

GESIDA/PETHEMA recommendations on the diagnosis and treatment of lymphomas in patients infected by the human immune deficiency virus

Pilar Miralles^a, Carmen Rubio^b, Juan Berenguer^a, José María Ribera Santasusana^c, Felipe Calvo^a, Joaquín Díaz Mediavilla^d, José Luis Díez^a, José López Aldeguer^e, Eulalia Valencia^f and Rafael Rubio^g

^aHospital General Gregorio Marañón. Madrid. ^bClínica Nuestra Señora de la Concepción. Madrid.

^cHospital Univesitari Germans Trias i Pujol. Badalona (Barcelona).

^dHospital Clínico de San Carlos. Madrid. ^eHospital La Fe. Valencia.

^fHospital Carlos III. Madrid. ^gHospital 12 de Octubre. Madrid.

Introduction

Malignant tumors have been one of the most important complications of infection by the human immune deficiency virus (HIV)¹. Some of them, such as Kaposi's sarcoma (KS), primary central nervous system lymphoma (PCNSL), systemic non-Hodgkin's lymphoma (NHL) and carcinoma of the cervix were considered from the beginning of the pandemic as diseases which were diagnostic of AIDS. Curiously, Hodgkin's lymphoma has not been included in this category despite the fact that its incidence among HIV-infected individuals is eleven times greater than in the general population².

The introduction of highly active antiretroviral therapy (HAART) in 1996 radically changed the natural history of HIV infection and drastically reduced the incidence of tumors such as PCNSL and KS. A similar effect has not yet been reported for systemic NHL, or for HL^{3,4}, probably because the process of lymphomagenesis, which starts in a situation of immunodepression, has a prolonged latency period and does not stop immediately after initiating HAART. It is hoped that,

as these treatments are administered earlier in the course of HIV infection, a decrease in these tumors will also be observed⁵.

This document reviews the diagnosis and treatment of the main tumors associated with HIV infection. The recommendations are accompanied by categorization of the amount of scientific evidence following the classification schema for clinical practice of the United States Public Health Service and the Infectious Diseases Society of America (USPHS/IDSA) (table 1).

Systemic non-Hodgkin's lymphoma

Aggressive systemic non-Hodgkin's lymphoma has been included in the list of AIDS-defining diseases since 1985 and is the second most frequent neoplasia after KS in HIV-infected patients⁶. In most cases these are B-cell lymphomas, in particular diffuse large B-cell cell lymphoma (DLBC-NHL) and less frequently in Burkitt's or Burkitt-like lymphomas (Burkitt-NHL) according to the recent REAL classification⁷. In recent years, there have been reports of subtypes, such as primary cavity lymphoma, which has been associated with human herpes virus type 8 (HHV-8)^{8,9}.

TABLE 1. Rating scheme for clinical practice

Strength of recommendation

- A: strong, should always be offered
- B: moderate, should usually be offered
- C: optional
- D: should generally not be offered
- E: should never be offered

Quality of evidence for the recommendation

- I: at least one randomized trial with clinical endpoints
- II: clinical trials with laboratory endpoints
- III: expert opinion

United States Public Health Service/Infectious Diseases Society of America (USPHS/IDSA).

The prevalence of NHL in AIDS patients is 3%-5% and it causes 12%-16% of deaths in these patients. The prevalence of these tumors is similar in all risk groups and their appearance is strongly related to the degree of immunodepression in the case of DLBC-NHL; this is not so with Burkitt-NHL, which is usually present in patients with no previous diagnosis of AIDS and a relatively well preserved immune system.

Clinical aspects, diagnosis, extension study and prognostic factors

In AIDS patients, systemic NHL is normally present in advanced stages of the Ann Arbor classification¹⁰ and with frequent extranodal involvement. There is invasion of bone marrow in 20% of cases, digestive involvement in 4%-28% and hepatobiliary involvement in 9%-26%. CNS involvement is very common both at the time of diagnosis and during evolution. Leptomeningeal involvement is the predominant form in the initial stages and can evolve asymptotically; it is more frequent when there is invasion of the bone marrow or the ENT area. Involvement of the cerebral parenchyma in the form of masses is more common in the context of a treatment-resistant, progressive lymphoma¹¹⁻¹⁵.

