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Matthew C. Cheung, Liron Pantanowitz and Bruce J. Dezube

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AIDS-Related Malignancies: Emerging Challenges in the Era of Highly Active Antiretroviral Therapy

MATTHEW C. CHEUNG, a LIRON PANTANOWITZ, b BRUCE J. DEZUBE c

a Sunnybrook and Women’s College Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; b Baystate Medical Center, Tufts University School of Medicine, Springfield, Massachusetts, USA; c Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

Key Words. Kaposi’s sarcoma · HIV-infection · AIDS · Non-Hodgkin’s lymphoma · Hodgkin’s lymphoma · Multiple myeloma · Antiretroviral therapy

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the pathogenesis and clinical presentation of Kaposi’s sarcoma, with a special emphasis on Kaposi’s sarcoma herpesvirus/human herpesvirus-8, and outline treatment approaches.
2. Discuss the pathogenesis, epidemiology, and treatment of AIDS-related lymphomas.
3. Discuss the increasing incidence of non-AIDS-defining malignancies such as Hodgkin’s lymphoma and plasma cell disorders in patients with HIV infection.
4. Explain how, in the era of highly active antiretroviral therapy, both AIDS-related lymphoma and Hodgkin’s lymphoma patients may be treated with therapies previously reserved for their immunocompetent counterparts.

ABSTRACT

Human immunodeficiency virus (HIV)-infected patients are at increased risk of developing cancer, particularly in the later stages of acquired immune deficiency syndrome (AIDS). Despite the advent of highly active antiretroviral therapy (HAART), malignancy in this population is a leading cause of morbidity and mortality. Kaposi’s sarcoma (KS) and AIDS-related non-Hodgkin’s lymphoma (ARL) are the most common AIDS-defining malignancies. AIDS-related KS varies from minimal to fulminant disease. Treatment decisions for AIDS-related KS are guided largely by the presence and extent of symptomatic disease. In addition to HAART, excellent treatments exist for both localized disease (topical gel, radiotherapy, and intralesional therapy) and advanced disease (liposomal anthracyclines, paclitaxel). Novel therapies that have become available to treat AIDS-related KS include angiogenesis inhibitors and antiviral agents. ARL comprises a heterogeneous group of malignancies. With the immune restoration afforded by HAART, standard-dose chemotherapies now can be safely administered to treat ARL with curative intent. The role of analogous treatments used in HIV-negative patients, including monoclonal antibodies and autologous stem cell
transplantation, requires further clarification in HIV-positive patients. HIV-infected patients also appear to be at increased risk for developing certain non-AIDS-defining cancers, such as Hodgkin’s lymphoma and multiple myeloma. Although the optimal treatment of these neoplasms is at present uncertain, recent advances in chemotherapy, antiretroviral drugs, and supportive care protocols are allowing for more aggressive management of many of the AIDS-related cancers. This article provides an up-to-date review of the epidemiology, pathogenesis, clinical features, and treatment of various AIDS-related malignancies that are likely to be encountered by an oncologist practicing in the current HAART era. The Oncologist 2005;10:412–426

**INTRODUCTION**

Patients infected with human immunodeficiency virus (HIV) are at a significantly increased risk of developing cancer compared with the general population. In fact, the onset of the acquired immune deficiency syndrome (AIDS) epidemic was heralded by an increased incidence of a rare malignancy, Kaposi’s sarcoma (KS), in 1981 [1, 2]. In 1982, the U.S. Centers for Disease Control and Prevention (CDC) proposed the initial case definition for AIDS, including such AIDS-defining malignancies as KS and primary central nervous system lymphoma (PCNSL) [3]. Subsequent revisions of the CDC definition for AIDS resulted in the addition of non-Hodgkin’s lymphoma (NHL) not restricted to the CNS [4] and invasive cervical cancer [5].

In addition to the aforementioned AIDS-defining malignancies, patients infected with HIV are also at increased risk for developing certain non-AIDS-defining cancers. In large database studies of linked AIDS and cancer registries, the overall rates of several neoplasms including Hodgkin’s lymphoma, invasive anal carcinoma, multiple myeloma, leukemia, lung cancer, as well as malignancies involving the oral cavity, lip, esophagus, stomach, liver, pancreas, larynx, heart, vulva, vagina, kidney, and soft tissues (e.g., leiomyosarcoma in children), were found to be in excess in patients infected with HIV [6-9]. However, unlike the AIDS-defining malignancies, the association of many of these non-AIDS-defining cancers with progressive immunosuppression has not been established [6-10]. Other oncogenic mechanisms are therefore likely involved, including confounding epidemiologic associations (e.g., smoking) or viral co-infections (e.g., human papilloma virus). Of note, the most common epithelial cancers found in the general population do not appear to occur more frequently in HIV-positive patients, including carcinoma of the breast, prostate, and colon [6, 7, 9, 11].

