Recent Advances in Acquired Immunodeficiency Syndrome (AIDS)-related Lymphoma

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ABSTRACT Human immunodeficiency virus-infected patients are at an increased risk for developing both Hodgkin and non-Hodgkin lymphoma when compared with the general population. With the remarkable decrease in the incidence of opportunistic infections since the availability of highly active antiretroviral therapy (HAART), acquired immune deficiency syndrome-related lymphoma (ARL) is now the second most common cancer associated with human immunodeficiency virus after Kaposi sarcoma. Over the last few years, advances in our understanding of the molecular biology of this heterogeneous group of lymphomas have led to the adoption of new classification systems. The prognosis of patients with ARL has improved dramatically with the availability of HAART, and the survival of many of these patients is now comparable to patients in the general population. Apart from the contribution of HAART, this improvement in prognosis can also be attributed to new initiatives in treatment of these patients, such as the use of effective infusional regimens, the feasibility of high-dose therapy with peripheral stem cell rescue for relapsed or refractory disease, and better supportive care. Nonetheless, several controversial issues persist, including the optimal timing of HAART with combination chemotherapy, the role of rituximab when incorporated into treatment regimens, and the optimal therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma. This article reviews the changes in the epidemiology of ARL in the era of HAART, advances in the biology of ARL, new developments in the management of patients with ARL, and several of the controversial issues that oncologists may encounter in the care of these patients. (CA Cancer J Clin 2005;55:229–241.) © American Cancer Society, Inc., 2005.

INTRODUCTION

Human immunodeficiency virus (HIV)-infected patients are at an increased risk for developing both Hodgkin and non–Hodgkin lymphoma when compared with the general population. The excess of high-grade non–Hodgkin lymphoma (NHL) was first reported in 1984, following the description of NHL in 90 homosexual men with acquired immunodeficiency syndrome (AIDS).1 Since 1985, aggressive B-cell lymphoma has been classified as an AIDS-defining illness (ADI) and is the second most common cancer associated with HIV. Over the last few years, there has been significant improvement in the understanding of the molecular pathogenesis of AIDS-related lymphoma (ARL) as well as in the therapy and prognosis of patients with ARL. Apart from the availability of highly active antiretroviral therapy (HAART), much of the improvement made in the prognosis of these patients could also be attributed to the development of novel and effective chemotherapeutic regimens and better supportive care.

IMPACT OF HAART ON THE EPIDEMIOLOGY OF ARL

Incidence and Prevalence

Using data obtained by linking AIDS and cancer registries in selected areas in the United States, Cote and colleagues2 demonstrated that the relative risk of developing lymphoma within 3 years of an AIDS diagnosis was increased by 165-fold when compared with people without AIDS, documented within the cancer surveillance...
system. The same study also demonstrated that the increase in risk ranged from 652-fold for high-grade diffuse immunoblastic tumors to 261-fold for Burkitt lymphomas, 113-fold for intermediate-grade lymphomas, and 14-fold for low-grade lymphomas. However, these figures may be underestimates, because almost one half of the lymphoma cases that occurred in patients with a prior diagnosis of AIDS were not reported to AIDS registries.

Infection with HIV also increases the risk of Hodgkin disease (HD) but to a lesser extent. Epidemiologic studies consistently indicate that HIV-infected individuals have an 8- to 10-fold increase in risk of developing HD.3,4

AIDS-related Lymphoma as an ADI

As a percentage of first ADI, ARLs have increased since the widespread use of HAART (Table 1). In Western Europe, the annual occurrence of ARL as a percentage of all ADIs rose from 3.6% in 1994 to 4.9% in 1997.5 In another prospective observational multicenter study of over 7,300 patients in 52 European HIV-1 clinics, Mocroft and colleagues6 reported that the proportion of ADIs attributable to NHL has increased from less than 4% in 1994 to almost 16% in 1998. A similar trend has been observed in both the United States and Australia.7,8

Impact of HAART on the Incidence of AIDS-related Lymphoma

Many studies have been conducted to determine whether the use of HAART has led to a change in the incidence of ARL, similar to the decline in incidence now seen in Kaposi sarcoma (Tables 2 and 3). Results of these studies have been somewhat inconsistent. While the Swiss HIV Cohort Study and the Multicenter AIDS Cohort Study as well as investigators from both Los Angeles and London found no decline in the incidence rates of ARL between the pre- and post-HAART eras,9–13 results from the International Collaboration on HIV and Cancer and the EuroSIDA studies documented a significant decline in the HAART era.14,15 The International Collabo-

ration on HIV and Cancer showed a decline in the incidence of ARL from 6.2 to 3.6 cases per 1,000 person-years when the period from 1992 to 1996 was compared with the period from 1997 to 1999. Similarly, the EuroSIDA study showed a decline from 199 to 30 cases per 10,000 person-years in the periods before September 1995 and after March 1999.