Initial diagnosis of NHL requires a tissue biopsy and histological confirmation. Fine-needle aspiration is only useful in patients who have been previously diagnosed with NHL for the diagnosis of relapses or to confirm involvement of other organs, although in these cases biopsy is also recommended when possible. After diagnosis, the tumor stage should be established in order to decide on treatment and to be able to evaluate its efficacy in homogeneous patient groups (table 2). In recent

TABLE 2. Diagnosis of extension of NHL in HIV-infected patients

Anamnesis	B signs (any of the following in a period of < 3 months) Fever Excessive night sweats Over 10% weight loss
Physical examination	Palpable adenopathies (number, size and location) Hepatomegaly and splenomegaly Visible or palpable nodules or masses
Laboratory test	Complete blood count Biochemical tests with determination of LDH, β -2 microglobulin, transaminases, bilirubin, calcium, uric acid, serum proteins and immunoglobulins Serology: HBV, HCV, CMV, toxoplasma and varicella zoster Determination of HIV viral load in plasma CD4 lymphocyte count
Histopathology	Aspiration and biopsy of bone marrow Examination of CSF by cytocentrifugation
Imaging techniques	Chest X-ray CT of neck, chest, abdomen and pelvis Gammagram with Gallium-67 (optional). Occasionally: ultrasound scan, MR and PET

HBV: hepatitis B virus; HCV: hepatitis C virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus; CSF: cerebrospinal fluid; CT: computed tomography; MR: magnetic resonance; PET: positron emission tomography.

years, an NHL prognostic evaluation system, known as the International Prognostic Index (IPI), has become popular. This index has also been used in patients with AIDS and NHL, and a good inverse correlation has been observed between the IPI and the CD4+ T lymphocyte count in peripheral blood. This suggests that the degree of immunodeficiency is the circumstance which most influences the possibility of curing these patients^{14,15} (table 3).

Treatment

In the non-HIV-infected patient, DLBC-NHL is potentially curable using several different chemotherapy regimens although there is no evidence that any is better than CHOP (cyclophosphamide, adriamycin, vincristine and prednisone)¹⁶. At present, this regimen achieves complete remission (CR) in 60%-80% of patients in stages II-IV and cures approximately 40%.

In the pre-HAART era, HIV-infected patients with systemic NHL who were receiving standard chemotherapy reached CR in 50% of cases with a median survival of 5 to 7 months. These poor results are due to tumor and pa-

TABLE 3. Application of the International Prognostic Index* (IPI) to systemic NHL in HIV-infected patients

Risk group	No. of patients (%)	Complete remission (%)	Median survival (months)	CD4 lymphocytes ($\times 10^6/l$)
Low: 0-1	5 (7%)	100	> 60	313
Low/intermediate: 2	12 (17%)	88	17	230
Intermediate/high: 3	16 (25%)	50	19	151
High: 4-5	36 (52%)	32	6,8	72

IPI*: Each of the following points has a value of 1. Age > 65 years. Stage III/IV. High LDH. Extranodal involvement ≥ 2 . ECOG ≥ 2 (evaluation of ECOG: 0: normal activity; 1: symptomatic but with normal activity; 2: in bed less than 50% of time; 3: in bed more than 50% of time; 4: postrate 100% of time)

tient-dependent factors. The former include the usually large tumor burden of these patients, although the possibility that HIV-associated DLBC-NHL may have molecular peculiarities, which confer a worse prognosis¹⁷, or greater expression of the MDR-1 multiresistance gene¹⁸ must also be taken into account. Patient-dependent factors include HIV infection itself (lethal before HAART), deterioration of the immune system induced by chemotherapy¹⁹ and the deficient hematopoiesis which affects these patients²⁰. To get round the problem of low bone marrow reserve, low-dose cytotoxic regimens were proposed. These led to lower morbidity and mortality due to infection at the expense of a worse oncological response, which did not result in significant changes in global survival or in illness-free survival²¹⁻²⁶ (table 4).

Given that the cause of death used to be progression of the lymphoma in patients in good immunological condition and opportu-

nistic infections in patients with severe immunodepression, intensive chemotherapy regimens were proposed for those patients with factors that were less unfavorable²⁷⁻³³ (table 5). Intensive chemotherapy achieved better results from the oncological point of view, but did not improve the prognosis with regard to overall survival, probably because of poor control of HIV infection.

Adequate control of HIV infection with HAART has had a significantly favorable effect on the prognosis of HIV-associated systemic NHL. The available information suggests that with this treatment, chemotherapy obtains more CRs and longer survivals³⁴⁻³⁸, so that it is reasonable that the prognosis of patients with HIV and NHL who respond favorably to HAART will be increasingly similar to that of the general population and will be less conditioned by the natural history of HIV infection.

Practical recommendations for the treatment of systemic lymphomas in HIV-infected patients

Type of chemotherapy

Diffuse large B-cell NHL in HIV-infected patients should be treated with CHOP (AII)^{16,34,35} or with other regimens which contain anthracyclines such as EPOCH (etoposide, adriamycin, vincristine, cyclophosphamide and prednisone) (BII)³⁴. Each group should treat patients with the regimen with which it has most experience. Administration of appropriate doses and intervals of cytotoxic drugs is important, given that reduction in dose intensity

TABLE 4. Studies on the treatment of NHL in HIV-infected patients with low-dose cytotoxic regimens

