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Consensus statement

GESIDA/PETHEMA recommendations on the diagnosis and treatment of lymphomas in patients infected by the human immunodeficiency virus☆,☆☆

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ABSTRACT

The incidence of non-Hodgkin's lymphoma and Hodgkin's lymphoma is higher in patients with HIV infection than in the general population. Following the introduction of combination antiretroviral therapy (cART), the prognostic significance of HIV-related variables has decreased, and lymphoma-related factors have become more pronounced. Currently, treatments for lymphomas in HIV-infected patients do not differ from those used in the general population. However, differentiating characteristics of seropositive patients, such as the need for cART and specific prophylaxis and treatment of certain opportunistic infections, should be considered. This document updates recommendations on the diagnosis and treatment of lymphomas in HIV infected patients published by GESIDA/PETHEMA in 2008.

Abbreviations: ABC, abacavir; ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; Ara-C, cytosine arabinoside; AZT, zidovudine; BCNU, carmustine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone; CDC, Centers for Disease Control and Prevention; CHOP, cyclophosphamide, adriamycin, vincristine and prednisone; CMV, cytomegalovirus; CODOX-M/IVAC, cyclophosphamide, adriamycin, vincristine and methotrexate/ifosfamide, etoposide and cytarabine; d4, Testavudine; dd, Ididanosine; DH, double hit; DHAP, dexamethasone, cytosine arabinoside and cisplatin; MCD, multicentric Castleman disease; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin hydrochloride; AD-EPOCH-R EPOCH-R, adjusted doses; MRS, spectroscopy by MR; ESHAP, etophoside, cisplatin, methylprednisolone and cytarabine; FDG18, fluorodeoxyglucose; FTC, emtricitabine; G-CSF, granulocyte colony stimulating factor; GESID, AIDS Study Group; Gy, grays; HBs, HBV surface antigen; HHV-8, herpes human virus type8; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; ICE, ifosfamide, etoposide and carboplatin; IL-6, interleukin-6; IMRT, intensity-modulated radiotherapy; INSTI, inhibitors of the integrase; PI, protease inhibitors; IPI, international prognostic index; IT, intratecal; NRTI, nucleoside or nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; LANA-1, latency-associated nuclear antigen 1; BL, Burkitt's lymphoma; DLBCL, diffuse large B-cell lymphoma; CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; HL, Hodgkin's lymphoma; LMP1, latency membrane proteins; NHL, non-Hodgkin's tumours; SOL, the occupant of space; PCNSL, Primary lymphoma of the central nervous system; Lymphomatous LM, lymphomatous meningosis; MTX, methotrexate; MTX-HD, methotrexate-high doses; PCR, polymerase chain reaction; PD-1/PDL-1, programmed cell death protein 1/programmed death-ligand 1; PET-CT, positron emission tomography-computed tomography; PETHEM, Spanish Haematology Treatment Program; CT, chemotherapy; R-CHOEPR-CHOP, with etoposide; R-CHOP, rituximab-CHOP; R-EPOCH, rituximab-EPOCH; CR, complete remission; RT, radiotherapy; MRI, magnetic resonance imaging; OS, overall survival; KS, Kaposi's sarcoma; EFS, event-free survival; SNC, central nervous system; SPECT, single photon emission tomography; Stanford V, doxorubicin, mechlorethamine, vincristine, vinblastine, bleomycin, etoposide and prednisone; TAF, tenofovir alafenamide; cART, combination antiretroviral therapy; TDF, tenofovir disoproxil fumarate; TH, triple hit; HSCT, hematopoietic stem cell transplant; 3TC, clamivudine; UGT1A1, uridinadiphosphate glucuronosyltransferase; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

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Recomendaciones de GESIDA/PETHEMA sobre el diagnóstico y tratamiento de los linfomas en pacientes infectados por el virus de la inmunodeficiencia humana

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RESUMEN

La incidencia de linfoma no hodgkiniano y linfoma de Hodgkin es mayor en pacientes con infección por el VIH que en la población general. Tras la introducción del tratamiento antirretroviral de combinación (TARc) ha disminuido la importancia pronóstica de variables relacionadas con el VIH, adquiriendo mayor peso factores relacionados con el linfoma. Actualmente, los tratamientos de los linfomas en pacientes infectados por VIH no difieren de los empleados en la población general. Pero existen algunos aspectos diferenciales de los pacientes con VIH como la necesidad de TARc, de profilaxis y de tratamientos de algunas infecciones oportunistas. En este documento se actualizan las recomendaciones sobre el diagnóstico y el tratamiento de los linfomas en pacientes infectados por VIH publicadas por GESIDA/PETHEMA en 2008.

