Burkitt’s lymphoma Associated with HIV Infection

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Abstract

Non-Hodgkin lymphoma of the B-cell type is the second most common neoplasm in patients with human immunodeficiency virus infection after Kaposi’s sarcoma. The majority of the cases of non-Hodgkin lymphoma associated with the acquired immunodeficiency syndrome involve extranodal sites, specially the digestive tract, including the oral cavity and the central nervous system. The estimated relative risk of NHL associated HIV infection is 100 times greater than in general population and this risk increases with the progressive immunosuppression related to the retrovirus Burkitt's lymphoma has frequently been reported as a neoplasm in HIV infected patients. These lymphomas are now better described as AIDS-related BL.

Keywords: Non-Hodgkin lymphoma; Burkitt’s lymphoma; AIDS; HIV

Introduction

Burkitt's lymphoma (BL) is an uncommon highly aggressive B-cell non-Hodgkin lymphoma (NHL) with a high incidence in immunocompromised patients in non-endemic areas, especially those with HIV infection. The immunosuppression associated with HIV/AIDS disease predisposes to develop NHL, including BL. In patients with AIDS, BL is characterized for the compromise of extranodal sites as clinical presentation of the disease [1].

Clinical Forms of BL

The world health organization (WHO) classification of the lymphoid tissue describe 3 clinical variants of BL: endemic, sporadic and the subtype associated with immunodeficiencies [8,9]. The endemic form occurs in African children and affects the jaw, other bones of the face and other extranodal sites. This clinical form is strongly associated with the EBV infection (98%). Sporadic BL occurs outside of Africa and the digestive tract is the most common location. The association with EBV is about 20%. The immunodeficiency subtype is seen predominantly in HIV-positive patients; extranodal location is frequent as clinical presentation of the disease and the association with EBV in the pathogenesis is 30% to 40% [10-12].

Pathogenesis

BL was first described in African children by the Irish surgeon Denis Burkitt in 1958 [2]. In his pathogenesis, this subtype of NHL is strongly associated with the Epstein-Barr virus (EBV). EBV was the first human tumor virus described in 1970; the virus genome is identified in the atypical tumor cells of BL and other lymphoid neoplasms. In consequence, DNA sequences of this virus may be found in B cells and elevated titers of anti-EBV antibodies are detected in patients with BL [3]. However, not all the cases of BL are associated with EBV infection. For example, only 40% to 50% of the cases associated with HIV-infected patients express at least one viral antigen (EBNA1) and the encoding viral RNAs (EBERs) [4,5]. In contrast, all cases of BL exhibit the c-myc/Ig chromosomal translocations related to the activation of C-myc gene as an important finding in the development of the neoplasm disease [6]. Translocation involving MYC gene is highly characteristic but not specific for BL [4]. Translocation of the myc gene usually to the immunoglobulin (lg) heavy chain gene on chromosome 14 and rarely to light-chain genes on chromosome 2 or 22. Any BL with secondary cytogenetic abnormalities are considered to have adverse prognostic implications. Complex chromosomal abnormality indicates poor prognosis and increase the risk of treatment outcome [7].
Histopathological Diagnosis

Histopathological examination of biopsy smears showed a diffuse monotonous pattern of medium-sized monomorphic cells with round nuclei, multiple nucleoli and basophilic cytoplasm. The nuclei are round with clumped chromatin and contain multiple basophilic nucleoli. Scattered macrophages, impart the image that is described as a ‘scary sky pattern’. Ki 67 antigen is >95% in all patients. Regardless of subtype or variant, BL typically expresses monotypic surface IgM, pan-B-cell antigens, including CD19, CD20, CD22, and CD79a, and pan-B-cell antigens, including CD19, CD20, CD22, and CD79a, and some cases may co-express with CD10, Bcl-6, CD43, and p53, but not CD5, CD23, Bcl-2, CD138, or TdT. The immunophenotype suggests follicle center origin for this lymphoma [16].

Treatment

The gold standard treatment of BL in HIV-seropositive patients is the combination of chemotherapy plus highly active antiretroviral therapy (HAART). The impact of HAART on NHL, including BL, response and survival has been well demonstrated in several studies. Patients receiving HAART plus chemotherapy have a more significantly opportunity to achieve a complete remission [17-19]. Advanced neoplasm disease at presentation, bone marrow infiltration, prior diagnosis of AIDS and a poor performance status are associated with a shorter survival in HIV-associated NHL [17,18].

Treatment of BL is similar to other aggressive lymphomas; CHOP or CHOP-like regimens are common therapeutic alternatives [17]. However, actually, some authors use more intensive regimens to the treatment of HIV-associated BL. In this aspect, the Magrath regimen, CODOX-M (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose of systemic methotrexate) e IVAC (ifosfamide, cytarabine, etoposide and intrathecal methotrexate) has been associated with a good clinical response [20-22].

The CODOX-M/IVAC regimen was developed by Magrath et al., showed a similar and excellent rate of response in adults and children with BL. CODOX-M/IVAC is a short regimen with a cure rates nearly 90% [23]. When a greater number of older patients with BL were included to evaluate Magrath regimen, the cure rates was approximately 64%, substantially less in comparison with the initial Magrath results [24]. Better prognosis with Magrath regimen is associated with stage I or stage IIR and normal levels of LDH.

Other short and intensive regimens have also been used in HIV-positive patients with BL. Dose-adjusted rituximab-EPOCH (DA-EPOCH-R) including doxorubicin, etoposide, vincristine, cyclophosphamide and prednisone, has been demonstrated a very high response rate [25]. Some studies suggested increasing infectious deaths when rituximab is added to standard regimens, especially in those patients with low CD4T cell counts (less than 200 cell/µL) [26]. However, other studies suggested a non-statistically significant increasing in the risk of infections with an excellent outcome clinical rates, when rituximab is incorporated to chemotherapeutic regimens as EPOCH, hyper-CVAD or CODOX-M/IVAC [27]. Actually, this agent is considered as safely when is administered concurrently with chemotherapy and HAART [28,29].

Patients with extranodal BL, especially those with oropharyngeal involvement, have been received treatment or prophylaxis with intrathecal chemotherapy based on cytarabine and methotrexate [29].

Finally, based on the results of different studies, patients with HIV and BL should be treated with intensive chemotherapeutic regimens with the addition of HAART [23].

Conclusion

NHL accounts or approximately one third of AIDS-related malignancies and the frequency of BL is 2.4% to 20% of AIDS-related lymphomas [20]. The estimated relative risk of NHL associated with HIV infection is 100 times greater than in general population and this risk increases with the progressive immunosuppression related to the retrovirus [30]. BL may be the first manifestation of AIDS but often can occur in patients with a CD4 T-cell count >200 cell/µL in an early...
stage of the immunodeficiency associated with the retrovirus. A high diagnosis suspicion should be necessary to make an early biopsy due to the rapid clinical course of this neoplasm. An aggressive combination of HAART and chemotherapy should be initiated to improve the poor prognosis of this kind of patients. If HIV opportunistic infections are adequately controlled with HAART, intensive chemotherapy even including rituximab could achieve a survival similar to HIV-negative patients with BL without differences in the therapy-related toxicity [31].

References