Interpretations of these studies were limited by their particular study design, because they examined the influence of HAART on ARL by simply dividing the study period into two different time intervals and failed to look into the actual effects of HAART on individual patients. Factors such as differences between the populations, access to drugs, adherence to therapy, and drug resistance patterns were not taken into consideration. Furthermore, the availability of HAART in a community does not necessarily mean that individual patients will have access to treatment or that the HAART treatment will actually be effective. However, when HAART therapy is available and effective in a population, it has been shown to be associated with a decline in the incidence of ARL.

The study from Besson and colleagues16 best illustrates this point. Using data from the French Hospital Database on HIV, the incidence of systemic ARL fell between the pre-HAART (defined as 1993–1994) and the post-HAART eras (defined as 1997–1998).16 The incidence of systemic ARL decreased from 86.0 per 10,000 person-years during the pre-HAART era to 42.9 per 10,000 person-years during the post-HAART era, while the incidence of primary central nervous system lymphoma (PCNSL) fell even more dramatically, from 27.8 per 10,000 person-years to 9.7 per 10,000 person-years.

Of interest, however, when determining the incidence rates of systemic ARL and PCNSL within strata of patients with similar CD4 cell counts, the French study16 documented no change in the incidence of ARL between the two time periods (Table 4). For instance, in patients with CD4 counts between 200 and 349 cells/mm3, the incidence of systemic ARL was similar between the pre-HAART and post-HAART eras (34.8 per 10,000 person-years versus 33.6 per 10,000 person-years).
### TABLE 1  Studies Showing an Increase in AIDS-related Lymphoma (ARL) as a Percentage of ADI

| Author (Date) / Type of Study | Population | Time Periods Compared | Main Findings |
|-----------------------------|------------|-----------------------|---------------|
| Franceschi (1999) Prospective/observational | 17 centers in Europe n = 7,148 | 1988 to 1997 | As a % of ADI,* ARL † from 3.6% in 1994 to 4.9% in 1997 RR‡ of lymphoma ranged between 14 for low-grade to over 300 for high-grade NHL; RR † 10 for Hodgkin disease |
| Mocroft (2000) Prospective/observational | 7,300 patients in 52 European HIV clinics European HIV-1 outpatient clinics | 1994 to 1998 | As a % of ADI, ARL † from 4% in 1994 to 16% in 1998 |
| Dore (2002) Retrospective analysis | Australia n = 5,017 | 1993 to 1995 versus 1996 to 2000 | As a % of ADI, non-Hodgkin lymphoma † from 4.4% to 6.3% P = 0.005 No change in median survival of non-Hodgkin lymphoma, stable at 7.5 to 8.8 months |

*ADI, AIDS-defining illness. †RR, relative risk.

### TABLE 2  Studies Showing No Impact of HAART in Decreasing Incidence of ARL

| Author (Date) / Type of Study | Population | Time Periods Compared | Main Findings |
|-----------------------------|------------|-----------------------|---------------|
| Ledergerber (1999) Retrospective observational | Swiss HIV Cohort Study n = 6,638 | 1992 to 1994 versus July 1997 to June 1998 | No significant trend for ARL* Significant ↓ in the progression to OIs and Kaposi sarcoma |
| Jacobson (1999) Longitudinal study | MAC Cohort Study, US n = 1,813 | Patients diagnosed with HIV between 1984 and 1985 and followed up | Incidence of ARL continues to ↑ at a rate of 21% per year since 1985 (P < 0.01), possible recent decrease Kaposi sarcoma as ADI† ↓ significantly from 25.6/1,000 PY† in early 1990s to 7.5/100 PY in 1996 to 1997 (P = 0.03) |
| Matthew (2000) Retrospective | UK, London n = 7,840 | Compare 1988 to 1995 with 1996 to 1999 | Characteristics of ARL post-HAART§: older patients, higher mean CD4 counts No change in incidence of ARL; mean incidence of ARL/1000 was 0.53 (pre-HAART) versus 0.47 (post-HAART) (P = 0.73) % of ARL as first ADI ↑ from 1.3 to 5.6/1000 population (P < 0.001) |
| Buchbinder (1999) Retrospective observational | US, San Francisco City Cohort n = 622 | 1993 to 1995 versus 1996 | No change in survival for ARL over time Incidence of Kaposi sarcoma ↓ from 3.5 to 0 per 100 PY between 1993 through 1995 and 1996 (P = 0.07) No decrease in incidence of ARL between these periods |
| Levine (2000) Retrospective | US, Los Angeles n = 369 | 1982 to 1998 | Characteristics of ARL evolved over time; ↑ in Hispanics, ↓ in Whites, ↑ in females, ↑ in heterosexual contact, ↓ in CD4 count at diagnosis of lymphoma over time Overall, no change in incidence of ARL over time; slight ↓ in small noncleaved but ↑ in large cell lymphoma and* no change in PCNSL¶ No change in survival for non-Hodgkin lymphoma over time |

