Management of HIV-Associated Lymphomas

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Since the beginning of the AIDS epidemic, HIV infection has been associated with the development of lymphomas. HIV-associated lymphomas are among the most common malignancies seen in these patients (second to Kaposi sarcoma), accounting for a substantial mortality. The pathogenesis of HIV-associated lymphomas relies on chronic antigenic stimulation, viral co-infection (e.g. EBV) and immunologic dysregulation, among others. Since the advent of **highly active antiretroviral therapy (HAART)** in the mid 1990s, the morbidity and mortality associated with HIV infection have decreased substantially, along with the incidence of HIV-associated lymphomas. In the last several years, our understanding of the biology of the disease and improvements of antiretroviral and supportive therapy have changed the treatment of patients with HIV-associated lymphoma. However, the treatment continues to represent a challenge to oncologists. The objective of this review is to highlight developments in the therapy of HIV-associated lymphomas.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of HIV-associated lymphomas, accounting for about 80-90% of cases.[1] HIV-associated DLBCL can present as either primary lymph node disease or at extranodal sites. In HIV-positive individuals, more than half of the patients have some site of extranodal involvement at diagnosis, with the most common sites being the gastrointestinal tract, bone marrow and the **central nervous system (CNS)**; but any organ may be involved. The patients affected by HIV-associated DLBCL tend to be young men with CD4 counts <200 cells/mm^3. The disease tends to be clinically aggressive, necessitating prompt treatment.

Prognostic factors in HIV-associated DLBCL can be divided into HIV-related (e.g. CD4 count, presence of opportunistic infections, HIV viral load, etc.) or lymphoma-related (e.g. stage, complete response rate, International Prognostic Index, etc). In the pre-HAART era, HIV-related and lymphoma-related factors seemed to have a prognostic value for survival. More recently in the HAART era, lymphoma-related prognostic factors, such as attainment of complete remission or high **International Prognostic Index (IPI)** scores remain as independent risk factors for survival.[1] However, an immunological response to HAART, manifested by an increase of CD4 counts and undetectable HIV viral loads, seems to confer an additional benefit in patients with HIV-associated DLBCL.

Hence, the markedly median overall survival for patients with DLBCL has gone from 6 months in the pre-HAART era to 4 years in the HAART era, an overall survival comparable to HIV-negative patients with DLBCL.[1] However, whether HAART should be used concomitantly or sequentially with chemotherapy is not well-established. One study showed virologic control of HIV infection was a significant factor in the ability to obtain complete remission of lymphoma, while another study showed that withholding HAART until completion of chemotherapy did not lead to lower overall survival.[2] Regardless, most experts agree that HAART should be given throughout the treatment of DLBCL. Zidovudine should be avoided since it is the most likely anti-retroviral to cause significant bone marrow suppression.[2]

Addition of rituximab to **CHOP (cyclophosphamide, doxorubicin, vincristine and oral prednisone)** has demonstrated a clear benefit in immunocompetent patients with DLBCL. Rituximab is a monoclonal antibody directed against CD20, a B-cell antigen expressed by normal B-lymphocytes and also by approximately 85% of NHL malignant cells. The use of rituximab in HIV-infected patients has remained controversial. Patients who received regimens containing rituximab appear to have higher rates of remission, lower rates of progressive lymphoma, but higher rates of treatment-related infection.[3] In particular, most of the infection-related deaths occurred in patients with CD4 counts <50 cells/mm^3.[2]However, several recent studies have evaluated the safety of rituximab-enhanced regimens in patients with CD4 counts >100 cells/mm^3. Nonetheless, clinicians should be vigilant about implementing appropriate antibiotic prophylaxis and promptly recognizing, diagnosing, and treating potentially life-threatening infectious complications. In the relapsed setting, **autologous hematopoietic stem cell transplantation (HSCT)** has shown feasibility, achieving similar results than in immunocompetent individuals with DLBCL.[4]

Primary Central Nervous System Lymphoma

Primary CNS lymphoma (PCNSL) accounts for approximately 1-2% of the cases of lymphoma in patients with HIV infection, but it accounts for 10% of the cases in patients with a diagnosis of AIDS. In contrast to HIV-associated Burkitt lymphoma, PCNSL is usually positive for **Epstein-Barr virus (EBV)**. The median CD4 count at the time of diagnosis is typically markedly low at <50 cells/mm^3, which may in part explain the poor prognosis for this subset of patients. With the advent of HAART, the incidence of PCNSL has decreased markedly. In fact, the incidence rate of PCNSL in HIV-positive patients has gone from 5.3 per 1000 person-years in the early 1990s (pre-HAART) to 0.3 per 1000 person-years by 1999 (post-HAART).

