and die of ARL, whereas those receiving full-dose therapy more frequently suffered fatal infections. At about this time, the first protease inhibitors became available, quickly ushering in the era of HAART.

Impact of HAART on ARL incidence and outcomes

As HAART was broadly implemented, obvious changes in the incidence of ARL were observed. Table 1 summarizes several studies examining the striking difference in incidence of systemic and CNS-only ARL from the pre- to the post-HAART era. Grulich et al5 examined the incidence of ARL in Australia using a national registry and found a decrease in the incidence of ARL of 43% from the period July 1994 to June 1996 (before HAART) to July 1996 to December 1998 (after HAART). The EuroSIDA group published
incidence rates from its database of 26,764 person-years of observation showing a significant fall in the rates of all subtypes of ARL with HAART use (1.99 cases/100 person-years [p-y]) before HAART to 0.30 cases/100 p-y after HAART, \( P < .001 \) with the most dramatic decline observed in primary brain lymphoma. Confirming the benefit of HAART on lymphoma incidence was the finding that the incidence rate of ARL within 12 months of HAART was 0.88 but fell to 0.45 after more than 2 years on HAART \( (P = .004) \). Likewise, Besson et al.\(^7\) reporting for the French Hospital Database on HIV, showed a fall in relative risk of ARL from the pre-HAART to post-HAART era to 0.50 and for primary CNS ARL, to 0.35.

Reports from several authors in 1998 indicated that HAART improved overall survival for patients with advanced HIV infection.\(^9\-11\) Shortly thereafter, several publications described the decreasing incidence and mortality for patients with ARL.\(^5,6,12,13\) Several of these papers examined outcome by comparing cohorts of consecutive patients grouped by year to determine whether or not patients were on HAART; however, this approach may have included some patients in the HAART group who were not actually receiving HAART. Nevertheless, despite the methodologic limitations of some of these publications, HAART clearly had a marked favorable impact on outcomes (Table 2).

Providing even more evidence of the importance of HAART-mediated HIV suppression, it was observed that those patients experiencing failure of virologic control on HAART suffered significantly higher incidences of ARL and poorer outcomes after therapy.\(^6,17,18\)

In view of these findings, HAART has now become an accepted and important component of therapy for ARL. Although questions still remain regarding the impact of HAART on the pharmacokinetics of chemotherapy, data from the AIDS Malignancy Consortium (AMC)\(^19\) suggest that the impact is modest for cyclophosphamide and doxorubicin and does not warrant dose adjustment. Many investigators agree that zidovudine is relatively contraindicated because it is the most marrow-suppressive antiretroviral agent. Although the protease inhibitor ritonavir has the most significant effect on the cytochrome p450 system and the greatest number of potential drug interactions, it has been regularly used uneventfully in patients receiving chemotherapy. Its inclusion in antiretroviral combinations is ubiquitous due to its potentiating effects on other protease inhibitors. In a retrospective Italian study published in 2001\(^15\) comparing toxicities between patients receiving cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone (CHOP) plus HAART (1997-1998) versus CHOP or a CHOP-like regimen without HAART (1988-1997), greater neurotoxicity and anemia were observed in the CHOP-HAART arm, but the CHOP-HAART arm also demonstrated a statistically lower incidence of infection. However, this observation may have been influenced by improvements in supportive care for the more contemporaneously treated patients in the CHOP-HAART arm.

### Infusional chemotherapy regimens in aggressive ARL

Recent experience with infusional chemotherapeutic approaches has generated enthusiasm for this administration method. Little and coinvestigators used dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) with growth factor support and temporary suspension of antiretroviral therapy in the treatment of 39 patients with ARL.\(^20\) In this regimen, doxorubicin, vincristine, and etoposide are administered as a continuous 96-hour infusion, based on in vitro studies suggesting that tumor cells are less resistant to continuous lower-dose exposure to these agents than to briefer higher-dose exposure. Fifty-nine percent of the patients were intermediate-high or high risk by the International Prognostic Index\(^21\) (IPI) and 41% had a CD4 count of 100 or less. Despite these adverse features of the group, the complete remission (CR) rate was 74% and at 53 months of follow-up, disease-free survival (DFS) was 92%, and overall survival (OS) was 60%. The treatment was generally well-tolerated with 2 secondary malignancies as the only treatment-related deaths reported but 3 opportunistic infections (OIs) occurred after completion of therapy. Although clearly an exciting result in ARL, the outcomes remain poorer than for HIV+ patients, as illustrated by a similar trial of dose-adjusted EPOCH where the CR rate was 92% and OS was 73% at 62 months of follow-up.\(^22\)