With the advent of highly active antiretroviral therapy (HAART), the morbidity and mortality associated with HIV infection dramatically improved [12]. As a result of the immune reconstitution afforded by effective combination antiretroviral therapies, the epidemiological and clinical profile of cancers in the setting of HIV infection also changed. While significant decreases in certain AIDS-defining cancers such as KS have been reported, similar declines for other malignancies such as AIDS-related lymphoma (ARL) are less evident [12, 13]. Moreover, with patients now living longer with chronic HIV infection and sustaining fewer opportunistic infections in the HAART era, malignancy in this population is becoming an increasingly prominent cause of death in the later stages of AIDS [14, 15]. Despite the emergence of AIDS-related cancers in the HAART era, concomitant advances in chemotherapy, antiretroviral drugs, and supportive care protocols are allowing for more aggressive management of AIDS-related cancers compared with the pre-HAART years [16]. It is in this current evolving clinical context that we review the epidemiology, pathogenesis, clinical features, and treatment of several AIDS-defining and emerging non-AIDS-defining malignancies.

**AIDS-RELATED KAPOSI’S SARCOMA**

Kaposi’s sarcoma is the most common neoplasm to arise in HIV-infected patients. Due to the explosive spread of AIDS in certain geographic regions, such as southern Africa, KS has reached epidemic proportions in these parts of the world. Patients in sub-Saharan Africa with AIDS-related KS have been shown to have high tumor burdens and rapid disease progression resulting in a diminished life expectancy of fewer than 6 months [17]. In the Western world, AIDS-related KS also continues to be a problem, despite a dramatic decline in incidence since the routine use of HAART [12, 18-20]. Although patients with KS on HAART exhibit a less aggressive presentation, the natural history of their KS appears not to be influenced by the prior use of these antiretrovirals [21].

**Clinical Features**

The clinical presentation of AIDS-related KS varies from minimal to fulminant disease, often resulting in significant morbidity and mortality. The importance of the profound psychosocial burden that can be associated with cutaneous presentations should be emphasized. Skin lesions appear mainly on the lower extremities (Fig. 1A), face (particularly the tip of the nose), and genitalia [22]. Cutaneous KS lesions are typically multifocal and papular, but on the thighs and soles of the feet may be plaque-like or fungating with breakdown of the overlying skin. Early lesions (patch stage) may evolve into more advanced lesions (plaque stage) as the lesional cells proliferate and involve more of the dermis. These lesions may eventually become ulcerating tumors (nodular stage).
Lymphedema, particularly in the face, genitalia, and lower extremities may be extensive. Extracutaneous spread is a common manifestation in HIV-infected individuals. KS in the oral cavity (Fig. 2) is particularly common (33% of cases) and can be the initial site of disease (15%) [23]. The palate is most frequently involved, followed by the gingiva [24]. In the head and neck region, any site may be involved, including the salivary glands [25] or larynx, in which case the patient may present with symptoms of airway obstruction [26]. Gastrointestinal involvement (Fig. 1B) has been reported in 40% of cases at initial diagnosis and up to 80% at autopsy [23]. Gastrointestinal KS can also occur in the absence of cutaneous disease and may be asymptomatic and cause weight loss, abdominal pain, nausea, vomiting, or bleeding [27]. Pulmonary KS is also common and in 15% of cases may occur without evidence of mucocutaneous disease [28]. Patients with pulmonary KS may be symptomatic or present with an asymptomatic finding on chest x-ray [29]. Radiological findings encompass nodular, interstitial, or alveolar infiltrates; isolated pulmonary nodules; and pleural effusions; as well as hilar or mediastinal lymphadenopathy [30]. Almost no organ is spared from involvement with KS. Autopsy series frequently describe KS involvement of lymph nodes, liver, pancreas, heart, and testes [31].

