The influence of antiretroviral therapy on clinical aspects of HIV-related lymphoma

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First draft submitted: 10 May 2017; Accepted for publication: 23 May 2017; Published online: 17 November 2017

Similar to the other immunosuppressed patients, individuals with HIV infection have an increased incidence of lymphomas. However, since 1996, the introduction of combination antiretroviral therapy (cART) has modified the natural history of some infections and malignancies, including lymphomas, which may affect HIV-infected individuals. The prognosis of both non-Hodgkin (NHL) and Hodgkin lymphoma (HL) has drastically improved in the cART era. The different chemotherapy regimens used in the general population are currently being administered to treat HIV-related NHL and HL with similar results to those obtained in the HIV-negative population.

Several epidemiological studies have confirmed that the incidence of HIV-related lymphomas has decreased in the cART era along with other AIDS defining malignancies. On the other hand, the incidence of non-AIDS-defining cancers has increased [1,2]. However, lymphoma is still the most frequent malignancy among HIV-infected individuals and a frequent neoplastic cause of death among HIV-infected patients [2,3]. A better control of the HIV infection has been observed concomitant with the decrease in the incidence of lymphoma in the cART era. However, the changes in the incidence of HIV-related lymphoma since cART became available have not been homogenous regarding the different subtypes of lymphoma. The risk of NHL has decreased, but it is still around tenfold compared with the general population [4]. Cases of diffuse large B-cell lymphoma (DLBCL), especially primary CNS lymphoma, have decreased, while the incidence of others, such as Burkitt's lymphoma (BL), has increased [5,6]. Unlike NHL, the incidence of HL has increased since the widespread use of cART [7,8]. This different epidemiological behavior could be due to the better control of the immune system in the majority of HIV-infected individuals, and consequently, lymphomas typically arising in severe immunosuppressed patients have diminished. On the other hand, the incidence of lymphomas that arise in patients with relatively better immune function (CD4⁺ lymphocyte counts of 150–200 cells/ μ l or higher), such as BL and HL, has increased among the HIV-infected population.

In the pre-cART era, the unfavorable lymphoma prognostic factors were mainly related to the HIV-infection and the performance status of the patients, rather than to the lymphoma. With the advent of cART, lymphoma-related factors became more important and HIV-related features were losing impact on the prognosis. The prognostic scores for both NHL and HL used in the HIV-negative population have demonstrated to be useful in HIV-infected patients as well. The International Prognostic Index (IPI) and the age-adjusted IPI, created in 1993, have demonstrated their value in stratifying the risk of patients with aggressive HIV-related NHL. Although some studies did not find any relationship between HIV-related variables and the prognosis of NHL, others have reported that the CD4⁺ lymphocyte count, HIV load and prior history of AIDS still have an impact on patient outcome in the cART era [9,10]. In fact, a new prognostic score for HIV-related lymphoma has been created including these variables as well as age adjusted IPI and the number of extranodal sites [11]. The international scoring system for advanced HL has demonstrated its applicability in HIV-infected patients as well [12]. To our knowledge, there are no prognostic scores for HIV-related HL combining both lymphoma and HIV variables. However, some studies have reported a negative prognostic impact for the CD4⁺ lymphocyte count [12].

Treatment of HIV-related lymphoma in the cART era includes the same regimens as those used for all the lymphoma subtypes in HIV-negative patients. Before the introduction of cART, treatment with standard chemotherapy doses was extremely toxic and, therefore, the relative dose intensity of the chemotherapy regimens administered was usually lower than scheduled. The generalized use of cART has led to better HIV control. This fact along with the use of colony-stimulating factors (G-CSF) have allowed chemotherapy to be administered at standard doses, with similar results to those obtained in HIV-negative patients.

The most frequent lymphoma subtype in the HIV-population is DLBCL, which classically shows more aggressiveness at presentation than in the HIV-negative population. Among HIV-positive individuals with DLBCL, those receiving cART seem to have less aggressive features. Localized stages are treated with the combination of immunochemotherapy and radiotherapy, while advanced stages are treated with immunochemotherapy. The standard regimens employed to treat DLBCL in patients with HIV infection are R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab). Using these immunochemotherapy regimens, similar response rates and survival have been reported in HIV and non-HIV infected patients [13,14]. Data regarding the use of rituximab in patients with CD20-positive NHL have shown that it can be safely administered without an increase of toxicity. However, in cases with a CD4⁺ lymphocyte count below 50/μl, its use is questionable because an increase of the infectious complications has been reported in this setting.

