

A PEER-REVIEWED ARTICLE

Does ARV therapy reduce incidence of non-Hodgkin lymphoma?

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HIV infection predisposes patients to the development of neoplasm through impairment in immune surveillance. In the 1980s, it was recognized that HIV-infected individuals had a hundred-fold increased risk of developing non-Hodgkin lymphoma (NHL).¹ In 1985, NHL was added to the list of AIDS-defining illnesses. Effective control of HIV's immunosuppressive effects with highly active antiretroviral therapy (HAART) has reduced the incidence of NHL, most notably primary CNS lymphoma, but it remains the second most common AIDS-associated malignancy worldwide and is associated with substantial mortality and morbidity. This review will focus on the pathophysiology, classification, epidemiology, and advances in prognosis and treatment of AIDS-related lymphoma (ARL).

The AIDS-related lymphomas can be divided into three groups: 1) those in immunocompetent patients that occur with increased frequency in HIV, such as Burkitt lymphoma and diffuse large B cell lymphoma (CNS lymphoma in HIV is of this type), 2) those which occur exclusively in the setting of HIV such as primary effusion lymphoma (PEL) and plasmablastic lymphoma (PBL) of the oral cavity, and 3) those that occur in the setting of immunosuppression from other causes, such as less aggressive B cell lymphomas.

Diffuse large B cell lymphoma (DLBCL) and Burkitt lymphoma are the most common types of AIDS-related lymphomas and account for roughly 90% of cases. Primary effusion lymphoma and plasmablastic lymphoma of the oral cavity account for less than 10% of ARL cases and are limited to advanced HIV infection.

Epidemiology

ARL is a late complication of HIV disease, most often occurring in patients with CD4 count less than 100 cells/ul. As in patients without HIV infection, the diagnosis is more common in men than in women.

Antiretroviral therapy greatly reduces the incidence of NHL and its beneficial effect remains after ten years of treatment, according to the results of the largest, longest study into the effects of HAART on the incidence of this AIDS-defining cancer.² The study identified 429 cases of NHL between 1984 and 2006. Pre-HAART, the incidence of NHL was 13.6/1000; from 2002 to 2006, incidence declined to 1.6/1000 person years. In this study, HAART decreased the risk of NHL regardless of CD4 count.

Since the advent of HAART, there has been a decrease in the number of new cases of NHL in HIV. However, this decline has not been as pronounced as the decline in opportunistic infections, thus resulting in a relative increase in ARL as a presenting AIDS-defining illness.

Pathophysiology

ARLs frequently carry Epstein-Barr virus (EBV) genetic material and have plasma-cell-related phenotypes. These arise in the setting of HIV-associated immunosuppression that allows the unchecked proliferation of EBV- and Kaposi sarcoma herpesvirus (KSHV)-infected lymphocytes. The following table shows the percentage of various ARLs that are infected with either EBV or KSHV.

| ARLs | EBV | KSHV |
|-----------------|------|------|
| DLBCL | 100% | - |
| Burkitt | 60% | - |
| PEL | 90% | 100% |
| PBL oral cavity | 80% | |

These herpes viruses have multiple strategies that act as cofactors in lymphoma development in HIV, which act in concert with immunosuppression. Multiple viral mechanisms lead to development of lymphoma. In the systemic lymphomas, the transforming EBV protein LMP-1 is frequently expressed and plays a crucial role in transforming B lymphocytes. In animal studies when this protein is expressed, there is increased development of lymphomas. LMP-1 deletion mutants of EBV fail to immortalize B cell lines. Therefore, it seems that EBV-associated DLBCL may be due to EBV-driven lymphoproliferation in the context of defective immunity to EBV. Although not essential, EBV facilitates tumor development in Burkitt lymphoma. EBMA 1, a protein required for latent viral episomal EBV DNA, is universally present.

The role of HIV in development of ARLs is poorly understood. Although HIV has not been shown to be oncogenic in itself, HIV gene products appear to be growth factors for KS.⁴

Clinical

Primary CNS lymphoma (PCNSL)

PCNSL makes up 15% of NHL in HIV as compared to less than 1% of NHL in the general population. Incidence in HIV is 2-6%.⁵ Nearly all are diffuse large B cell lymphoma immunoblastic variants.⁶ Involvement is limited to the central nervous system in PCNSL.