*ARL, AIDS-related lymphoma. †ADI, AIDS-defining illness. ‡PY, person-years. §HAART, highly active antiretroviral therapy. ¶PCNSL, primary central nervous system lymphoma.
Similarly, for patients with CD4 counts between 50 and 99 cells/mm$^3$, the incidence of PCNSL was similar between both periods (29.6 per 10,000 person-years versus 28.0 per 10,000 person-years). Thus, while the risk of ARL did not change between the periods among patients with similar CD4 counts, the proportion of patients with low CD4 cell counts (less than 200/mm$^3$) decreased from 49.5% to 24.5% between the periods, thus decreasing the overall proportion of individuals at risk for ARL in the second period.

Therefore, with the introduction of HAART, the observed fall in the incidence of ARL in the Besson study was because of the overall decrease in the proportion of patients with low CD4 counts. This observation is important because it implies that the incidence of ARL in a population with HIV will fall only if HAART therapy is effective in improving the immune status of that population. If access to HAART therapy is not uniformly available, or if general adherence to or effectiveness of therapy is poor, the overall immune status of the population will remain low and, consequently, there will be no decline in the incidence of ARL, even if HAART is available.

There appears to be no decrease in the incidence of HD since the introduction of HAART.

**TABLE 3** Studies Showing Impact of HAART in Decreasing the Incidence of ARL

| Author (Date) / Type of Study | Population | Time Periods Compared | Main Findings |
|------------------------------|------------|-----------------------|---------------|
| Kirk (2001)                  | Europe     | May 1994 to December 2000 (comparing non-Hodgkin lymphoma developing before and after taking HAART*) | Characteristics of ARL† post-HAART: older patients, higher CD4 counts, higher % of heterosexual transmission, lower % of PCNSL‡ |
| EuroSIDA Prospective          | n = 8,556  |                       | Incidence rate for ARL ↓ from 1.99/100 PYF$ before 9/95 to 0.83/100 PYF after 3/99 ($<0.01$); ↓ seen in all histologies |
| International Collaboration on HIV and Cancer (2000) Retrospective observational | North America, Europe, Australia | 1992 to 1996 versus 1997 to 1999 | No change in survival over time |
| Besson C (2001) Retrospective | Incidence analysis based on French Hospital Data Base. Detailed analysis of lymphoma cases based on 3 centers | 1993 to 1994 versus 1997 to 1998 | Incidence of ARL ↓ from 86.0 per 10,000 PY to 42.9 per 10,000 ($<10^{-30}$), most dramatic for PCNSL |
| Eltom (2002) Retrospective observational | From 9 population based registries in the SEER program | 1973 to 1998 | The incidence rates of both Kaposi sarcoma and ARL ↑ greatly in the 1980s and peaked in early 1990s and then declined dramatically between 1996 and 1998 |

*HAART, highly active antiretroviral therapy. †ARL, AIDS-related illness. ‡PCNSL, primary central nervous system lymphoma. §PYF, person-years of prospective follow up. ¶PY, person-years.

**TABLE 4** Categories of HIV-associated Lymphomas: WHO Classification

- Lymphomas also occurring in immunocompetent patients
  - Burkitt lymphoma
  - Classic
    - With plasmacytoid differentiation
    - Atypical
  - Diffuse large B-cell lymphoma
  - Centroblastic
  - Immunoblastic
  - Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue lymphoma (rare)
  - Peripheral T-cell lymphoma (rare)
  - Classic Hodgkin lymphoma
  - Lymphomas occurring more specifically in patients who are HIV* positive
  - Primary effusion lymphoma
  - Plasmablastic lymphoma of the oral cavity
  - Lymphomas occurring in other immunodeficiency states
  - Polymorphic B-cell lymphoma

*HIV, human immunodeficiency virus.
The International Collaboration on HIV and Cancer Study, which involves the analysis of cancer incidence data of 47,936 HIV-seropositive individuals from North America, Europe, and Australia, reported no statistically significant change in the HD incidence rates between the pre-HAART and the post-HAART eras (rate ratio \( \frac{0.77}{1} \), 95% confidence interval [CI], 0.32–1.85; \( P = 0.4 \)). Some investigators have suggested that the incidence of HD in the post-HAART era may, in fact, have increased. A report from the French Hospital Database on HIV found a statistically significant increase in the standardized incidence ratio of HD in the post-HAART era compared with the pre-HAART era (overall standardized incidence ratio post-HAART/pre-HAART HD = 1.39; 95% CI, 1.14–1.67).17