Although a trained observer can often make a presumptive diagnosis of KS quite readily, a skin biopsy should be used for confirmation. Early lesions can easily be mistaken clinically for purpura, hematomas, angiomas, and dermatofibromas. It is especially important to obtain a biopsy of lesions that are less typical of KS, are associated with systemic symptoms, or progress rapidly to rule out mimics, such as bacillary angiomatosis. This latter entity is caused by *Bartonella* species, a slow-growing, fastidious, gram-negative bacillus, which can be identified by Warthin-Starry silver staining and which is readily treated by antibiotics.
The clinical course of KS occasionally can be marked by exacerbations and more rarely, spontaneous regression. Corticosteroid therapy has been associated with the induction and exacerbation of KS, and such treatment should thus be used with caution in the HIV setting [23]. Opportunistic infections have also been associated with exacerbation of KS, possibly related to the associated high levels of proinflammatory cytokines during infection [23]. AIDS-related KS may flare dramatically following the initiation of effective HAART, and may represent a protean manifestation of the immune reconstitution syndrome [32]. This syndrome is an unusual inflammatory reaction to an infection or other disease process that occurs in HIV-positive patients with profound immunosuppression during the reconstitution of immunity associated with HAART. More commonly, initiation of HAART or chemotherapy results in regression of KS [33]. Regressing lesions flatten, shrink, and change from purple-red to orange-brown macules. Pigmentation of regressed lesions may still be of cosmetic concern.

Pathogenesis
Kaposi’s sarcoma lesions are characterized histologically by neoangiogenesis and proliferating spindle-shaped cells admixed with an inflammatory infiltrate of lymphocytes, plasma cells, and macrophages. Gene-expression profiling has confirmed that the lesions consist of a mixture of aberrant endothelial cells and inflammatory cells [34]. Spindle cells likely represent the malignant cells in KS. Immunohistochemical studies using novel monoclonal antibodies and the expression of lineage-specific genes by these cells suggest that they are derived from lymphatic endothelial lineage [35-39].

Multiple factors likely contribute to the development of KS. Infection with the gammaherpes virus human herpesvirus-8 (HHV8), also known as Kaposi’s sarcoma herpes virus, has been detected in all forms of KS [40]. Therefore, it is not surprising that HHV8 viremia has been shown by some investigators to serve as an early marker of KS [41]. The risk of developing disease increases with HHV8 antibody titers [42]. Among population groups at risk for HIV infection, the epidemiology of KS has been found to correlate well with that of HHV8 [43]. The oncogenic role of HHV8 in KS development is likely associated with the expression of several of its viral proteins, including those that are homologous to human interleukin-6 (IL-6), chemokines of the macrophage inflammatory protein family, cell cycle regulators of the cyclin family, and apoptosis molecules of the bcl-2 family [44-47]. Viral IL-6-driven expression of vascular endothelial growth factor provides an explanation for the angiogenic environment that results from the inflammatory milieu generated by HHV8.

Additional inflammatory cytokines and chemokines also have been shown to contribute to KS development. Expression of chemokines such as stromal cell-derived factor-1 may explain the predilection of KS for cutaneous sites [48]. KS lesional cells have also been shown to express chemokine receptors that signal through coupled G proteins [49]. Persistently activated G protein-coupled receptors can transform cells and act as oncogenes in human malignancies [50]. HHV8 itself encodes a constitutively active G protein-coupled receptor, homologous to the human IL-8 receptor, that leads to cell transformation and further signals the expression of proangiogenic and angiogenic factors. These findings are in keeping with the inflammatory and autocrine nature of KS lesions [51].

The HIV virus itself may play a direct role in KS tumorigenesis. The Tat protein, a regulatory protein of HIV-1 released by infected cells, protects KS cells from apoptosis [52], promotes the growth of lesional spindle cells in synergy with inflammatory cytokines [53, 54], and upregulates the synthesis and release of matrix metalloproteinases (MMPs) from endothelial and inflammatory cells [55, 56]. MMPs, normally responsible for degradation of the extracellular matrix, may contribute to the profound neoangiogenesis found in KS lesions and represent novel targets for therapy [55].

Prognosis and Treatment
AIDS-related KS is most commonly staged according to the AIDS Clinical Trials Group (ACTG) classification system, which originally (pre-HAART) characterized patients into good- or poor-risk groups based on tumor burden, immune function as measured by CD4+ T-lymphocyte count, and the presence of systemic illness [57]. More recently, a prospective evaluation of the ACTG staging system conducted in the HAART era showed that only the combination of poor tumor stage and systemic illness adequately identified patients with unfavorable prognosis [58].

Because KS is not considered curable with standard therapies, treatment decisions are instead guided by the presence and extent of symptomatic and extracutaneous KS. It is now accepted that most, if not all, patients with KS should be treated with antiretroviral drugs [23, 59]. The benefits of HAART include the inhibition of HIV replication, diminished production of Tat protein, amelioration of the host’s immune response to HHV8, and the direct antiangiogenic activity of some protease inhibitors [60, 61]. There are data demonstrating that effective antiretroviral regimens alone are associated with regression in the size and number of existing KS lesions [62-64]. More recently, it has been shown that both protease inhibitor- and non-nucleoside reverse transcriptase inhibitor-based HAART regimens are
equally effective as protection against KS [65]. Finally, HAART taken together with chemotherapy prolongs the time to treatment failure of anti-KS therapies [66].