References	Regimen	Design	Number of cases	AIDS (%)	CD4 lymphocytes ($\times 10^6/l$)	B-NHL (%)	ART	CNS prophylaxis	Growth factors	CR (%)	Remission (%)	MS (months)	Death by NHL (%)	OI
Levine et al ²¹	m-BACODr	CS	42	25	150	40	AZT	AraC	No	36	27	5,6	50	21
Tirelli et al ²²	CHVmp-vincristine-Bleo	CS	37	32	305	ND	AZT	MTX	No	14	SD	3,5	SD	SD
Walsh et al ²³	m-BACODr	CS	17	18	ND	47	No	AraC	G-CSF	47	SD	14	SD	SD
Levine et al ²⁴	m-BACODr	CS	25	20	164	60	ddC	AraC	G-CSF	56	36	8,1	12	12
Kaplan ²⁵	m-BACODr vs m-BACOD	RCT	98/94	55/48	100/107	24/28	Optional	AraC	GM-CSF	41/52	25/40	8,7/7,7	70/57	22/25

AIDS: patients with previous diagnosis of AIDS; CD4: median of CD4 lymphocytes; B-NHL: Burkitt's NHL; ART: antiretroviral therapy; CSF: colony-stimulating factor; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte macrophage colony-stimulating factor; CR: complete remission; MS: median survival; OI: AIDS-defining opportunistic infections during treatment of lymphoma; CS: case series; RCT: randomized clinical trial; AraC: cytosine arabinoside; MTX: methotrexate; AZT: zidovudine; ddC: zalcitabine; ND: no data.

TABLE 5. Studies of treatment of systemic NHL in HIV-infected patients with intensive chemotherapy regimens

References	Regimen	Design	Number of cases	AIDS (%)	CD4	LNH-B (%)	ART	CNS prophylaxis	Growth factors	CR (%)	REL (%)	MS (months)	Death by LNH (%)	OI
Schneider et al ²⁷	MACOP-B	S	8	0	Nc	0	No	BM/PS MTX o AraC	No	50	ND	10,6	25	ND
Sawka et al ²⁸	MACOP-B	S	30	47	60	17	No	All AraC	No	35	ND	8,1	ND	ND
Gisselbrecht et al ²⁹	LNH84	S	141	15	227	42	AZT	All MTX	No	65	24	9,5	50	ND
Saparano et al ³⁰	CDE	S	21	14	87	51	No	LB/MO MTX	Optional	62	ND	18	35	ND
Gabarre et al ³¹	LNH84	S	32	12	143	47	AZT	All MTX	BM-CSF	56	22	6,7	34	ND
Schurmann et al ³²	MACOP-B	S	8	50	65	12	No	MTX in 5	No	50	50	5	37,5	ND
Rossi et al ³³	ProMACE-	S	35	21	SD	SD	No	All MTX	G-CSF compared to GM-CSF	40/80	ND	ND	55/18	27
Little et al ³⁴	CytaBOM EPOCH	S	35	SD	198	15	HAART	MTX	G-CSF	79%	0	25	ND	No
Saparano et al ³⁵	CDE + ddI/CDE + HAAET	S	48/59	SD	78/227	SD	ddl/HAART	BL/BM	G-CSF	46/42	SD	8,2/17,8	38	ND

AIDS: patients with previous diagnosis of AIDS; LNHB: patients with Burkitt's lymphoma; CSF: colony stimulating factor; G-CSF: granulocyte stimulating factor; GM-CSF: macrophage and granulocyte stimulating factor; ART: antiretroviral therapy; CR: complete remission; REL: relapse; MS: median survival; OI: AIDS-defining opportunistic infections during treatment of lymphoma; CS: case series; BM/PS: Involvement of bone marrow or paranasal sinuses; BL/BM: Burkitt's LNHB or bone marrow involvement; AraC: cytosine arabinoside; MTX: methotrexate; AZT: zidovudine. ddI: didanosine; ND: no data.

(particularly with adriamycin and cyclophosphamide) reduce the percentage of CR and cures (AI)^{26,27}. In stage IA, combined-modality therapy with chemotherapy (3-4 cycles) and involved-field radiotherapy (AIII) may be considered. This option is clearly established in immunocompetent individuals³⁹.

Burkitt's NHL, unlike large cell NHL, is usually present in patients with no previous diagnosis of AIDS and with a relatively well-preserved immune system. In spite of this, response to treatment with the regimens used in DLBC-NHL is worse. For this reason, there are serious doubts as to whether Burkitt's-NHL should be treated with the aforementioned chemotherapy regimens. In fact, in the general population, the standard regimens for aggressive NHL have had very poor results with Burkitt's-NHL. The situation changed with the use of intensive regimens specifically designed for this tumor. These reached CR in 90% of patients and lymphoma-free survival above 2 years in 50%-70%⁴⁰. Among these cycles it is worth pointing out protocol 89-C-41 of the National Cancer Institute: CODOX-M (cyclophosphamide, adriamycin, vincristine and methotrexate) alternating with IVAC (ifosfamide, etoposide and cytarabine)^{41,42}. These intensive regimens should be used by experienced teams as they involve mortality due to toxicity of 7%-10%, generally in elderly patients or in those with advanced illness.