RECENT ADVANCES IN THE BIOLOGY OF ARL

ARL consists of a heterogeneous group of malignant disorders. The pathologic range includes Burkitt lymphoma, large cell lymphomas, and other more uncommon entities such as primary effusion lymphoma (PEL) and plasmablastic lymphoma of the oral cavity. In an effort to standardize the nomenclature, the World Health Organization classified ARL into three groups: those occurring specifically in HIV-infected patients, those also occurring in other immunodeficiency states, and those that also arise in immunocompetent patients (Table 4).18

The possible mechanisms and pathways responsible for the development of this heterogeneous group of lymphomas include chronic B-cell stimulation induced by HIV itself, as well as other coinfecting viruses, such as Epstein Barr virus (EBV) and human herpes virus 8, genetic aberrations, and cytokine deregulation. Polyclonal B-cell expansion from chronic antigenic stimulation, driven by HIV, coinfecting viral agents, and deregulated cytokine production, results in populations of proliferating cells at risk of acquiring genetic mutations that may lead to malignant transformation. Common oncogenes involved include the classic \( c-MYC \) oncogene in Burkitt lymphoma, \( BCL-6 \) mutations in diffuse large B-cell lymphoma, as well as abnormalities of tumor suppressor genes. As an example, in AIDS-related Burkitt lymphoma, which accounts for approximately 30% of ARL, the transforming events occur in the germinal centers, resulting in the translocation of the \( myc \) gene on chromosome 8 with the promoter for the heavy chain locus on chromosome 14, or the kappa or lambda light chain genes on chromosomes 2 and 22, respectively. However, EBV infection occurs in only 30% to 50% of ARL cases, indicating that pathogenetic mechanisms other than EBV must also be operative.

In the World Health Organization classification, AIDS-related diffuse large B-cell lymphomas (DLBCL) are divided into the centroblastic and the immunoblastic subtypes. While the centroblastic subtype has features of large cell lymphoma similar to those seen in the general population without HIV, the immunoblastic subtype is more characteristic of HIV infection. Infection with EBV occurs more commonly with the immunoblastic subtype (90%) when compared with the centroblastic subtype (30%).19 EBV-encoded LMP-1 antigen is found in 90% of the immunoblastic cases but is usually not found in the centroblastic subtype.20–22 Amplification of \( bcl-6 \), a protooncogene product selectively expressed in B cells located within germinal centers, is associated with the centroblastic but usually not the immunoblastic subtype. CD138/syndecan-1, normally expressed by B cells in late stages of B-cell differentiation, is more commonly expressed in the immunoblastic subtype.

These phenotypic differences have led to the suggestion that AIDS-related DLBCL can be divided into two categories: the LMP-1\(^-\)/CD138\(^-\)/BCL-6\(^+\) phenotype, which corresponds to the centroblastic subtype, and the LMP-1\(^+\)/CD138\(^+\)/BCL-6\(^-\) phenotype, which corresponds to the immunoblastic subtype.23 These differences in immunophenotypic expression reflect their different histogenesis, with the centroblastic subtype arising from germinal centers and the immunoblastic variant arising from postgerminal center lymphocytes.
Primary central nervous system lymphoma (PCNSL) belongs to the category of DLBCL and commonly displays immunoblastic features. It occurs in patients with severe immunodeficiency, is universally associated with EBV, and expresses LMP-1. The pathologic role of EBV in this subtype has recently been used to assist in the diagnosis of PCNSL. While tissue biopsy remains the definitive standard for the diagnosis of PCNSL, recent studies have shown that the detection of EBV-DNA in cerebrospinal fluid (CSF) by means of polymerase chain reaction may be an effective surrogate diagnostic test if biopsy is not possible. In 1 study, this technique was shown to have a sensitivity of 80% and a specificity of 100% (75).

PEL is an uncommon but fascinating subtype of lymphoma that classically occurs in HIV-infected patients. Cesarman et al. were the first to provide evidence of an association between HHV-8 and PEL. The neoplastic cells in PEL are classically large, have features ranging from immunoblastic to anaplastic large cell lymphoma, and do not express B-cell antigens on their surface, although they are clearly of B-cell origin as indicated by the presence of immunoglobulin gene rearrangement. In addition to HHV-8, PEL cells also demonstrate EBV within the nucleus. Although classically presenting as malignant effusions in the absence of underlying infiltrating masses, PEL has also recently been reported to occur as tumor masses, most commonly in the gastrointestinal tract.