PCNSL generally presents with focal neurologic deficits, including cranial nerve findings, headaches, and/or seizures. The diagnosis is made by cerebrospinal fluid examination and imaging studies. The lesions on CT scans often show ring-enhancement with intravenous contrast administration and may occur at any location. PCNSL may be difficult to differentiate from cerebral toxoplasmosis, which is the most common cause of focal cerebral lesions in HIV-infected patients. Once a diagnosis of PCNSL is made, staging is not usually

necessary, since systemic involvement is rare. The survival of HIV-positive patients with PCNSL before HAART was extremely short at 3 months in patients receiving brain radiation and 1 month in patients who did not receive treatment; in the HAART era, the 2-year overall survival approaches 30%.

In terms of treatment, whole-brain radiation therapy has been used for palliation and can induce improvement in up to 50% of the patients but responses are brief. HAART is recommended in HIV-positive patients with a diagnosis of PCNSL, since there is evidence that it can improve survival concurrently with radiotherapy and steroids if an improvement in the CD4 count is achieved.[5] The role of systemic chemotherapy in HIV-associated PCNSL is unclear; however, high-dose methotrexate was associated with an overall survival of 19 months in a small pilot study.[6] In our opinion, these patients should be considered for clinical trials.

Plasmablastic lymphoma

Plasmablastic lymphoma (**PBL**) is an aggressive variant of DLBCL. The cell of origin is thought to be a mature activated B-lymphocyte in transition to become a plasma cell. The majority of cases are seen in HIV patients; however, several cases have been reported in immunocompetent individuals. PBL tends to present involving the oral cavity of HIV-positive individuals with CD4 counts <200 cells/mm^3. The association with EBV is reported at 74%. These tumors have an aggressive clinical course with a high rate of relapses and a median overall survival of 15 months.[7]

A review of 112 cases of HIV-positive PBL failed to identify prognostic indicators;[7] however, a more recent study in 70 HIV-positive PBL patients showed that clinical stage and response to chemotherapy were associated with overall survival.[8] Standard regimens such as CHOP are thought to be inadequate to treat PBL, and current guidelines recommend treating PBL with high-intensity regimens such as hyperCVAD or CODOX/M-IVAC. Due to the lack of CD20 expression by the malignant cells, the use of rituximab in PBL is unclear. Antiretrovirals should be started and administered throughout the treatment, if possible.

Primary Effusion Lymphoma

Primary effusion lymphoma (**PEL**), a rare lymphoma seen more commonly in HIV-positive patients, accounts for 3% of all the cases of HIV-associated NHL. It usually presents as an effusion without evidence of detectable masses in HIV-positive patients with severe immunodeficiency (CD4 count <150 cells/mm^3). PEL is universally associated with human herpesvirus 8 (HHV8), which is also associated with Kaposi sarcoma. The co-infection rate with EBV is reported at 70%. The median overall survival is 6 months.

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A study in 28 patients with HIV-positive PEL identified a poor performance status (ECOG 2 or higher) and absence of HAART prior to PEL diagnosis as prognostic factors for survival.[9] Despite its inherent chemoresistance, PEL should be treated, whenever possible, with anthracycline-based regimens, such as CHOP or dose-adjusted EPOCH with or without intrathecal chemotherapy. Rituximab should be given to the rare cases that express CD20 in the lymphoma cells, as long as their CD4 count is >100 cells/mm^3. All patients should receive G-CSF support and antiretrovirals should be started and administered throughout the treatment.