An increasing number of B cells enter the CNS as HIV progresses. Since greater than 95% of adults have latent EBV infection, it is likely that EBV-positive B cells enter the CNS as T-cell-specific EBV immunity wanes. As previously mentioned, nearly all HIV patients with PCNSL harbor EBV in their tumors. EBV DNA sequences can be detected in the CSF of these patients and are useful in establishing the diagnosis. EBV DNA can be detected in 80% of patients with PCNSL as compared to 0% of those without the disease.⁷

PCNSL requires a more severe degree of immunosuppression than other AIDS-related complications and is therefore rarely an AIDS-defining illness. Clinical presentation of PCNSL is variable and can be characterized by changes in mental status, hemiparesis, aphasia, and other focal neurologic signs depending on the location of the lesion. Seizures are common, occurring in 50% of patients. Fever and B symptoms are also common, occurring in 80% of affected patients. Interestingly, increases in intracranial pressure are relatively infrequent, occurring in only 14% of patients in one series.⁸

Patients presenting with the above signs and symptoms should be evaluated with neuroimaging. MRI has a high diagnostic yield but CT can also be effective. The usual appearance on CT scan is of a hyperdense well-defined lesion. Calcification or hemorrhage is unusual. MRI shows isodense or hypodense T1 weighted images. A high degree of enhancement is common in the absence of corticosteroids. The enhancement appears irregular due to a high rate of necrosis from rapid tumor growth. Posterior fossa lesions, which occur primarily in the periventricular area and corpus callosum, are rarely due to PCNSL. Lesions over 4 cm are more likely to be lymphoma. The presence of mass effect differentiates PCNSL and toxoplasmosis from progressive multifocal

leukoencephalopathy (PML), which occurs in less than 20% of PML. Steroid treatment affects the evaluation and appearance of lesions and should be delayed if there is no evidence of herniation or if it would be detrimental to the patient. SPECT scanning is 100% sensitive but only 64% specific with toxoplasmosis being the most common false positive. The combination of SPECT scanning and identification of EBV DNA in the CNS by PCR improves specificity to 97% in one series.⁹ 20-30% of HIV patients presenting with CNS lesions are found to have PCNSL with most of the remaining cases found to be toxoplasmosis or PML.¹⁰ Nearly half of patients with PCNSL will have multiple lesions. The usual diagnostic dilemma is between toxoplasmosis and PCNSL, which can usually be resolved with a combination of peripheral toxoplasmosis serology and CNS EBV DNA determination.¹¹ Monitoring for response to a two-week trial of empiric toxoplasmosis-effective antibiotic and brain biopsy can be useful in establishing the diagnosis.

Optimal treatment for primary CNS lymphoma has not been defined. Median survival in untreated patients is one to three months. HAART should be initiated early for any chance of increased survival.¹² Surgical resection is not effective as multicentric disease is frequently present even in patients with solitary lesions on imaging studies. The standard first line therapy for patients with PCNSL is radiation therapy and corticosteroids. Response rates are in the range of 20-50%, however, survival is not appreciably affected. Deaths are primarily due to opportunistic infections, and the addition of aggressive HAART has improved mean survival to >12 months.¹³

High dose methotrexate therapy (3mg/m²) with leucovorin rescue has recently become the treatment of choice, due in part to a small pilot study that showed an increase in median survival from the usual 1-3 months to 19 months.¹⁴

Systemic non-Hodgkin lymphoma (SNHL)

SNHL accounts for the majority of AIDS-related lymphomas. SNHL is a late manifestation of HIV, usually associated with CD4 counts of less than 100 but, unlike PCNSL, it can occur at any CD4 count. Nearly 25% of cases occur when HIV viral loads are undetectable. Histology is high-grade, usually large cell immunoblastic variant in 70-90%.³ Burkitt lymphoma, a subtype of SNHL, more often occurs when the CD4 count is high (i.e., over 200cell/ml) and accounts for 30% of SNHL.¹⁵

SNHL clinical presentations are similar in HIV-positive and HIV-negative patients. Frequently they present with an enlarging mass and B symptoms such as night sweats, weight loss, and fever in up to 30%. Extranodal disease occurs in 60% of patients with GI tract being the most common site. Bone marrow involvement is present in 30% of patients. Meningeal involvement is more common in the HIV-infected individual and occurs in up to 20% of patients, therefore CSF examination should be performed routinely in these patients.