Like PEL, plasmablastic lymphomas of the oral cavity are closely associated with HIV infection and are classically negative for CD20 and CD45. However, the genetic mechanisms responsible for the pathogenesis of this subtype are less well understood and are at present controversial. Unlike PEL, HHV-8 is consistently absent in these tumors, while EBV is present in about 50% of cases.

In contrast to de novo HD, in which only about one third are associated with EBV, EBV is likely to play a vital role in the pathogenesis of HD in patients with HIV infection, as it is nearly always detected. LMP-1 expression is present in most cases and can be demonstrated in Reed-Sternberg cells.

Recent Advances in AIDS-related Lymphoma

ADVANCES IN THE MANAGEMENT OF ARL

Historical Background

In the era before the widespread use of HAART, treatment of patients with ARL using standard doses of combination chemotherapy was complicated by poor tolerability, severe hematologic toxicity, and increased deaths due to opportunistic infections. Complete remissions occurred in the minority of patients, and median survival was less than 6 months. To improve tolerability, the use of less intensive chemotherapy regimens was explored. The AIDS Clinical Trials Group compared standard-dose chemotherapy consisting of methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) and granulocyte-macrophage colony-stimulating factor support with reduced-dose m-BACOD without granulocyte-macrophage colony-stimulating factor. There was no difference in either response rate (full dose, 52% versus reduced dose, 41%) or median survival (full dose, 6.8 months versus reduced dose, 7.7 months) between the 2 groups. Reduced dose m-BACOD was associated with a statistically superior toxicity profile. Based on this large randomized trial, dose-reduced chemotherapy was considered by many to be the preferred regimen for HIV-infected patients with lymphoma in the pre-HAART era.

Combining HAART with Combination Chemotherapy

With the availability of HAART, administration of standard dose chemotherapy became feasible as infectious complications were reduced. However, there were initial concerns of potential drug interactions between chemotherapy and concurrent HAART. Ratner and colleagues subsequently demonstrated that HAART could be delivered safely and effectively with standard dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Although Grade 3 and 4 neutropenia were more common among patients receiving full dose CHOP, other nonhematologic toxicities were similar. Concomitant use of HAART did not have an effect on the pharmacokinetics of doxorubicin and indinavir. Although the clearance of
cyclophosphamide was 1.5-fold reduced compared with historical controls, it was not clinically significant. It should be noted, however, that use of azidothymidine with chemotherapy is contraindicated, because it is associated with potential marrow failure and may worsen chemotherapy-induced hematologic toxicities.31

To avoid the potential pharmacokinetic interactions between HAART and chemotherapy, Little and colleagues32 from the National Cancer Institute (NCI) investigated the feasibility of omitting HAART during the administration of full dose chemotherapy. In this study, 6 cycles of dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) were administered to 39 patients with newly diagnosed ARL (Table 5). The dose of cyclophosphamide on cycle 1 was based on the patient’s CD4 cell count at study entry (<100 cells/mm3 versus >100 cells/mm3) and was thereafter adjusted in increments or decrements of 187 mg/m2 (maximum dose, 750 mg/m2) according to the absolute neutrophil nadir. Antiretroviral agents were not used during chemotherapy but were restarted immediately at the completion of chemotherapy. Three-quarters of the patients received all 6 planned cycles of chemotherapy, and the administered dose intensity was 100% for doxorubicin, 99% for etoposide, 99% for vincristine, and 65% for cyclophosphamide. This dose intensity was achieved with acceptable toxicity. The complete response rate was an unprecedented 74%. Among patients with CD4 cell counts >100 cells/mm3, the complete responsive rate was even higher, at 87%, while the overall survival was 87% at 56 months. However, patients with CD4 cell counts <100 cells/mm3 continued to do poorly, with an overall survival of only 16% at 56 months. Although the median CD4 cell count fell by 189 cells/mm3 and the mean viral load increased by 0.5 to 1.0 log10 copies/mL by the time the last cycle of chemotherapy was given, these values returned to baseline within 6 to 12 months following the reinstatement of HAART at the completion of chemotherapy. While no new opportunistic infections occurred during chemotherapy, 3 patients developed opportunistic infection within the first 3 months after completion of chemotherapy.

Of importance, the response rate and overall survival in this study were the best reported to date. Outside the context of a clinical trial, dose-adjusted EPOCH would be a very reasonable regimen to use in the management of patients with ARL. From the results of this study, it is apparent that withholding antiretroviral therapy does not result in progression of AIDS and allows the full delivery of chemotherapy. In addition, the results suggested that good viral control during chemotherapy was not essential for optimal tumor response. However, it is important to stress that this approach requires the immediate reinstitution of HAART on completion of chemotherapy.