HIV-infected patients with Burkitt's-NHL, who have good immunological status and good general health, can receive intensive chemotherapy with CODOX-M/IVAC or a similar protocol (BII)⁴⁴. In patients with significant comorbidity, regimens such as EPOCH or CDE (cyclophosphamide, adriamycin and etoposide), which have included approximately 30% of Burkitt's-NHL in their series, may be used^{34,35}. It is important to know that in patients with this type of lymphoma, complications stemming from the tumoral lysis syndrome may be present at the time of diagnosis, with the result that staging and initiation of therapy should be delayed. Similarly, urinary alkalization and hyperhydration should be carried out.

It is difficult to give a recommendation for the most appropriate treatment for Burkitt-like NHL, since, although it is considered a variety of DLBC-NHL from a histological viewpoint, many groups believe that this tumor should be treated in the same way as Burkitt's-NHL.

Prophylaxis of the CNS and treatment of lymphomatous meningitis

This point deserves special comment, given that there is CNS involvement at the time of diagnosis in 20% of patients and because the CNS is a frequent site of relapse of the lymphoma. Some groups perform prophylaxis of the CNS only in «high risk» patients

such as those who suffer from Burkitt's NHL, or those with involvement of bone marrow, paranasal sinuses or epidural spaces (AII)^{27,30,41}. However, most authors are inclined to prophylaxis in all patients (BII). There are as many prophylaxis regimens as chemotherapy protocols^{13,22-25,29,31,32,41}, however, this consensus group recommends intra-the-cal administration of methotrexate (12 mg), cytosine arabinoside (30 mg) and hydrocortisone (20 mg) on day 1 of each cycle. For treatment of lymphomatous meningitis, this same regimen should be used every 3 or 4 days until the tumor cells disappear in CSF and afterwards 2 further doses, administering a minimum of 5 doses (table 6).

Craniospinal radiotherapy for prophylaxis or treatment of CNS involvement is not usual for several reasons. First, because there are efficacious alternatives, such as intrathecal and/or systemic chemotherapy. Second, because it produces severe toxicity, both hematologic and non-hematologic, for example, in the digestive tract. And finally, because it is technically complex, since there is risk of overlapping irradiation volumes on various anatomical regions. Exclusively holocranial irradiation (without extension to the spinal meninges) is a questionable procedure, since neoplastic contamination of the cranial meninges is unavoidable due to the free circulation of cerebrospinal fluid.

Hematopoietic growth factors

Administration of colony-stimulating factor is recommended to counter the poor tolerance of cytotoxic drugs and to guarantee adequate dose-intensity of chemotherapy (AI)⁴⁵. Granulocyte-CSF is preferred, given that there is indirect evidence that granulocyte macrophage-CSF increases HIV replication wi-

thin the reservoir of activated macrophages and monocytes^{25-30,46}.

CHOP should be accompanied by G-CSF at 5 µg/kg on days 7 to 12. With EPOCH, the same doses are administered from the sixth day of the cycle until an absolute neutrophil count above 1 × 10⁹/l is achieved for two consecutive days. If CODOX-M/IVAC is used, treatment should start on day 13 of regimen A and on day 7 of regimen B until the following cycle or until a neutrophil count above 1 × 10⁹/l is reached. If other therapeutic regimens are used, G-CSF schedules should be adapted appropriately.

Prophylaxis of opportunistic infections

After administration of chemotherapy, the total CD4 lymphocyte count drops by 30%–50% with respect to baseline, depending on the intensity of treatment and when the count is taken⁵¹⁻⁵². This is why the risk of suffering from HIV-associated opportunistic infections in these patients is twice as high as in patients without NHL at a similar stage⁴⁸. In fact, AIDS-defining infections complicate the treatment of lymphoma in 12%–33% of patients and are the second cause of death after the lymphoma itself^{21,24,32,33}. Therefore, prophylaxis of opportunistic infections is an unquestionably important aspect of NHL therapy in these patients. In principle, primary or secondary prophylaxis must be performed according to the number of CD4 lymphocytes and the previous history of opportunistic infections⁴⁹, although it is advisable to consider that the degree of immunosuppression of patients is greater than that reflected by the CD4 lymphocyte figure at the time of diagnosis of the tumor, and to act accordingly. In practice, systematic use of prophylaxis for

TABLE 6. Prophylaxis and treatment of lymphomatous meningitis

	Prophylaxis	Treatment
Recommended regimen (except for CODOX M/IVAC)	MTX 12 mg + AraC 50 mg + HC 20 mg; 1 dose at beginning of each cycle	MTX 12 mg + AraC 50 mg + HC 20 mg every 3 or 4 days until CSF normal and then two further doses. Minimum 5 doses
Cycle A: CODOX-M +	With A cycles: AraC 70 mg/day 1 y 5 + MTX 12 mg/day 15	With A cycles: AraC 70 mg/days 1, 3 y 5 MTX 12 mg/day 15 and 17
Cycle B: IVAC	With B cycles: MTX 12 mg/day 5	With B cycles: AraC mg/days 7 and 9 and MTX 15 mg/day 5

MTX: methotrexate; AraC: cytosine arabinoside; HC: hydrocortisone; CSF: cerebrospinal fluid; CODOX-M: cyclophosphamide, adriamycin, vincristine and methotrexate; IVAC: ifosfamide, etoposide and cytosine arabinoside.