Tissue biopsy is the diagnostic procedure of choice. If a lymph node is to be sampled, an excisional biopsy is preferable. Unlike PCNSL, staging evaluation is necessary for SNHL and should include bone marrow biopsy, CNS evaluation, and CT of chest, abdomen and pelvis.

Poor prognostic factors include age >60, advanced stage (more common in ARL), more than one site of extranodal involvement, poor performance status, and absence of CCR5-32 deletion mutation. In the post-HAART era, only lymphoma-related factors, not HIV-related factors, affect prognosis.

There is still disagreement on the optimal therapy for ARL. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) has shown some benefit in duration of remission. The aggressive nature of the tumor in HIV suggests the need for more intensive treatment regimens. The recent reports of impressive responses with the monoclonal anti CD-20 antibody (Rituximab) in non-HIV-related lymphomas, and the fact that most ARLs are CD-20 positive, has lead to several trials to assess the efficacy of this agent in ARL.¹⁶ In spite of early concerns about infectious complication of this regimen, it is now routinely used in ARL with improvement in survival in comparison to historical controls. The inclusion of a protease inhibitor in the HAART regimen can lead to an increase in toxicity of chemotherapeutic agents. One study showed little effect of a three-month HAART treatment interruption during ARL chemotherapy. The use of granulocyte colony-stimulating factor (G-CSF) has allowed for the use of standard dose rather than reduced dose chemo regimen which has been a factor in improving survival. Burkitt lymphoma has been more resistant to therapy and optimal treatment regimens have not been defined.

Primary effusion lymphoma (PEL)

PEL occurs primarily in HIV patients. It consists of monoclonal B cells, and has a predilection for body cavities such as peritoneal, pleural and pericardial spaces. Most often a primary tumor site is not identified. PEL occurs in advanced HIV infection usually with a large lymphomatous effusion. It is consistently associated with Kaposi sarcoma herpesvirus infection. There is an increased risk of this tumor in HIV patients who have been diagnosed with Kaposi sarcoma.¹⁷ Optimal therapy is not defined in this relatively rare tumor, but

prognosis is poor with combined chemotherapy and HAART in comparison to other ARLs.

Plasmablastic lymphoma

This ARL presents primarily in the oral cavity and perioral area with later development of distant metastasis. As with PEL, it occurs in advanced HIV and is a rapidly progressive tumor. Histologically it shows marked plasma cell differentiation and a high proliferation rate.¹⁸ Prognosis of these tumors is uniformly poor.

Prognosis

Two thirds of HIV-positive patients with non-Hodgkin lymphoma are alive one year after diagnosis, as reported in the COHERE (Collaboration of Observational HIV Epidemiological Research Europe) study group.¹⁹ This group looked at data collected from 33 European cohort studies. Of nearly 68,000 patients, 947 developed NHL. None of the patients had received HIV treatment before 1998. Of these patients, 10% were diagnosed with primary CNS lymphoma and 10% had Burkitt lymphoma. Mean age was 41 years and 82% were male. Forty-three percent were not on HAART at the time of diagnosis, 14% had been on therapy less than 90 days. Mean CD4 count at diagnosis was 114 cell/mm³. Of the patients with systemic NHL, 37% died. 66% were alive one year after diagnosis and 54% were alive at five years. Prognosis for primary CNS lymphoma was worse with 45% mortality. Survival at one year was 54%; data for five years was insufficient. Other factors significantly associated with poorer prognosis were older age, IV drug use, and CD4 count over 25cell/mm³ or lower.

The finding that in the HAART era, 50% of these patients were alive five years later provided more evidence that the survival gap in NHL patients with and without HIV is closing.

Progress has been made in the control of AIDS-related lymphoma. However, most controlled therapeutic trials in the HIV population either have lacked enough patients to show significant differences or have many HAART-naïve patients in the mix.²⁰ HAART has reduced the incidence of these tumors and more aggressive treatment regimens appear to have improved survival. More studies need to be done to elucidate the optimal therapy for these tumors. Clinicians who encounter patients with ARL should refer these patients to clinical trials for optimal care. ♦

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