Currently, there are five agents approved by the U.S. Food and Drug Administration for the treatment of KS. These include altretinoin gel for topical administration, liposomal doxorubicin (DOXIL®; Tibotec Therapeutics, a division of Ortho Biotech Products, L.P., Bridgewater, NJ, http://www.tibotec.com), liposomal daunorubicin (Daunoxome®; Gilead, Cambridge, UK; http://www.gilead.com), paclitaxel, and interferon-alpha for systemic administration.

Local therapy is most useful for localized bulky KS lesions and/or cosmesis, but will not prevent the development of new lesions in untreated sites. Altretinoin gel 0.1% (PanRetin®; Ligand Pharmaceuticals, San Diego, CA, http://www.ligand.com) is the only topical, patient-administered therapy approved for the treatment of KS [23]. Altretinoin has been shown to be effective after at least 4 to 8 weeks of treatment, with responses in up to 50% of patients [67]. Alternative local treatments include intralesional chemotherapy, radiation therapy, laser therapy, and cryotherapy. Vinblastine is the most widely used intralesional agent and has a proven response rate of approximately 70% [68]. Although treated lesions may fade and regress, they unfortunately do not resolve completely. For KS that is too extensive to be treated with intralesional chemotherapy but not extensive enough to warrant systemic therapy, radiation therapy can be employed to palliate symptoms. Complete responses to radiation therapy are found in 50%-80% of patients [46].

Individuals with more advanced or progressive disease may warrant systemic chemotherapy. Advantages to using the liposomal anthracyclines include a longer plasma half-life, higher tumor concentration of drug, and less toxicity in nontarget organs [69, 70]. Large randomized studies have established liposomal anthracyclines (liposomal doxorubicin 20 mg/m^2 every 3 weeks, liposomal daunorubicin 40 mg/m^2 every 2 weeks) as first-line chemotherapeutic agents with favorable response rates and durations compared with combination chemotherapy regimens [64, 69-71]. Paclitaxel is the most recent systemic chemotherapeutic agent to be approved for KS. Paclitaxel is typically given at a dose of 100 mg/m^2 every 2 weeks with premedication of dexamethasone 20 mg intravenously given just prior to the chemotherapy. This agent has shown striking efficacy, even for patients with anthracycline-resistant disease. Response rates to paclitaxel range from 60%-70% in phase II reports [72, 73]. Compared with other regimens for KS, the duration of sustained response for paclitaxel (approximately 10 months) is among the longest observed. Although paclitaxel is well tolerated, it is less desirable than the liposomal anthracyclines as first-line therapy for disseminated KS because of the need for a 3-hour infusion and the increased risks of alopecia, myalgia, arthralgia, and bone marrow suppression. In view of the fact that serious drug interactions may occur with HAART, dose reductions of paclitaxel may be required if this drug is being coadministered with HAART drugs that are metabolized by the same cytochrome P450 pathways [74]. For patients who have attained appropriate immune reconstitution with HAART therapy but have residual cutaneous KS, systemic interferon-alpha can also be considered, with responses detected in 20%-40% of patients [46]. Unfortunately, high-dose interferon therapy is often associated with significant side effects, including fever, chills, neutropenia, hepatotoxicity, and cognitive impairment.

Recent advances in our understanding of KS pathogenesis have uncovered many potential targets for KS therapies, which are now the focus of several trials. Angiogenesis inhibitors are one group of investigational agents currently being tested in patients with AIDS-related KS. These include fumagillin, thalidomide, the MMP inhibitor COL-3, and imatinib mesylate [23, 75-79]. In the phase I trial of the MMP inhibitor COL-3, tumor response rate was encouraging (44%) and correlated with biomarker evidence of decreased angiogenesis [77]. As both platelet-derived growth factor (PDGF) [80] and c-kit [81] signaling have a proven role in KS tumorigenesis, it is not surprising that the administration of imatinib mesylate, a c-kit and PDGF receptor inhibitor, results in regression of AIDS-related KS lesions [78]. Finally, another obvious target worth pursuing involves antiviral therapy to target HHV8. This notion is reinforced by the observation that the use of ganciclovir and foscarnet to treat cytomegalovirus disease in patients with AIDS reduced their risk of KS [82].