Pneumocystis carinii (AII) is recommended and special attention must be given to tuberculosis, given the high prevalence of this disease in Spain.

Administration of HAART during chemotherapy

All patients with NHL and HIV infection should receive HAART, since available data suggest a beneficial effect in the response to chemotherapy (AII)⁵⁴⁻⁵⁸. However, it is not clear which is the best strategy. One option is to administer HAART once chemotherapy is completed, which could make sense with some high-intensity chemotherapy regimens of short duration such as CODOX-M/IVAC. Nevertheless, with other regimens such as CHOP or EPOCH, which can last approximately 5 months, this option involves foregoing the benefits of HAART during the treatment of NHL.

When designing the combination of antiretrovirals, it is very important to consider the toxicologic profile of the drugs. It is appropriate to bear in mind the myelotoxicity of AZT, neurotoxicity of ddI, ddC and d4T and the potential renal toxicity of indinavir in patients who do not receive adequate hydration. It is also important to consider the possible pharmacokinetic interactions between cytotoxic drugs and antiretrovirals, as both protease inhibitors (especially ritonavir) and non-nucleoside reverse transcriptase inhibitors are metabolized in the liver and act on cytochrome P450. They could potentially modify the area under the curve of cytotoxic drugs which are metabolized in the liver such as vinca alkaloids (vincristine and vinblastine), anthracyclines (doxorubicin and daunorubicin), cyclophosphamide and etoposide. There is little information on this available in the literature, although reduced cyclophosphamide clearance with no clinical effect on patients treated with indinavir⁵⁰

and possible fostering of mucositis by etoposide or adriamycin in patients treated with saquinavir⁵¹ (table 7) have been reported.

In the absence of solid information, the recommended strategy is not to administer HAART with the first cycle of chemotherapy, since this is when treatment complications are more frequent, including the tumor lysis syndrome. Starting or continuing chemotherapy is recommended after the second cycle of chemotherapy. In the EPOCH regimen, which involves continuous infusion of cytotoxic drugs over four days, transitory interruption of antiretroviral treatment during this period may be considered.

News treatments

After the introduction of HAART, the prognosis of many HIV-infected patients with NHL is no longer conditioned by the natural history of the viral infection and increasingly reflects the natural history of the tumor. This has allowed many patients to receive an oncological therapy which is no different from that used in the general population. However, recurrences are still common and the percentage of patients who remain in CR in the long term is lower than 25%. Therefore, the need for new treatments is unquestionable, especially for those patients with controlled HIV infection who do not have significant comorbidity, who enjoy good general health and whose prognosis depends exclusively on the efficacy of antitumor therapy. At present, the therapeutic options are hematopoietic stem cell transplantation and immunotherapy.

Hematopoietic stem cell transplantation

In non-HIV-infected patients, administration of high-dose chemotherapy with (out) radiotherapy followed by stem cell transplantation (SCT), is considered the treatment of choice for first relapse or chemosensitive

TABLE 7. Medication interactions between chemotherapy and HAART*

Antineoplastic	Indinavir	Ritonavir	Nelfinavir	Saquinavir	Amprenavir	Nevirapine	Efavirenz	Delavirdine
Cyclophosphamide	PI	PI	PI	PI	PI	NCI	PI	PI
Doxorubicin	NCI	ND	NCI	ND	NCI	NCI	NCI	NCI
Vinblastina	PI	PI	PI	PI	PI	PI	PI	PI
Vincristine	PI	PI	PI	PI	PI	PI	PI	PI
Paclitaxel	PI	PI	PI	PI	PI	PI	PI	PI

* www.hiv-druginteractions.org PI: potential interaction; NCI: no clinical interactions; ND: no data.