### Table 2. Retrospective studies of ARL outcomes before and after HAART

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type and comments</th>
<th>CR, %, HAART</th>
<th>Median OS, mo, HAART</th>
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</thead>
<tbody>
<tr>
<td>Navarro et al(^16)</td>
<td>CHOP regimen; all systemic ARL in this series; 2 yr OS (previous report): 60% vs 22%</td>
<td>No: 39  60 .019</td>
<td>NR: NR —</td>
</tr>
<tr>
<td>Hoffmann et al(^17)</td>
<td>CHOP regimen; HAART response associated with much better OS</td>
<td>No: 61  71 .006</td>
<td>NR: NR —</td>
</tr>
<tr>
<td>Besson et al(^7)</td>
<td>Mostly CHOP-like regimens; higher CD4 count at diagnosis after HAART</td>
<td>No: 42  63 .004</td>
<td>21.2 .004</td>
</tr>
<tr>
<td>Gerard et al(^14)</td>
<td>Half of patients treated with intensive regimens; after HAART, fewer received dose-reduced regimens</td>
<td>No: 115  131 .04</td>
<td>9.5 NR &lt; .001</td>
</tr>
</tbody>
</table>

NS indicates not significant; NR, not reported; and —, not calculated.
Sparano and coworkers used infusional cyclophosphamide, doxorubicin, and etoposide (CDE) over 96 hours every 28 days with concurrent antiretroviral therapy and growth factor support, resulting in a CR rate of 45% and OS of 43% at 2 years.\textsuperscript{25} This trial included patients in the pre- and post-HAART era (43 and 55 patients, respectively) and showed a clear improvement in outcomes for the group in the post-HAART era. The OS at 2 years in the post-HAART group was 47%, with no treatment-related mortality (TRM), compared to the pre-HAART era patients with a 10% TRM and 30% OS. Salman and colleagues used infusional cyclophosphamide, idarubicin, and etoposide (CIE) in first- and second-line therapy in the HIV\textsuperscript{-} setting. The CR rate was 42% in the 24 first-line–treated patients. One-year OS was 64%. The results of CDE and CIE therapy have not achieved the same responses or survival as dose-adjusted EPOCH.

It remains unclear whether there are differences in the risk stratification of patients treated or whether indeed EPOCH is superior to other regimens, particularly in view of the dose-adjustment strategy. The EPOCH regimen is currently being studied in a multicenter clinical trial through the National Cancer Institute (NCI)–sponsored AIDS Malignancies Consortium to ascertain if these promising early results can be confirmed.

### Rituximab use in ARL

The use of rituximab (humanized anti-CD20 antibody) dramatically increased in all CD20\textsuperscript{+} lymphomas following publication of the randomized Groupe d’Etude de Lymphome de l’Adulte (GELA) data showing a survival advantage for HIV\textsuperscript{-} patients older than age 60 receiving CHOP plus rituximab versus CHOP alone.\textsuperscript{24} However, in the setting of concurrent HIV infection, the risk and benefit of rituximab remain unclear. The AMC randomized trial of CHOP versus rituximab-CHOP (R-CHOP) showed a significant increase in bacterial infection-related deaths in those receiving rituximab plus CHOP at 14% versus 2% in the CHOP alone arm (P = .035), with the majority of deaths occurring in those with CD4 counts less than 50/mm\textsuperscript{3}. This toxicity may have outweighed any survival advantage associated with the use of rituximab.\textsuperscript{26} In the phase 2 setting, Spina and collaborators reported the pooled results of an international 3-center trial of 74 patients receiving rituximab plus CDE.\textsuperscript{26} With the addition of rituximab to CDE for this group with 57% intermediate-high or high IPI scores, similar in risk features to the Sparano trial, the CR rate improved to 70% and the 2-year OS rose to 64%. However, there were a striking number of infectious complications with a 14% rate of OIs and 23% rate of non-OIs. Importantly, as in the Little trial, 3 of the OIs occurred more than 1 month after completion of treatment. The TRM, all infection-related, was 8%, again raising concern about the immunosuppression risk of rituximab in this population. As noted, there appeared to be a significant risk of infections with rituximab plus infusional CDE as well. Although response rates improved from the CDE to the CDE-R trials, these findings may have been confounded by improved supportive care preventing OIs and allowing greater dose intensity compared to the older CDE trial. Other groups have not found an increased rate of infections in other phase 2 trials,\textsuperscript{27-30} but it is evident that late infections may occur and it is not clear how long the surveillance for infections was carried out in these studies. Rituximab should be used cautiously in those with CD4 counts less than 50 cells/mm\textsuperscript{3} and, if used, it may be advisable to include antibiotic prophylaxis for bacterial infections in addition to standard prophylaxis against *Pneumocystis carinii* pneumonia.