**AIDS-RELATED NON-HODGKIN’S LYMPHOMA**

**Clinical and Epidemiologic Features**

Although AIDS-related lymphomas (ARL) comprise a heterogeneous group of tumors, B-cell derivation is found in the overwhelming majority (>95%) of patients [83, 84]. The World Health Organization has divided ARL into three categories: A) lymphomas also occurring in immunocompetent patients such as Burkitt’s lymphoma (Fig. 3A) and diffuse large B-cell lymphoma (DLBCL) that includes centroblastic (Fig. 3B), immunoblastic (Fig. 3C), and anaplastic variants; B) lymphomas occurring more specifically in HIV-infected patients such as primary effusion lymphoma (PEL) and plasmablastic lymphoma; and C) lymphomas also occurring in other immunodeficiency states such as polymorphic or post-transplant lymphoproliferative disorder-like B-cell lymphoma associated with HIV infection [85]. Notable differences of ARL from NHL encountered in
the general population include the propensity for advanced disease (Fig. 4); presence of B symptoms; extranodal disease including bone marrow involvement [16, 83, 86], leptomeningeal disease, and disease in unusual locations (e.g., body cavities, jaw, rectum, soft tissues) [87, 88]; frequent plasmacellular differentiation shared by many of these lymphomas; and their prominent association with Epstein Barr virus (EBV) and HHV8. PCNSL represents a distinct extranodal presentation of DLBCL in HIV infection, usually of the immunoblastic type, that is associated with severe immunosuppression (CD4<50/mm$^3$), EBV-positivity, and a poor prognosis. Lymphomatous involvement in HIV-infected persons with PCNSL is typically confined to the craniospinal axis without systemic involvement [89]. Imaging alone cannot distinguish between PCNSL and cerebral toxoplasmosis, the latter being the most common cause of focal cerebral lesions.

DLBCL and Burkitt’s lymphoma represent the most common (approximately 90%) of ARL [83, 90]. PEL represents <5% of ARL [85] and is associated with infection by HHV8 and frequent coinfection with EBV [91]. Two variants of HIV-associated PEL have been described [92]. These include classic PEL or “body cavity-based lymphoma,” which has a unique tropism for serous body cavities, and extracavitary or solid PEL, which is an extraserous lymphoma reported in HIV-positive patients with or without associated effusions. In classic PEL lymphomatous effusions may involve the pleural, pericardial, and/or peritoneal body cavity, whereas solid PEL primarily involves

Figure 3. A) Burkitt’s lymphoma showing the classic starry-sky appearance created by scattered tingible-body macrophages. B) Diffuse large B-cell lymphoma, centroblastic variant. C) Immunoblastic lymphoma with many immunoblasts containing prominent nucleoli and focal coagulative necrosis (*).

Figure 4. Burkitt’s lymphoma involving A) the bone marrow and B) brain (within vascular spaces) in an HIV-infected individual.
extrasserous sites such as the large bowel, skin, lung, and lymph nodes [92]. Plasmablastic lymphoma is another unique lymphoma subtype that typically involves the jaw and oral cavity of HIV-infected individuals [93]. More recently, HIV-related plasmablastic lymphoma has been documented in other sites such as the anorectum, nasal and paranasal regions, skin, testes, bones, and lymph nodes [94, 95]. The neoplasm is highly associated with EBV infection and is comprised of large plasmablasts, cells that retain the blastoid morphology of immunoblasts but have otherwise acquired immunophenotypic features of plasma cells.

Aside from morphologic and clinical differences observed in ARL, variation in the epidemiology of certain ARL has also been noted. Multiple cohort studies have addressed the impact of HAART on the overall incidence of ARL. A European cohort study (EuroSIDA) reported that the proportion of AIDS-defining illnesses attributed to NHL increased from 4% in 1994 to 16% in 1998 [13], partly as a result of more notable declines in KS and other HIV complications. The only lymphoma shown not to increase with the introduction of HAART was PCNSL. A Swiss HIV cohort study was also unable to detect a significant decline in the incidence of NHL when comparing data from the pre-HAART with post-HAART time period [12]. In contrast, a large meta-analysis of 23 cohort studies found a decline in ARL from 1992-1996 (0.62% per year) to 1997-1999 (0.36% per year) [18]. The decline was most marked for PCNSL and other immunoblastic NHL, but was not found in Burkitt’s lymphoma. The reason for the discrepancy may be that individual cohort studies possibly yield inconsistent findings as a result of inadequate power to detect differences in trends or reliance on incomplete AIDS registry databases that may underestimate the incidence of ARL [96]. Clearly, the results do indicate a more pronounced decline in PCNSL incidence relative to other ARLs [13, 18, 97]. This variable decline in only certain NHL subsets underscores a possible differential involvement of immune function in lymphoma development in the HIV setting [59].