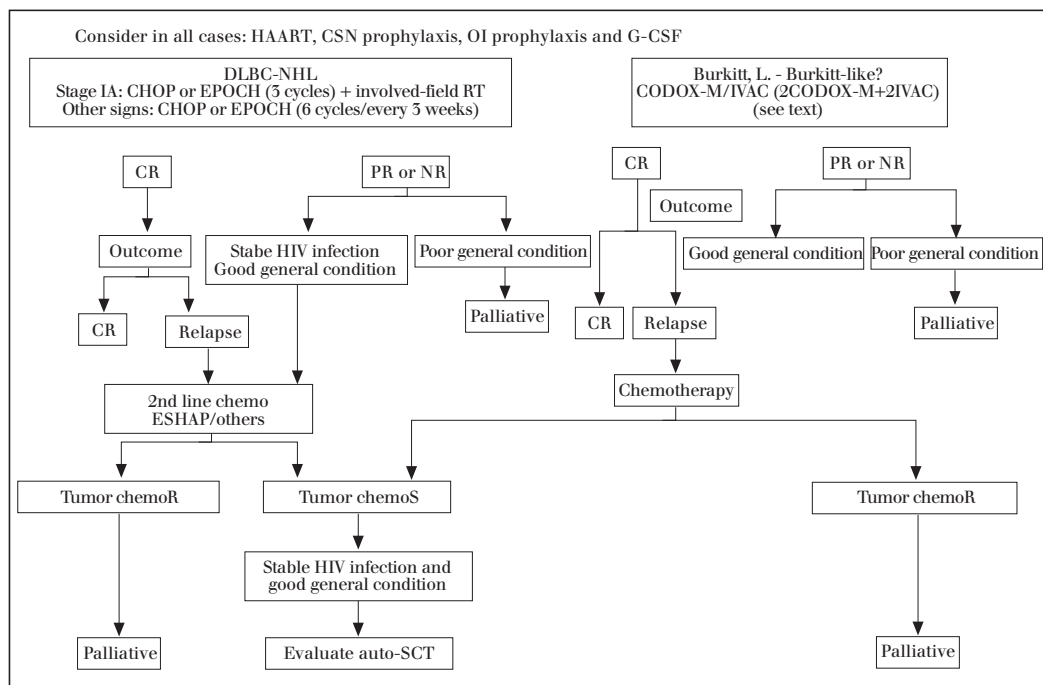


Figure 1. Treatment of AIDS-related systemic NHL. G-CSF: granulocyte colony stimulating factor; OI: opportunistic infections; LBCLNH: large B cell systemic lymphoma; RT: radiotherapy; BL: Burkitt's lymphoma; CR: complete remission; PR: partial remission, NR: no response; chemoS: chemosensitive; chemoR: chemoresistant; SCT: hematopoietic progenitor transplant.

systemic NHL. With this end in mind, autologous stem cell transplantation (auto-SCT) is preferred as it has lower morbidity and mortality (approximately 5%-10%). Mortality of allogeneic stem cell transplantation (allo-SCT) is as high as 20%-30% unless non-myeloablative conditioning regimens are used, with which peritransplant mortality can be reduced to 15%. Some authors also recommend immediate auto-SCT as therapy for consolidation of NHL with poor prognostic factors and high IPI.

Pilot studies and clinical trials of auto-SCT for the treatment of NHL in HIV-infected patients are being carried out, although no long series have been published. There have been reports on short series, such as that by Gabarre et al which includes 9 patients with mediocre results, although it must be remembered that only 5 had chemosensitive tumors⁵²⁻⁵⁶. In the last 10 years, the International Bone Marrow Transplant Register (IBMTR) has received data from 25 auto-SCT, carried out by 18 different teams, for the consolidation of therapy of different hemato-oncological dise-

ases in HIV-infected patients. Of these patients, four suffered from NHL and 1 HL. With a median follow-up of 45 months, all five are alive, four in CR and 1 relapsed (report with permission of IBMTR). In Spain, some similar experience exists, but data have not yet been reported.

Hematopoietic stem cell transplantation could be used as treatment of NHL in relapse as long as the tumor is chemosensitive and the following requirements are fulfilled: good control of the HIV infection, good general health and absence of significant comorbidity (BII). The indication of auto-SCT as consolidation of treatment of NHL with a poor prognosis after having reached the first CR is a very attractive option which deserves to be explored in a pilot study. Allo-SCT, as previously mentioned, has a high mortality. Its indication would be limited to those patients in whom an auto-SCT cannot be carried out because of insufficient «mobilization» of hematopoietic progenitors.

In Spain, moreover, laws on transplants and the use of biological products from HIV-

infected patients must be taken into account. In this sense, Law 1854/1995 of 20-11-1995 (BOE 278/1995) on blood donation, which prohibits the extraction and transfusion of blood derivatives from HIV-infected patients, should be pointed out. Similarly, the Law of 24-6-1987 (BOE 167), which establishes protective measures against the transmission of HIV, prohibits the use of biological products from HIV-infected individuals. On the other hand, Royal Decree 411/1996 of 25-3-1996 (BOE 72/1996) which regulates the use of human tissue, to facilitate its use in therapy and to avoid the transmission of infectious diseases, could be interpreted in the sense that the use of hematopoietic stem cells from HIV-infected individuals would not transmit the disease to these subjects and could provide a greater therapeutic benefit if auto-SCT is

indicated because of the patient's hematological disease. As these laws are subject to possible contradictory interpretation, a new ministerial order on «health safety procedures in activities with the clinical use of organs and tissue» is to be proposed which specifically authorizes the obtainment, cryopreservation and autologous transplantation of hematopoietic growth factors in HIV-infected patients who, for medical reasons, might need them, as long as their manipulation and storage do not represent a risk for other patients.