### Hematopoietic-cell transplantation for ARL

Exploration of the utility of allogeneic or syngeneic bone marrow transplantation in the setting of HIV disease in the 1980s resulted in poor outcomes.\textsuperscript{31-34} Lymphocyte infusions from allogeneic donors were attempted as early as 1983,\textsuperscript{32} before the discovery of HIV, with only transient engraftment and no significant clinical improvement. Adverse effects in these early trials were frequent and benefit was difficult to demonstrate. In the early 1990s, several case reports of allogeneic transplants in the setting of HIV infection for the treatment of aplastic anemia, acute lymphoblastic leukemia (ALL), and HIV-associated NHL, and as primary treatment for symptomatic HIV disease were published.\textsuperscript{35-38} Results from these studies showed that allogeneic transplantation could be performed safely, though the efficacy in these trials was limited. The first report in the literature of an autologous hematopoietic-cell therapy involved in vitro isolation, stimulation, and expansion of autologous CD8 cells with reinfusion 5 times during therapy with interleukin 2 (IL-2).\textsuperscript{39} Little clinical benefit could be shown, however. In all of these trials, it is critical to consider that antiretrovirals were often omitted altogether or limited to the nucleoside analogues, usually zidovudine (ZDV) alone.

More recently, several authors have reported on small series of patients treated at single institutions for high-risk first remission, relapsed, or refractory ARL with autologous hematopoietic cell transplantation (HCT; Table 3). Because of small patient numbers and heterogeneity among these patients, no definitive conclusions can be drawn regarding efficacy. However, concerns regarding stem-cell collection feasibility should now be allayed. Based on these reports, there does not seem to be any unusual difficulty with the quantity or quality of harvested hematopoietic stem cells (HSCs).\textsuperscript{40,42-44} Success rates for adequate HSC collections have ranged from 80% to 100%. With a low reported incidence of graft failure, the quality of the cells harvested appears to be intact as well. One patient of 20 given transplants at City of Hope experienced delayed engraftment after treatment with ZDV.\textsuperscript{41} Although it was unclear if ZDV directly led to graft failure, the authors recommend avoiding ZDV in the context of autologous HCT. With respect to safety, there were few OIs noted in the patients receiving transplants. The French group\textsuperscript{43} reported 2 of 5

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**Table 3. Studies of hematopoietic stem cell transplantation for ARL**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type and comments</th>
<th>No.</th>
<th>Transplantation rate</th>
<th>CR at report</th>
<th>Median follow-up</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabarre et al\textsuperscript{40}</td>
<td>Ref/rHL, Hodgkin; PBSC collections OK</td>
<td>8</td>
<td>NR</td>
<td>5/8</td>
<td>NR</td>
<td>50% at 9 mo</td>
</tr>
<tr>
<td>Krishnan et al\textsuperscript{41}</td>
<td>Relapsed NHL, CBV preparation, 20/20 harvested, 1 delayed engraftment</td>
<td>20</td>
<td>100%</td>
<td>17/20</td>
<td>32 mo</td>
<td>85% at 32 mo</td>
</tr>
<tr>
<td>Re et al\textsuperscript{42}</td>
<td>Rel/rHL, BEAM preparation, 85% PBSC collection rate</td>
<td>20</td>
<td>65%</td>
<td>8/16</td>
<td>12 mo</td>
<td>55% at 9 mo</td>
</tr>
<tr>
<td>Diez-Martin et al\textsuperscript{43}</td>
<td>Ref/ref/high risk 1st CR NHL, Hodgkin disease</td>
<td>14</td>
<td>79%</td>
<td>8/14</td>
<td>30 mo</td>
<td>71% at 21 mo</td>
</tr>
</tbody>
</table>