While it may seem reasonable from the conclusions of this study to defer HAART until the completion of chemotherapy, we disagree. Thus, while results for patients with CD4 count >100 cell/mm3 were encouraging, the outcome for patients with CD4 cell counts <100 cells/mm3 remained unsatisfactory. It might also have been possible to avoid the three cases of opportunistic infections if HAART had not been discontinued during administration of chemotherapy.

Impact of HAART on Tumor Response and Survival

In a multicenter cohort study from Germany involving 203 patients, response to HAART therapy, defined as a CD4 cell count increase of \(\geq 100 \times 10^6\) cells/mm3 and/or at least one viral load <500 copies per mL during the first 2 years following diagnosis of lymphoma, was independently asso-

| TABLE 5 Dose-adjusted EPOCH* Regimen† |
|--------------------------------------|
| Etoposide, 50 mg/m²/d × 4 days |
| Vincristine, 0.4 mg/m²/d × 4 days |
| Doxorubicin, 10 mg/m²/d × 4 days |
| Cyclophosphamide, 187 mg/m² intravenously on day 5 for CD4 < 100 cells/mm³ or 375 mg/m² intravenously on day 5 for CD4 ≥ 100 cells/mm³ |
| Prednisolone, 60 mg/m² orally, days 1–5 |
| Granulocyte colony-stimulating factor: start on day 6 |

*EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin.
†Cycle is repeated every 21 days for 6 cycles.
Associated with prolonged survival. Patients receiving HAART (n = 61) were significantly more likely to achieve a complete remission (CR) (71% versus 48%; P = 0.006). Of these 61 patients, those who were HAART responders (n = 47) had a higher CR rate when compared with those who did not respond to HAART (77% versus 50%; P = 0.09). Among patients with both a response to HAART and complete tumor remission, 83% were still alive at 39 months. Similarly, Antinori and colleagues reported that a good virologic response to HAART therapy was associated with an improved CR rate and a prolongation in survival. However, in a recent prospective study to evaluate the safety and efficacy of liposomal doxorubicin, cyclophosphamide, vincristine, and prednisone in 24 patients with ARL, Levine and colleagues did not find a statistically significant relationship between virologic response to HAART and antitumor response to the chemotherapy, consistent with the NCI data on EPOCH. Table 6 depicts some of the studies that have been done to evaluate the impact of HAART on tumor response and survival in patients with ARL. As summarized, use of HAART will clearly improve survival in such patients, although attainment of virologic control does not appear to be mandatory for achievement of complete response to chemotherapy.

TABLE 6  Studies Showing Impact of HAART on Response Rate and Survival

| Study (date) | Population | Study Design | Main Findings |
|--------------|------------|--------------|---------------|
| Ratner (2001) | 17 US centers n = 65 | Prospective observational: compared full dose CHOP* with HAART† and GCSF‡ versus reduced dose CHOP | No change in pharmacokinetics of doxorubicin and indinavir; clearance of cyclophosphamide 1.5-fold reduced but no clinical impact |
| Antinori (2001) | Two Italian centers n = 65 | Retrospective: HAART was administered concomitantly with chemotherapy and followed for 27 months | Complete response to chemotherapy was achieved in 71% of HAART responders and 30% of nonresponders (odds ratio, 5.67; 95% confidence interval, 1.54–20.78) |
| Tam (2002) | United States Multicenter AIDS Cohort (MAC) n = 100 | Retrospective observational: Analyses performed using data from 100 men in the MAC study with a diagnosis of non-Hodgkin lymphoma | HAART treatment was associated with improved survival for non-Hodgkin lymphoma patients (P = 0.0001) |
| Gerard (2002) | France n = 47 | Retrospective single institution study of HIV-related§ Hodgkin disease | Higher complete response for Stage I to III in the post-HAART period (100%), than for patients from the pre-HAART period (65%) (P = 0.008); no difference for patients with Stage IV disease |
| Vaccher (2003) | Italy n = 235 | Retrospective single institution analysis | Overall, complete remission occurred in 49% of patients, and the 3-year rates of overall progression-free survival, and disease-free survival were 19%, 49%, and 73%, respectively |
| Hoffmann (2003) | Germany multicenter cohort study n = 203 | Retrospective observational | GREATEST risk for shortened overall survival was associated with no HAART use, with hazard ratio of 17.42 (95% confidence interval, 17.42–40.25) |

*CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone. †HAART, highly active antiretroviral therapy. ‡GCSF, granulocyte colony-stimulating factor. §HIV, human immunodeficiency virus.
In considering whether HAART should be omitted during chemotherapy, the degree of immunosuppression in the individual patient, which would in turn influence the risk of death from bacterial and opportunistic infections, and the benefit of viral suppression in relation to survival and tumor response must be balanced with the potential of overlapping toxicities between HAART and chemotherapy. Nonetheless, these toxicities have been largely no different from those of chemotherapy alone.