To summarize, before recommending an SCT in an HIV-infected patient it would be wise to: a) evaluate the relevant laws; b) contact the corresponding bone marrow transplant unit, which will then establish indication (preferably in chemosensitive relapse)

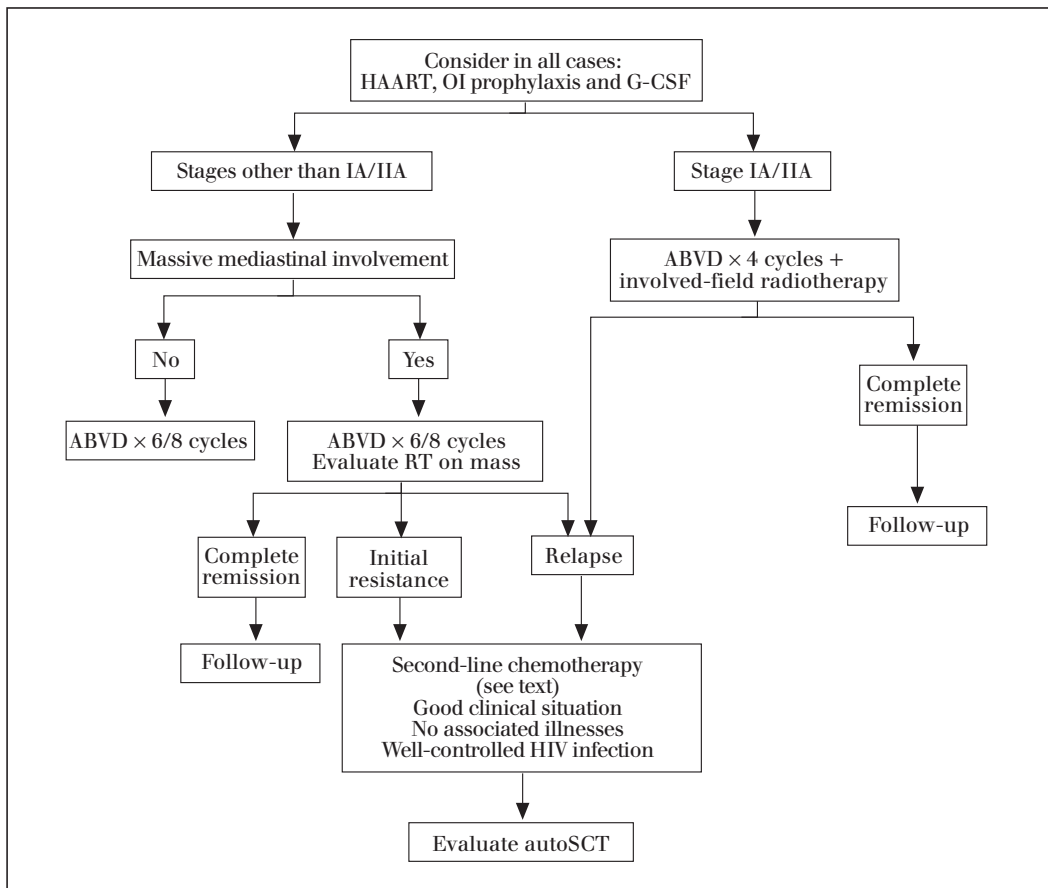


Figure 2. Treatment of AIDS-related HL. HAART: highly active antiretroviral therapy; OI: opportunistic infections; G-CSF: granulocyte colony stimulating factor; RT: radiotherapy; SCT: hematopoietic proteins transplant.

and program the regimen for the «mobilization» and storage of hematopoietic growth factors and studies up to the SCT, and c) obtain the informed consent of the patient and inform the corresponding institutional review board.

Immunotherapy

Rituximab is a chimeric IgG1κ anti-CD20 antibody with the Fab portion of murine origin and the Fc portion of human origin. This antibody is indicated for the treatment of follicular NHL (low grade) alone or in combination with CHOP⁵⁷. Studies on rituximab therapy in combination with chemotherapy for the treatment of DLBC-NHL are also being carried out. Given that about 90% of HIV-related NHL infections express antigen CD20, the use of rituximab has been considered for treatment of these tumors. To date, little information on the subject is available^{58,59}. The efficacy and safety of therapy with this antibody will be established with the results of a controlled clinical trial being carried out in the USA, in which CHOP is compared with CHOP plus rituximab as first-line therapy for DLBC-NHL, which expresses CD20 in HIV-infected patients. However, the results of a French study of approximately 400 non-HIV-infected patients over 60 with DLBC-NHL that has shown the superiority of CHOP with rituximab over CHOP with no additional toxicity⁶⁰ are encouraging. Nevertheless, for the moment, this treatment is not indicated for patients with HIV-associated NHL, unless they are included in clinical trials.