ARL is generally a late event in the course of HIV infection. Risk factors for the development of NHL in the current era include a low CD4+ T-cell count, high HIV viral load, increased age, and male gender [97]. Burkitt’s lymphoma is unique in that presentations occur at relatively higher CD4+ T-cell counts (>200 cells/mm³) than with immunoblastic lymphomas, like PCNSL (CD4 <50 cells/mm³) [98]. In general, the most recent CD4+ T-cell count (as opposed to nadir) is predictive for the development of ARL, suggesting a reduced risk of developing lymphoma if immune reconstitution with HAART occurs. Indeed, a recent prospective study confirmed a reduced risk of NHL development with HAART exposure compared with single-agent or no antiretroviral treatment [99].

**Pathogenesis**

The heterogeneity of ARL likely reflects the various pathologic mechanisms important in lymphomagenesis, including HIV-induced immunosuppression, chronic antigenic stimulation, genetic abnormalities, cytokine release and dysregulation, dendritic cell impairment, and the role of herpesviruses EBV and HHV8 [100]. The classic antigen-driven model of HIV-associated lymphomagenesis proposes that hyperstimulation of B lymphocytes induced by EBV, HIV, and other infectious agents elicits the continuous release of various growth factors and cytokines promoting B-cell proliferation [84].

Soluble cytokines found to be elevated in HIV-infected patients who develop ARL include IL-6, IL-10, sCD23, sCD27, sCD30, and sCD44 [101-103]. Many of these stimulatory cytokines are potent growth and antiapoptotic factors for B cells.

Host factors and cytokine genes may also influence NHL development. HIV-infected individuals, heterozygous for a deletion of the chemokine receptor CCR5, have a three-fold lower risk for NHL compared with individuals without this mutation [104]. In contrast, those with stromal cell-derived factor-1 mutations are two- to four-fold more likely to develop NHL [105].

**Prognosis**

Prognosis in ARL is related to the underlying severity of HIV infection and the extent of lymphomatous involvement. In a pre-HAART analysis, the following factors were demonstrated to have independent prognostic value: age >35 years, stage III/IV disease, CD4 <100/mm³, and history of intravenous drug use [106]. When 0 or 1 of these factors was present, overall survival was 46 weeks, but when 3 or 4 factors were present, survival was just 18 weeks. In addition, the age-adjusted International Prognostic Index has been validated in HIV patients [107].

Control of HIV viral replication through the use of HAART also appears to be a major positive prognostic factor for patients with ARL [90]. A virologic response to HAART within 2 years following a lymphoma diagnosis was independently associated with improved overall survival in a recent cohort study [108]. This study suggested that the benefit of HAART was not an increase in response rate or lymphoma outcome, but an overall improvement in HIV-related mortality.

**Treatment**

Prior to the advent of HAART, patients with AIDS-related NHL were managed with low-dose regimens due to concerns of unacceptable toxicity [109]. Survival at 2 years was approximately 10%. With the advent of HAART and
anticipated restored immunity, more recent regimens have reported the use of standard-dose chemotherapies without excessive toxicity. Whether HAART needs to be administered concomitantly with chemotherapy or immediately restarted after chemotherapy is completed remains unclear.

In 2001, the AIDS Malignancy Consortium (AMC) reported the feasibility of combining CHOP chemotherapy (dose-reduced or full-dose CHOP) with concomitant HAART in 65 patients [110]. Complete response rates were 30% and 48% in the reduced- and full-dose groups, respectively. Only one opportunistic infection occurred during chemotherapy administration. Cyclophosphamide clearance was reduced compared with historical controls, without clinical significance. No long-term outcomes have been reported in this study. Other studies of CHOP-based chemotherapy and HAART have yielded median survival periods in the range of 2 years [90, 111]. An infusional regimen of cyclophosphamide, doxorubicin, and etoposide (CDE) confirmed the feasibility of combining chemotherapy and HAART [112].

Chemotherapy without concomitant HAART has also been studied. Reasons for HAART omission include concerns of drug interactions with chemotherapy and inconsistent compliance with antiretrovirals resulting in increased resistance [98]. The National Cancer Institute described a dose-adjusted infusional regimen (EPOCH) consisting of a 4-day infusion of etoposide, vincristine, and doxorubicin, and daily oral prednisone for 5 days. The infusion was followed by an adjusted dose of cyclophosphamide according to initial CD4 count [113]. Thirty-nine patients were enrolled, and HAART therapy was not administered until after the final cycle of chemotherapy. Median CD4 count was 198/mm³ and 59% of patients were considered high or high-intermediate risk. A complete remission rate of 74% was achieved. Impressive disease-free and overall survival after 53 months follow-up were reported to be 92% and 60%, respectively. Patients with an initial CD4 count <100/mm³ had a worse survival compared with patients with a CD4 count >100/mm³. During treatment, the median CD4 count fell to 189 cells/mm³, but returned to baseline by 6-12 months after completion of dose-adjusted EPOCH. Three patients developed opportunistic infections within 2 months of chemotherapy. Infusional therapy was postulated to reduce the risk of multi-drug resistance by overcoming the drug efflux associated with multi-drug resistance-1 gene expression [114]. Similar benefits may be attained by substitution of liposomal doxorubicin for standard doxorubicin used in CHOP chemotherapy [115].