Role of Rituximab

The role of rituximab in patients with HIV is somewhat controversial. In a randomized Phase III trial conducted by the AIDS Malignancy Consortium (AMC) of the NCI, standard-dose CHOP was compared with CHOP with rituximab (R-CHOP). Although CR was higher in the 96 patients who received R-CHOP (57%) compared with the 47 patients who received CHOP alone (47%), this difference did not reach statistical significance. Death due to lymphoma and early withdrawal due to lymphoma progression were higher in the CHOP-treated patients. However, this study suggested that the additional use of rituximab was associated with a statistically increased risk of death from infection. Of the 16 patients who died of infection, 15 occurred in the group randomized to receive R-CHOP, while 1 occurred in the group randomized to CHOP alone (15% versus 2%; P = 0.027). While this study seems to suggest that the use of rituximab was associated with potentially fatal infectious complications, it should be noted that 9 of the 15 patients who died had a CD4 cell count of less than 50 cells/mm$^3$. Moreover, more patients in the R-CHOP arm had a CD4 count less than 50 cells/mm$^3$, a condition that is known to be associated with an increased risk of bacterial infection, even in the era of HAART. The fact that over 60% of the deaths occurred in patients with CD4 counts less than 50 cells/mm$^3$ raises the possibility that the higher infectious death rate seen among patients receiving R-CHOP could have been because of the severely immunodeficient state of these individuals. Furthermore, in contrast to the AMC trial, other studies have documented high CR rates with the additional use of rituximab without an increase in infectious mortality.

To address the controversy regarding the safety as well as the efficacy of rituximab, the AMC has initiated a randomized trial comparing concurrent administration of rituximab with EPOCH to EPOCH followed sequentially by rituximab weekly for 6 weeks. Thus, the role of rituximab in the treatment of AIDS-related lymphoma remains controversial and final conclusions await further investigation.

Our current practice is to treat patients with systemic ARL using the dose-adjusted EPOCH regimen, with or without rituximab. All our patients receive concomitant HAART, particularly important for those with CD4 $<$ 100 cells/mm$^3$. We routinely use prophylactic granulocyte colony-stimulating factor in all patients and erythropoietin as appropriate. All of our patients also receive prophylaxis for *Pneumocystis carinii*, regardless of their CD4 cell count.

Relapsed or Primary Refractory Disease

Until recently, patients with relapsed or refractory ARL after first-line chemotherapy have had little possibility of cure with standard-dose salvage regimens. Complete response rates with salvage chemotherapy have ranged from 10% to 30%, with median survival ranging from 2 to 7 months. Slightly more encouraging results were seen in a retrospective study of patients treated with cisplatin-based salvage regimens. The advent of effective antiviral therapy has improved the immune function of HIV-infected patients and their hematologic reserves. These facts, together with better supportive care, have made stem cell mobilization and high-dose chemotherapy approaches possible in HIV-infected patients. Krishnan and colleagues at the City of Hope have reported their experience with progenitor cell transplantation in 20 relapsed/refractory patients with ARL. Stem cell mobilization was successful, with a median collection of $10.6 \times 10^6$
CD34+ cells per kg. The time required for white cell engraftment was a median of 11 days (range, 9–23 days), which is comparable to non–HIV-infected patients. Toxicity was acceptable but manageable. One patient developed cardiomyopathy and died on day 22 posttransplant. Before engraftment, four patients developed Gram-positive bacteremias, while eight patients developed neutropenic fever. Although opportunistic infections did occur in six patients during the postengraftment period, all responded to therapy. These included two patients with documented N. meningitidis pneumonia, of whom one also had cytomegalovirus retinitis, while the other developed pulmonary aspergillosis after steroid therapy. In the remaining four patients, two had herpes zoster, while the other two developed asymptomatic cytomegalovirus viremia. The results reported were, however, impressive. Thus, with a median follow-up period of 31.8 months, 17 of the 20 patients remained alive and in CR. The progression-free survival was 85% (95% CI, 69–100), and overall survival was 85% for the entire group. Similar encouraging results have also been reported by other investigators. These studies suggest that suitable patients with refractory or relapsed ARL should now be considered for high dose chemotherapy with peripheral progenitor cell transplant.