High-grade B-cell lymphomas, with *MYC* and *BCL2* or *BCL6* translocations are included in a new entity considered by the 2016 revision of the WHO classification of lymphoid neoplasms. These lymphomas are extremely aggressive with poor response to standard treatment for DLBCL and represent 2–10% of DLBCL in HIV-negative patients. Their prevalence among HIV-infected people may be similar although there are no consistent data regarding this population. The presence of the *MYC* translocation and the high aggressiveness, similar to BL, have led to the use of intense chemotherapy regimens for BL, but with little improvement in the results compared with R-CHOP, curing only a small proportion of patients. Hence, it is necessary to look for new treatments for these patients. In this regard, the DA-EPOCH-R regimen has shown promising results and can be administered to patients with high-grade B-cell lymphomas with *MYC* and *BCL2* or *BCL6* translocations [15].

HIV-related BL usually arises in individuals without a previous diagnosis of AIDS and with a relatively preserved immune system. These patients can be treated with the same intensive regimens as HIV-negative subjects, such as CODOX-M/IVAC and Hyper-CVAD [16]. Some studies among HIV-positive patients have shown that the addition of rituximab to intensive regimens for BL can improve the results, although the toxicity reported has been higher than in HIV-negative patients [17]. The EPOCH-R regimen has been used in 11 patients with HIV-related BL included in a prospective trial with progression-free survival and an overall survival of 100 and 90%, respectively.

Plasmablastic lymphoma is a rare, highly aggressive subtype of lymphoma different from DLBCL and is predominantly presented in HIV-infected individuals. Although it was initially described involving the oral cavity, other localizations have also been reported. The prognosis is dismal even in the cART era, with a median overall survival probability of less than 12 months. The use of intensive chemotherapy regimens has not achieved better results than CHOP; hence, if possible, autologous hematopoietic stem cell transplant should be carried out after first line chemotherapy. It is also recommended to perform prophylaxis of CNS involvement. Based on the plasmatic differentiation of this lymphoma, some drugs which are active in multiple myeloma, have been tested. Among these drugs, the most used is bortezomib, which has been administered both alone and in combination with the infusional DA-EPOCH regimen, the latter showing promising provisional results [18].

Primary effusion lymphoma typically arises in deeply immunosuppressed HIV-infected patients. Its prognosis is still very poor, and there are no specific strategies for this lymphoma.

In the cART era, HL is typically diagnosed during the first months after the onset of the antiretrovirals. In HIV-related HL, mixed cellularity is the most frequent subtype and Epstein-Barr virus is constantly present in the tumor cells in all histology subtypes. The proportion of patients with aggressive clinical features has been reported to be higher in the HIV-infected population even in the cART era [19]. However, the response to treatment and survival have been reported to be similar to HIV-negative patients using the same chemotherapy regimens such as ABVD, Stanford V or BEACOPP [19,20]. As in HIV-negative patients, the combination of chemotherapy and radiotherapy is recommended in initial stages, whereas chemotherapy alone should be used in advanced stages.

Other additional issues should be taken into account in the management of patients with HIV-related lymphoma. Primary infectious prophylaxis with colony-stimulating factors (e.g., G-CSF) given after every cycle of chemotherapy should be administered to guarantee adequate dose intensity of chemotherapy. Furthermore, prophylaxis should

be administered according to the CD4⁺ lymphocyte count and the previous history of opportunistic infections. Systematic prophylactic treatment against *Pneumocystis jirovecii* is recommended, and in some countries, against tuberculosis. Some intensive regimens, such as those used for BL, may lead to severe neutropenia, therefore, the same prophylactic measures as those used in acute leukemias should be taken in these patients.

Nowadays, CNS prophylaxis can be administered under the same criteria as that used in the general population, at least in patients on cART with good immune control at lymphoma diagnosis. Imaging studies of the CNS, as well as cytologic and immunophenotypic study of cerebrospinal fluid should be included in the initial evaluation of all aggressive NHLs to disclose CNS involvement by lymphoma.

The use of cART during chemotherapy is also controversial. However, our recommendation is to give cART concomitantly during chemotherapy, because antiretrovirals have been shown to decrease the risk of death and improve the prognosis of lymphoma [13]. Nevertheless, since some antiretroviral drugs can enhance the side effects of some chemotherapeutic agents, we strongly recommend close collaboration with physicians experienced in HIV treatment to evaluate the possible interactions and to modify, if necessary, the cART regimen before a specific lymphoma treatment is started to avoid interactions.

In summary, the use of cART has changed the epidemiology of lymphomas among the HIV-infected population. The incidence of lymphoma subtypes associated with severe immunosuppression has decreased whereas those arising in moderately immunosuppressed patients, such as BL and HL, have increased. The treatment of all lymphoma subtypes should not differ from that of the HIV-negative population. Additional aspects of management such as primary and secondary prophylaxis of infections must be taken into account. Collaboration between professionals with expertise in treating lymphomas and those experienced in treating HIV infection is very important for the successful treatment of HIV-related lymphomas.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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