Ref/rel indicates refractory/relapsed; CBV, cyclophosphamide, BCNU, VC-16 (etoposide); BEAM, BCNU, etoposide, ara-C, melphalan; PBSC, peripheral-blood stem cell.
surviving patients with OIs, whereas Re and colleagues saw no TRM nor unexpected infections. The City of Hope series reports one TRM but no unusual infections. Outcomes in autologous HCT for lymphoma appear promising with long-term survivors reported. It now appears that sufficient numbers of patients with ARL have undergone autologous HCT to state that it is a safe, feasible, and reasonable approach for ARL patients who otherwise meet criteria for transplantation. Perhaps the only caveat is that all but the French series have required HIV disease to be under control as manifest by modest to undetectable HIV viral loads or CD4 counts greater than 100/mm³.

Much less known is known about allogeneic transplantation for ARL. An article by Kang and colleagues described 2 patients undergoing reduced-intensity allogeneic transplantation, one for acute myelogenous leukemia (AML), the other for primary refractory Hodgkin lymphoma. Both patients engrafted well with no unusual complications. The patient with AML remained in remission at the time of the report; the patient with Hodgkin lymphoma died of relapsed disease at 12 months. It would appear from these reports that allogeneic transplantation is possible, although the incidence of HIV-related transplantation complications cannot be assessed from only 2 patients.

Unusual lymphoproliferative disorders associated with HIV infection

There are several unusual lymphoproliferative entities occurring more frequently in the setting of HIV infection: primary effusion, plasmablastic, and peripheral T-cell lymphomas; Castleman disease; and an entity with similarities to posttransplantation lymphoproliferative disorder (PT-LPD).

Primary effusion lymphoma

Primary effusion lymphoma (PEL) comprises approximately 1% to 5% of ARL cases and represents a distinct entity in the World Health Organization (WHO) classification of ARLs. Clinically, the disease is characterized by a lack of nodal disease with malignant effusions as the predominant feature. As with multicentric Castleman disease, Kaposi sarcoma–associated herpesvirus (KSHV, HHV-8) has been implicated in the pathogenesis of this uncommon entity. EBV is also detectable in a majority of cases. Phenotyping of PEL cells reveals a lack of expression of B-cell–associated genes, including surface immunoglobulin, but immunoglobulin gene rearrangements are usually positive, indicating a clonal B-cell origin. Although some previous studies hinted that PEL cells had transitioned through germinal center differentiation by virtue of point mutations in the immunoglobulin genes, Klein and colleagues explored the gene expression profile of PEL cells and found expression patterns common to both plasma cells and EBV-transformed immunoblasts. However, the unique expression pattern was not shared with immunocompetent host-associated NHL or with other ARL subtypes, suggesting in this study that PEL represents a variant of plasmablastic lymphoma. This intriguing finding, however, will need confirmation before that conclusion may be drawn. The treatment of this subtype remains unsatisfying with short OS in the 3- to 6-month range at least partially reflective of the advanced state of HIV infection commonly observed in patients suffering with this malignancy. Simonelli and colleagues published a series of 11 cases. Most patients were treated with a CHOP-like regimen, resulting in a CR rate of 42% and a median survival of 6 months.

Plasmablastic lymphoma

Plasmablastic lymphoma has been reported in patients without HIV infection but has occurred predominately in patients with advanced HIV infection. First described in the oral cavity of HIV+ patients in 1997 by Delecluse and coworkers, plasmablastic lymphoma can occur in a variety of sites. The average age of onset, 33 years of age, is much younger than would be expected for HIV+ individuals. Chetty and colleagues delineated the flow cytometric findings in these lymphomas, which are negative for B- and T-cell markers but are almost always positive for light chain, epithelial membrane antigen (EMA), immunoglobulin G; Ki-67
staining is typically quite high at 75% to 95%. Some tumors were also positive for VS38c, CD79a, and CD138. Morphologically, the malignant cells appear most like plasmablasts but carry a phenotype most typical of mature plasma cells. Monoclonal gammopathy is not commonly noted, helping to distinguish this entity from multiple myeloma. Available data from the pre-HAART era showed that plasmablastic lymphoma carries a poor prognosis with a dismal median survival of about 5.5 months, although Teruya-Feldstein and associates reported on 12 patients treated with a variety of regimens with 5 of 6 HIV+ patients in CR with a median follow-up of 22 months. Another small report of 2 patients suggests that the prognosis may have improved since the advent of HAART.