Burkitt Lymphoma

Currently, patients with HIV-associated Burkitt lymphoma are not treated differently from HIV-positive patients with other aggressive histologic subtypes. However, several investigators have suggested that more intensive chemotherapy regimens such as those used for HIV-negative patients may be more efficacious in this group of patients. Nonetheless, these studies are retrospective and involve relatively few patients. Thus, at the current time, it is still uncertain whether patients with AIDS-related Burkitt lymphoma should be treated differently from those with other pathologic subtypes.

Role of Central Nervous System Prophylaxis

The incidence of central nervous system (CNS) involvement at presentation in patients with systemic ARL has ranged from 10% to 20%. In a study of 50 patients with systemic ARL, Cingolani and colleagues showed that presence of EBV infection in the primary tumor was an independent predictor for CNS lymphomatous involvement at diagnosis or eventual relapse. In addition, the authors also demonstrated that detection of EBV DNA in CSF by polymerase chain reaction could predict eventual CNS lymphomatous involvement in almost 100% of patients, suggesting that the detection of EBV DNA in CSF may be used to select patients who would most benefit from CNS prophylaxis. Clinically, CNS chemoprophylaxis should be considered for patients with Burkitt lymphoma or with bone marrow, paraspinal, paranasal, epidural, testicular, or widespread systemic involvement. In the NCI trial of the dose-adjusted EPOCH regimen, CNS prophylaxis was added to the last 17 patients after late CNS relapse occurred in earlier patients who did not receive such therapy. Our own practice is to administer prophylactic intrathecal chemotherapy to all patients with systemic ARL.

PEL

There is no standard treatment for PEL. Outcome of PEL after polychemotherapy such as CHOP has generally been poor, with median survival ranging from 2 to 6 months. Immune reconstitution may play an important role in the management of PEL, and there have been reports of CR with HAART alone.

Management of HD

The majority of all patients with de novo HD experience long-term disease-free survival. In patients with Stage III or IV disease, doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy is associated with CR in 70% to 80% of patients, with relapse-free survival in 60% to 70% of responders.
In the pre-HAART era, however, treatment of HIV-HD with chemotherapy was associated with poor treatment outcomes. Treatment-related toxicities, especially hematologic, were substantial, even when hematopoietic growth factors were used. AIDS Clinical Trials Group conducted a nonrandomized trial in 21 HIV-infected patients with HD using the standard regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine with G-CSF.49 No antiretroviral therapy was used. The median CD4 count was 113/mm³, and 29% had a history of a clinical AIDS-defining condition before the diagnosis of HD. Of the 21 patients treated, CR was attained in only 43%. Despite routine use of G-CSF, 10 patients (47.6%) experienced life-threatening neutropenia, with absolute neutrophil counts <500 cells/mm³. In addition, 9 opportunistic infections occurred in 6 patients (29%) during the study or shortly thereafter. Median survival was only 1.5 years.

With the availability of HAART, better treatment outcomes with combination chemotherapy have now been reported. For instance, a Phase II study of the Stanford V regimen in 59 patients with HIV-HD reported an overall response rate of 89% and a complete response rate of 81%, with an estimated 3-year overall survival and disease-free survival of 51% and 68%.50 Of importance, 52 of the 59 patients (88%) received HAART concomitantly with the Stanford V regimen. In another study, Gerard et al51 retrospectively compared the treatment outcomes of patients with HIV-HD treated in the pre-HAART era with those treated in the post-HAART era. Although there was no significant difference in the chemotherapy regimens used between the 2 periods, the complete response rate rose from 64.5% in the pre-HAART to 74.5% in the post-HAART era. While the median survival of patients treated in the pre-HAART era was only 19 months, the median survival of patients treated in the post-HAART era had not been reached.

More recently, Hartmann and colleagues reported the results of a small Phase II study involving 12 patients with HIV-HD treated with 6 cycles of a regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) at standard doses.52 Only 5 of the 12 patients received concomitant antiretroviral therapy. Overall, toxicity with BEACOPP at standard doses was moderate, with Grade 3 and 4 neutropenia occurring in 75% of patients. All patients treated with BEACOPP in this study achieved CR of disease. Of these, 9 remained alive and in complete remission after a median follow-up of 49 months. Two patients died of opportunistic infections within the treatment period, while 1 patient died of a relapse after 26 months. While the results of this study are impressive, further confirmation will be required.

**CONCLUSIONS**

With the dramatic improvement seen in the prognosis of persons with HIV, leading to prolonged survival in the setting of an imperfectly reconstituted immune system, we may witness a further increase in the number of cases of ARL in the years ahead. Survival of patients with ARL has improved significantly over recent years and is now comparable to that of patients with aggressive lymphomas in the general population. Patients with ARL should thus be treated with curative intent.

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