The AMC has also studied the role of rituximab therapy in patients with ARL. Kaplan reported a randomized trial of CHOP versus CHOP and rituximab (375 mg/m²) given with each cycle (for a total of 6-8 cycles) with an additional three monthly doses after complete response was attained [116]. Complete response rates and median event-free survivals (approximately 1 year) were similar between the two groups. However, treatment with rituximab was associated with an increased risk of death from infection (14% versus 2%; p = 0.027). Up to 60% of deaths were in patients with a CD4 <50/mm³, and 40% occurred during the maintenance phase of rituximab. It is possible that by depleting normal B lymphocytes, rituximab may contribute to further immunosuppression in a group of patients already predisposed to infection from their underlying HIV status. In addition, the benefit of rituximab in the non-HIV setting is limited to lymphomas that overexpress bcl-2; this overexpression occurs less frequently with ARL, possibly explaining the lesser response to immunotherapy [113]. However, in contrast to the randomized report from the AMC, smaller phase II studies of R-CHOP or infusional R-CDE have demonstrated high complete response rates (76%-80%) without the same propensity for causing infectious complications [117, 118]. The role of rituximab requires further clarification prior to routine administration in ARL.

Attention to supportive care measures is vital in this patient population. The judicious use of hematopoietic stimulants such as G-CSF and erythropoietin may help reduce chemotherapy-induced cytopenic complications. For patients with pre-existent neutropenia or those who have experienced chemotherapy-induced neutropenic complications, alternatives to trimethoprim-sulfamethoxazole prophylaxis for Pneumocystis carinii prophylaxis can be considered, including dapsone or aerosolized pentamidine. Prophylactic intrathecal chemotherapy may be delivered at the time of initial cerebrospinal fluid analysis to reduce the risk of leptomeningeal relapse [119], particularly in patients with Burkitt’s lymphoma/Burkitt-like lymphoma histology, or bone marrow, paraspinal, or paranasal involvement [120]. Those patients who harbor an EBV-positive lymphoma are particularly prone to leptomeningeal spread and should receive prophylactic intrathecal chemotherapy. For those who elect to continue HAART while administering chemotherapy, zidovudine should be avoided due to an increased risk of myelosuppression, while caution should be exercised with didanosine, stavudine, and zalcitabine, which may potentiate vincristine-induced neuropathy. For the rare patient who is cytomegalovirus seronegative, leukoreduced blood products are indicated.

Our personal recommendation and practice are to treat patients with ARL, particularly those with CD4 counts >100 cells/mm³, with full-dose CHOP (either with or without rituximab) or dose-adjusted EPOCH. The majority of our patients receive concomitant HAART, as well as G-CSF. In
addition, we have a low threshold to prescribe ciprofloxacin during periods of neutropenia and erythropoietin as appropriate. All of these patients need to receive prophylaxis for *Pneumocystis carinii* pneumonia, regardless of the CD4 cell count. Many of our patients receive intrathecal prophylaxis based on the guidelines aforementioned.

Currently, prospective studies of ARL combine the high-grade DLBCL and Burkitt’s lymphoma/Burkitt-like lymphoma histologies, with no apparent difference in outcomes between the subtypes [98, 109, 121]. Recent small retrospective studies (14-16 patients) report the feasibility of using dose-intensive (nonmyeloablative) protocols with or without HAART with acceptable response rates [122-124]. Unfortunately, there are no prospective studies demonstrating superior responses with high-dose compared with standard-dose regimens [121]. Treatment for PCNSL may also require special considerations. Whole-brain radiation with concomitant corticosteroid administration was previously the cornerstone of management. Median survival was rarely beyond several months in duration [125]. Survival may be improved in the HAART era, with patients responding to HAART treatment demonstrating extended median survivals to beyond 1.5 years [126]. Smaller reports in this population have also shown responses to high-dose methotrexate-based regimens without the associated leukoencephalopathy of whole-brain radiation [127]. Pilot studies have also suggested promise for therapy directed against EBV and HIV in the form of parenteral zidovudine, ganciclovir, and IL-2 along with HAART [128], although these results are still preliminary.