Castleman disease

Multicentric Castleman disease is a clinicopathologic entity characterized by polyclonal hypergammaglobulinemia and plasmacytosis, generalized lymphadenopathy with characteristic pathologic findings within the lymph nodes of perifollicular vascular proliferation and germinal center angiosclerosis, and often hepatosplenomegaly and constitutional symptoms. Laboratory evaluation usually demonstrates an elevated C-reactive protein level, and sometimes, autoimmune hemolytic anemia. Cytokine dysregulation, particularly of IL-6, appears to form a centerpiece of the disease. In various studies examining tissues for evidence of HHV-8 involvement, viral antigens can usually be found, suggesting that there is a prominent role for HHV-8 in this disorder. Additionally, the observed increase in IL-6 levels appears to originate at least in part from HHV-8 itself (vIL-6), providing further evidence for a critical role of HHV-8 in the genesis of multicentric Castleman disease. A Japanese group found HHV-8 positivity in 3 of 3 HIV-associated multicentric Castleman disease (H-AMCD) cases but none of 79 non–HIV-associated cases. Treatment for H-AMCD has been largely unsatisfactory, with a median survival of only 14 months. Some patients die after transformation to NHL, whereas others succumb to chemotherapy-related toxicity and infections. Recent reports have suggested that there may be some benefit to the use of HAART alone, rituximab, or anti–herpesvirus drugs such as ganciclovir in the treatment of H-AMCD. In the retrospective splenectomy study, 10 of 18 consecutive patients with H-AMCD underwent splenectomy and all improved with respect to cytopenias or fevers with 8 of 10 alive at 41 months median follow-up. Six of 8 patients ultimately also received chemotherapy, 4 for Kaposis sarcoma and 2 for progressive lymphadenopathy. In the ganciclovir study using 21 days of daily administration, 3 of 3 patients manifest clinical improvement and decreased HHV-8 DNA titers on therapy. However, only one patient maintained a response. One patient died of fungal infection 12 days after starting therapy and the third experienced only a transient response. Cidofovir was administered with disappointing results by Berezne and colleagues with disease progression requiring chemotherapy in 5 of 5 patients treated for 21 to 60 days with weekly cidofovir thrice followed by every other week. Rituximab appears more promising based on a report of the largest case series of rituximab therapy for H-AMCD reported by Marcellin and associates in which 3 of 5 patients achieving a CR with follow-up from 4 to 14 months. The other 2 patients died rapidly without response. Exacerbation of active Kaposis sarcoma was observed in 2 of 3 responders. Multicentric Castleman disease remains a challenging clinical problem in the HIV-infected population for which there is no clear standard therapy.

EBV-associated lymphoproliferative disorder

Because there are some similarities between HIV-induced immunosuppression and that seen in solid organ transplantation, one may postulate that an ARL syndrome with characteristics of posttransplantation lymphoproliferative disorder (PTLD) might be observed. Interestingly, Nador and coworkers recently found 10 cases of ARL resembling polymorphic PTLD: all cases revealed clonal immunoglobulin gene rearrangements and, in 4 of the 10 cases, detectable clonal EBV infection. Thus, there appears to be a small subpopulation of ARL sharing the unusual characteristics seen in PTLD.

T-cell lymphoma

Unexpectedly, peripheral T-cell lymphoma has been recently described to occur more frequently in patients with HIV infection. Registry data published by Biggar and colleagues from 11 American regions reporting patients with AIDS diagnoses showed a rate of T-cell lymphoma of 1.4% from a total of 6788 cases of AIDS-related NHL. The relative risk was 15.0 (95% CI, 10.0-21.7), with multiple T-cell lymphoma subtypes described. Confounding this result, however, was the inability to correct for individuals who may have been at increased risk for T-cell malignancies such as Caribbean individuals infected with HTLV-1 or -2. Nevertheless, the relative risk of T-cell lymphoma in the setting of HIV infection appears increased. The risk may be underappreciated in this study, which included only patients with AIDS diagnoses, not earlier HIV infection. An Italian group reported data on 3 cases of peripheral T-cell ARL with a cytotoxic phenotype (CD3+/CD8+/TIA-1+/ granzyme B+) and with T-cell receptor γ (TCRγ) gene rearrangements. It may be informative to follow whether such an unusual lymphoma is more common in HIV-infected populations.