Burkitt lymphoma

Burkitt lymphoma (**BL**) is rare in adults in the United States, but is the second most common pathologic type of lymphoma in HIV-infected patients, accounting for 10-20% of the cases.[2] Most patients with HIV-associated BL present with B symptoms, peripheral lymphadenopathy, an intraabdominal mass and laboratory evidence of tumor lysis (hyperkalemia, hypocalcemia, hyperphosphatemia, metabolic acidosis, high LDH and uric acid levels with or without renal failure).[10] BL also tend to occur in patients with relatively higher CD4 counts (>200 cells/mm^3) than other lymphomas, such as PBL or PEL.[1] Furthermore, the incidence of BL in HIV-positive patients has not decreased with the advent of HAART. Clinically, the disease is typically rapidly aggressive, developing in a matter of days or weeks, with a propensity to involve the CNS. Therefore, it is imperative to confirm the diagnosis expeditiously in order to avoid delays in initiating therapy.

In contrast with the endemic variants of BL, in which the association with EBV is virtually 100%, the presence of EBV in HIV-associated BL has been reported in 25-40% of the cases. Potential adverse prognostic factors for HIV-associated BL are CD4 counts <100 cells/mm^3 and a high IPI score. The addition of HAART does not seem to have prolonged survival in these patients; however, it will likely allow more intensive therapies and the benefit could be seen in the near future.

Unfortunately, even with the addition of HAART to chemotherapy, patients with BL still have a median survival time of only 6 months, which is unchanged from the pre-HAART era;[11] but in this study, patients did not receive modern intensive regimens. The current treatment of BL resembles that for immunocompetent patients, and involves intensive combination chemotherapy regimens such as hyperCVAD and CODOX/M-IVAC with or without rituximab. Rituximab should not be used in patients with CD4 counts <100 cells/mm^3. Importantly, CNS prophylaxis is mandatory in these patients, and for this intrathecal methotrexate is commonly used. The guidelines render R-CHOP as inadequate for HIV-associated BL, except for the patients who will not tolerate intensive chemotherapy, in which case R-CHOP can be combined with high-dose methotrexate. Support with G-CSF should be given to prevent febrile neutropenia. Since tumor lysis syndrome is common, prophylaxis with intravenous hydration, urine alkalization and allopurinol or rasburicase is sometimes required during the first cycle of chemotherapy.[10]

Hodgkin lymphoma

Hodgkin lymphoma (HL) is a very common lymphoma seen in younger immunocompetent individuals. For this reason, the association of HIV infection and HL remained unclear. The WHO classification, however, includes HL as one of the HIV-associated lymphomas, although it is not considered an AIDS-defining cancer. The risk of HL in HIV-positive individuals is approximately 20-fold when compared with the general population. Several population-based studies have shown that in the HAART era the incidence of HL seems to have increased, in comparison with the patterns observed in Kaposi sarcoma or specific subtypes of NHL such as PCNSL. HL is an EBV-associated lymphoma since 80-100% of the Reed-Sternberg cells express EBV **latent membrane protein (LMP1).**

Clinically, HIV-associated HL present with advanced stages (75-90%) and systemic B symptoms such as fever, night sweats and unintentional weight loss (70-95%). The median CD4 count at presentation is almost invariably >200 cells/mm^3. In a retrospective study of 290 cases of HIV-associated HL, absence of B symptoms, absence of extranodal involvement and prior use of HAART were associated with a better overall survival. Prior to HAART the overall survival on these patients was 18 months.

Due to the scarcity of cases, randomized controlled trials have not been done in HIV-associated HL, but the overall survival seems longer in patients treated with standard regimens, such as ABVD and Stanford V. For example, a prospective study on 59 patients with HIV-associated HL treated with Stanford V plus HAART and G-CSF support reported a 3-year overall survival of 51% [12]. More recently, a Spanish study on 62 patients treated with ABVD concurrently with HAART showed a 5-year overall survival of 75%.[13] In the latter study, an immunological response to HAART has been associated with better survival. The relapse rate in HIV patients is higher than in the general population. In this setting, autologous HSCT have shown to be well tolerated and effective, obtaining survival benefits similar to immunocompetent patients.[4] HSCT after relapse is considered a standard of care in patients with HIV-associated HL.

Conclusions

In the last 30 years, the management of HIV-associated lymphomas has evolved. Some of the most significant advances include the introduction of HAART, the ability to administer standard and high-intensity chemotherapy regimens and the improvement of supportive therapy. Despite these advances, the management of HIV-associated lymphomas remains a challenge due to potential pharmacologic interactions and an increased risk of infectious complications. Patients with HIV-associated lymphomas should be treated by HIV oncologists in settings where they can benefit from research protocols.

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