Patients with relapsed or refractory ARL can be considered for high-dose therapy with stem cell support if appropriately selected. HAART therapy is feasible throughout the transplant process [129]. In one report, 16 of 19 patients remained in remission after 2 years of follow-up [130]. Infectious complications were similar to those noted in the HIV-negative population and no long-term deterioration in immune function was found. Larger studies with longer follow-up and with a focus on intent-to-treat analyses are needed to better define the role of stem cell transplantation for the treatment of chemosensitive but persistent or relapsed ARL.

**HODGKIN’S LYMPHOMA**

Although not considered an AIDS-defining malignancy, HIV-related Hodkin’s Lymphoma (HL) is similar to ARL in that there is an increase in occurrence [7, 131] and a clear relationship between the incidence of disease and progressive immunodeficiency [6-8]. Clinical features in this population are unique compared with HL in HIV-negative individuals. Patients are more likely to present with B symptoms, advanced disease stage, and extranodal disease [131-134]. Bone marrow involvement may be found in over 50% of patients, and may represent the presenting feature in 20% of cases [133]. Virtually all HIV-related Hls are EBV positive. The histologic subtypes most often seen in this setting include mixed-cellularity and lymphocyte-depleted variants [131, 135, 136]. Prior to HAART, patients with HL in the HIV setting had a limited median survival of 1-2 years. A trial of ABVD therapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) was associated with severe and common hematologic toxicity and a poor median survival (1.5 years) [137]. More recent outcomes in the HAART era may be improving [131, 138], although the precise timing of antiretroviral therapy requires clarification. Patients who receive and respond to HAART within 2 years of their HL diagnosis have improved survival rates compared with nonresponders [136]. Initial experience suggests that antiretrovirals can be used concomitantly even with dose-intensive regimens, including the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) [139]. Another recent trial studied the use of concurrent HAART with the Stanford V regimen (doxorubicin, vinblastine, melphalan, etoposide, vincristine, bleomycin, prednisone, and involved-field radiation for initial bulky disease) and documented a high complete response rate (81%), albeit at the cost of considerable myelosuppression and neurotoxicity [140].

**MULTIPLE MYELOMA**

Plasma cell disorders are being reported with increasing frequency in association with HIV infection [141]. Monoclonal gammopathy is found in 2.5% of HIV patients [142], while the risk of multiple myeloma (MM) is increased 4.5-fold compared with the general population [8]. MM in the context of HIV has some features that distinguish this plasma cell disorder from the typical presentation seen in non-HIV patients. HIV-related MM typically affects patients under the age of 40 and can manifest with atypical and aggressive features [142], with reports of large malignant effusions [143], hyperviscosity [144], and extramedullary plasmacytomas presenting in unusual locations [145]. The prognosis is generally poor, with reported patients dying within weeks to months of diagnosis, many from treatment-related toxicity [141].

The pathophysiology underlying the development of plasma cell disorders is unclear, but may be related to chronic antigenic stimulation from HIV and other viral coinfections, elevated serum IL-6 levels, and EBV-driven proliferation of infected B cells [146, 147]. Some HIV-related paraproteins have monoclonal specificity to HIV antigens, suggesting that viral proteins, such as the p24 gag protein, directly underlie the clonal selection of B cells [144, 148, 149].

Optimal treatment of HIV-related MM is unknown. Most regimens have been extrapolated from the non-HIV population.
Currently, high-dose chemotherapy with autologous stem cell transplant is the standard of care in HIV-negative patients [150, 151]. In the HIV setting, stem cell transplant has been tried in only one patient, who relapsed and died 1 year after high-dose therapy [152]. It is anticipated that the immune reconstitution afforded with HAART will enable further successful attempts with dose-intense regimens. Lower-dose regimens, including melphalan [144, 153, 154], anthracycline [155, 156], and thalidomide-based protocols [157] have been reported in the literature, with variable clinical effects [141]. A recent review of all published cases did not identify a superior treatment protocol, but suggested a possible association of HAART therapy with prolonged survival [141]. Further investigation is required to define the best treatment specific to HIV patients.

**CONCLUSION**

The use of HAART has resulted in a dramatic decline in HIV-related mortality over the last decade. However, patients who are living longer with HIV remain susceptible to many cancers, including hematologic malignancies and KS. Therefore, oncologists will likely play an increasingly prominent role in the care of these patients. Thankfully, an evolving selection of therapies is available for the treatment of AIDS-related malignancies. In the treatment of KS, exciting novel therapies address our improved understanding of the underlying pathophysiology of the disease. In AIDS-related lymphoma, patients are being treated with aggressive therapies previously reserved for their immunocompetent counterparts. In all of these conditions, the use of HAART appears to be central in optimizing control of the malignancy and long-term prognosis.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

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