A retrospective review of 429 consecutive cases of ARL in Los Angeles found 11 cases of T-cell ARL. No differences in demographics, prior OL, or immunologic criteria could be elucidated to differentiate T-cell from B-cell ARL, although the numbers of cases were small. T-cell cases were associated with skin and marrow involvement significantly more commonly than B-cell cases but survival was not different (10.6 versus 6.6 months for T-versus B-cell types, respectively; P = .13). The increased incidence of T-cell ARL again highlights that much remains to be elucidated about the influence of HIV infection on lymphomagenesis.

Primary CNS lymphoma

Primary CNS NHL (PCNSL) typically occurs in profoundly immunocompromised late-stage HIV-infected individuals, the vast majority of whom have CD4+ lymphocyte counts less than 50/mm3. Most HIV-PCNSLs are characterized as diffuse large B-cell lymphomas and tend to be multifocal in the brain. Confusion, memory loss, lethargy, and focal neurologic findings are the most frequent presenting symptoms and signs. Not surprisingly, the incidence of PCNSL has fallen significantly since the introduction of HAART. EBV appears to play a pivotal role in the development of AIDS-associated PCNSL and is frequently associated with detectable virus in the cerebrospinal fluid (CSF) of patients with PCNSL. Importantly, EBV is rarely detected in the CSF of HIV patients without PCNSL. In one study EBV DNA was detected by a nested polymerase chain reaction (PCR) in the CSF from 7 of 8 patients with PCNSL, confirmed by brain biopsy (87.5% sensitivity), and in none of the 11 controls with nonlymphomatous mass lesions (100% specificity). Twenty-one AIDS patients with or
without neurologic disorders but without focal brain lesions were PCR negative. In another study, EBV DNA was detected in the CSF from 16 (80%) of 20 patients with PCNSL. An Italian study combining single photon emission computed tomography (SPECT) imaging with EBV PCR in the evaluation of 13 cases of PCNSL and 18 nonmalignant brain masses showed 11 of 13 cases to be positive by EBV PCR and 18 of 18 controls to be negative. SPECT was positive in 12 of 13 cases and in 2 of 18 controls. For positive EBV DNA PCR and SPECT, the combined modalities yielded 100% specificity and 77% sensitivity. For those patients with both tests positive, the need for brain biopsy may be obviated. Limited studies using positron emission tomography (PET) have been performed with high sensitivity but the specificity of this modality is not yet sufficiently clear to use routinely.

Historically, the prognosis for AIDS-related PCNSL has been poor. Whole-brain radiotherapy has been used for palliation, with most patients ultimately dying from OIs. Median survival in the pre-HAART era was typically in the 1- to 3-month range. An exception to these abysmal outcomes was found in a pre-HAART study in which HIV-PCNSL patients with a median CD4 of 30/mm3 were treated using high-dose systemic methotrexate. This approach resulted in a 50% complete response rate and a median survival of 10 months. With the use of HAART, PCNSL therapy appears to have become more tolerable and as in non-HIV PCNSL, there has been more interest in using systemic chemotherapy with or without radiotherapy to improve quality of life and minimize long-term sequelae of radiotherapy alone. More recent cohort data suggest that immune recovery associated with HAART can dramatically improve survival. In a recent multivariate analysis, HAART use dramatically improved survival, yielding a hazard ratio for death of 0.06 (95% CI, 0.01-0.48). Decreasing HIV viral load and increasing CD4+ counts were likewise associated with improved survival. These findings were confirmed in a retrospective review of 111 patients with PCNSL, which demonstrated that the use of HAART and radiotherapy were each associated with significantly improved survival.

Recent findings in viral lymphomagenesis

EBV has an established role in the development of some cases of diffuse large cell B-cell lymphoma, whereas HHV-8 has been strongly associated with PELs. Further explorations of the role of EBV and HHV-8 involvement in lymphomagenesis of ARL have implicated one or both in the development of plasmablastic lymphoma and in multicentric Castleman disease.