Introduction

Lymphomas associated with HIV infection are grouped into three entities: systemic non-Hodgkin's lymphomas (NHL), primary central nervous system lymphoma (PCNSL), and Hodgkin's lymphoma (HL). Systemic NHL associated with HIV infection are more often B-cell lymphomas of great malignancy and some rare histological types that occur almost exclusively in this group of patients. PCNSL is a variety of NHL limited to the craniospinal axis that appears in patients with profound immunodeficiency. Both PCNSL and systemic NHL are considered AIDS-defining diseases. However, HL was not previously included as an AIDS-defining disease by the *Centers for Disease Control and Prevention* (CDC)[1] even though its incidence among people infected with HIV is much higher than that observed in the general population.

The introduction of combination antiretroviral therapy (cART) in 1996 radically changed the natural history of HIV infection and drastically reduced the incidence of tumours such as PCNSL, which occur with very low CD4+ T lymphocyte counts.[2] After the introduction of cART, lymphomas that usually occur with higher CD4+ T lymphocyte counts, such as Burkitt's lymphoma (BL) and HL also decreased, but not as significantly.[3,4] In addition, the use of cART has been decisive in the improvement of the prognosis of these tumours.[2,5–8]

This document updates the recommendations on the diagnosis and treatment of lymphomas in HIV-infected patients published in 2008 by a panel of experts from the AIDS Study Group (GESIDA) and the Spanish Program for Haematology Treatments PETHEMA.[9] As in the previous edition, these recommendations are accompanied by a categorization of the level of scientific evidence following the classification scheme for clinical practice of the *United States Public Health Service* and the *Infectious Diseases Society of America* (USPHS/IDSA) (Table 1).

Table 1
Clinical practice classification of the United States Public Health Service/Infectious Diseases Society of America (USPHS/IDSA).

	Strength of recommendation
A	Solid, it must be offered in all situations
B	Moderate, it should be offered regularly
C	Optional
D	It should generally NOT be offered
E	It should never be offered
	Quality of the findings on which the recommendation is based
I	At least one randomized trial with clinical assessment criteria
II	Non-randomized clinical trials
III	Expert opinion

Systemic non-Hodgkin's lymphomas

Histopathology and classification

The variety or histological subtype is the most important variable to predict clinical behaviour and to establish the prognosis of lymphomas. The WHO classification continues to be the accepted standard for terminology and classification of lymphoid neoplasms. Some changes were introduced in the latest edition of this classification, which is an update of the one published in 2008, including the subdivision of diffuse large B-cell lymphomas (DLBCL) depending on its germinal centre or non-germinal centre origin[10] (Appendix 1).

NHL associated with HIV infection are mainly of B-lineage, in particular DLBCL (73%) and less frequently BL (19%).[5] There are rare varieties but strongly linked to HIV infection, such as plasmablastic lymphoma and other related to type 8 human herpes virus (HHV-8), such as primary effusion lymphoma and multicentric Castleman's disease (MCD).

Diagnosis and extension study

Systemic NHL associated with HIV infection usually occur in young men with CD4+ lymphocyte values <200/mm^3, frequently being an AIDS-defining disease. The tumour is usually in advanced stages and is often accompanied by B symptoms and extranodal involvement, particularly of the bone marrow. There may also be central nervous system (CNS) involvement, both at the onset and during the course of the disease. The leptomeningeal involvement predominates in the initial stages, occurs more frequently when there is bone marrow or otorhinolaryngological area invasion and may be asymptomatic. The involvement of the brain parenchyma in the form of masses is more common in the context of a progressive and refractory lymphoma.

The diagnosis of lymphoma and the identification of the specific subtype require a histological study with immunohistochemistry and sometimes cytogenetic and molecular studies. It is recommended to study the complete lymph node or a large sample of infiltrated tissue. Samples obtained by fine needle aspiration are never enough to establish the correct diagnosis. However, in some cases, a needle biopsy may be used when it is not possible to obtain lymphadenopathy or tissue sample by biopsy.

Once the diagnosis is confirmed, an extension study should be done[11,12] (Table 2). In patients who are going to receive treatment with anthracyclines, it is also recommended to determine the ejection fraction of the left ventricle using echocardiography or isotopic ventriculography, both at baseline and during progression.