Viral antigens in lymphoma cells

In a study published in 2004 examining 5 cases of oral cavity ARL, the incidence of infection of lymphoma cells with HHV-8 and EBV was explored using reverse transcriptase in situ polymerase chain reaction (RT-PCR), in situ hybridization, and immunohistochmistry. In all 4 cases of oral plasmablastic lymphomas and in the only oral cavity diffuse large B-cell lymphoma, HHV-8–associated RNA and protein were detected in the malignant-cell population. Additionally, evidence of EBV infection was also found in the 4 plasmablastic lymphomas. HIV-1 RNA was not detected in tumor cells but was found in benign surrounding T cells. In oral lymphoma tissue from 5 HIV− patients and in 5 lymphoma samples from HIV+ patients from sites other than oral, no HHV-8 RNA was found. Another study of 24 ARL cases in patients with prior Kaposi sarcoma by Engels and colleagues, however, has shown HHV-8–infected cells in 3 of 7 evaluable immunoblastic lymphoma cases. In multicentric Castleman disease, Du et al showed that HHV-8 is associated with polyclonal but monotypic plasmablasts expressing IgM and that those cells did not harbor somatic mutations, indicating a naïve B-cell origin.

HHV-8 serology not associated with most ARL

A case-control study published in 2001 reported on the incidence of HHV-8 serum antibodies in HIV+ patients with and without NHL. HHV-8 antibodies were noted in 37% of HIV+ controls without ARL and 41.5% of ARL cases with no statistically significant difference (P = .73). A study from Italy also found no evidence for increased incidence of ARL in patients who are HHV-8+. However, given the relatively low incidence of lymphoproliferative disease types typically found to have HHV-8 infection such as plasmablastic lymphoma, body cavity lymphoma, and Castleman disease, these studies were underpowered to detect such a difference. Given the lack of evidence for HHV-8 viral infection by immunohistochemistry or by serology in most common types of ARL cells, it does not appear that HHV-8 plays a large or direct role in the genesis of common forms of ARL.

Impact of chemotherapy on virologic and immunologic parameters in ARL

Several trials have examined the impact of chemotherapy for ARL on CD4 counts, viral genotyping, and viral load. Powles and coworkers reported on 20 patients treated with several regimens including infusional CDE and BEMOP/CA (bleomycin, etoposide, methotrexate, vincristine, prednisolone/cyclophosphamide, doxorubicin) and concurrent HAART defined as containing at least 3 drugs including a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor (NNRTI). Complete response rates were 65% and 1-year OS was 75%. The CD4 T-cell counts and natural killer (NK)–cell populations fell significantly after 3 months of chemotherapy but this was followed by rapid recovery at 1 month after therapy. CD8 T cells also fell but not significantly at any point during or after treatment. CD19 B-cell recovery was delayed at 1 month after therapy but recovered by 3 months, not unlike the pattern observed in the HIV+ population. No significant differences occurred in HIV viral loads in that study. Little and colleagues examined CD4, CD8, and viral load parameters in 30 patients treated with dose-adjusted EPOCH during which antiretroviral therapy, if ongoing, was held and then initiated or reinstiututed after completion of chemotherapy. Not surprisingly, viral loads rose during chemotherapy but decreased to levels below baseline at 3- to 18-month time points after completion of treatment. The CD4 and CD8 counts reached nadir at cycle 6 but rebounded to pretreatment levels 6 to 12 months later. The Little study found 5 patients with transient suppression of previously documented resistance mutations, with 3 recurring after chemotherapy and 2 developing new resistance. An Italian study examining viral resistance found new HIV mutations but no change in pre-existing viral resistance patterns.

Conclusions

HIV infection increases the risk of the development of lymphoma with a spectrum of lymphoma subtypes modestly different from the HIV− population. Outcomes for ARL have improved substantially...
in the HAART era but are still not as favorable as in patients without concurrent HIV infection. In view of poorer lymphoma-free survival for ARL, autologous hematopoietic transplantation appears to be a sound method to improve on HAART-related gains in survival. During chemotherapy for ARL, transient falls in CD4 counts are followed by rapid recovery, though B-cell recovery is substantially slower, differing little from HIV-negative patients treated similarly.

References


AIDS-related lymphoproliferative disease

Willis H. Navarro and Lawrence D. Kaplan