Second line treatments

There is little information on second-line treatments in HIV-infected patients. It is important to differentiate treatment of NHL in relapse from treatment of resistant NHL.

Systemic lymphoma in relapse

Relapses of systemic NHL in HIV-infected patients are frequent and the percentage of patients who remain in long-term CR does not exceed 25%. In general terms, the tumor is the cause of death in half of the patients. There is no known regimen which is efficacious for NHL in relapse; from the published data it may be concluded that some patients in first relapse achieve a second CR after a second-line treatment. When choosing a se-

cond-line treatment three points should be evaluated: the patient's quality of life (general condition and associated illnesses), previous treatment and bone marrow reserves. In patients with a good general state of health and controlled HIV infection who have previously received CHOP or EPOCH, therapy with ESHAP (etoposide, cisplatin, methylprednisolone and cytarabine) may be considered⁶¹. In any case, the results are mediocre, with CR rates of less than 30% and very short-to-medium-term survival. In those who reach CR of NHL after second-line chemotherapy, consolidation with auto-SCT may be considered. For patients in poor general condition, palliative chemotherapy with acceptable toxicity profile protocols such as VMP (etoposide, mitoxantrone and prednisone) every three weeks is recommended⁶².

Resistant systemic lymphomas

To date, few studies have been published on the treatment of HIV-related resistant NHL. In general, the prognosis is very bad and a decision should be taken as to whether to treat, to administer palliative chemotherapy or to explore experimental treatments.

Hodgkin's lymphoma in HIV-infected patients

To date, Hodgkin's lymphoma (HL) is not considered an AIDS-defining disease, despite the fact that different epidemiological studies have observed that its incidence, adjusted by sex and age, is 8 to 11 times higher among the HIV-infected population than among the general population^{1,63,64}.

Clinical aspects, diagnosis and prognosis

More than 300 HIV-infected patients with HL have been reported in southern Europe and the USA, which has allowed the clinical and biological characteristics of this population group⁶⁵⁻⁶⁹ to be defined. It is predominant in young males⁶⁵⁻⁶⁷ and it is more common in intravenous drug users⁷⁰, although it is also present in homosexuals^{71,72}. In these patients, HL usually appears in advanced stages, with B signs, frequent extraganglionic involvement and invasion of bone marrow in approximately half of the cases. Spleen

and liver involvement are also frequent^{68,74}. However, voluminous involvement of the mediastinum is rare, and invasion of the CNS is exceptional. The median CD4 lymphocyte figure at the time of diagnosis varies between 100 and 300/ μ l according to several studies and between 20% and 30% of patients have already been diagnosed with AIDS⁶⁵⁻⁶⁷.

Diagnosis of HL is histological and the REAL classification is followed for it⁶. The histology of HL has some peculiarities in HIV-infected patients: first, there is a predominance of histologic subtypes such as mixed cellularity and lymphocyte depletion^{65,67,76}. This is contrary to is the case in the general population, where lymphocyte predominance subtypes and nodular sclerosis are more common. Second, the Epstein-Barr virus genome is detected more often^{65,73}. Staging according to the Ann Arbor classification¹⁰ is important in treatment planning and establishing prognosis (table 8), although in HIV-infected patients the classic prognostic criteria⁷⁷ must be complemented by others relating to the state of the HIV infection. In the series by Tirrelli et al⁶⁵, the factors associated with prolonged survival were achievement of complete remission, absence of AIDS at the time

of HL diagnosis and a baseline CD4 lymphocyte count above 250/ μ l. A recent international study establishes a numerical index for prognostic use in cases of advanced illness. Seven factors were identified, each of which reduces the probability of controlling the illness in five years by 7%-8% (age \geq 45 years, male sex, stage IV, albumin $<$ 4 g/dl, hemoglobin $<$ 10.5 g/dl, leukocytes \geq 15,000/ μ l and lymphocytes $<$ 600/ μ l)⁷⁸. This prognostic index could also be useful in the HIV-infected patient⁷⁹.

Treatment

There is no known optimum treatment for HL in HIV-infected patients and to date no studies on chemotherapy associated with HAART have been published. Most of the published studies are retrospective and show worse results than in immunocompetent patients, with CR rate of 40%-80% of patients and a median survival of 8 to 20 months (table 9). There are very few prospective studies. Errante et al used EBV (epirubicine, bleomycin and vinblastine) together with zidovudine in 17 patients, with a reduction in dose of epirubicine and vinblastine for those with poor prognosis criteria⁸⁴. CR was 20% for the latter and 67% for the remaining patients. Median survival was 11 months. In another study a similar regimen was used with prednisone (EBVP) combined with zidovudine or didanosine and G-CSF. Toxicity was moderate and CR was achieved in 74% of patients, with a relapse rate of 38%. Median survival was 16 months⁸⁵. Levine et al used ABVD in a group of patients with advanced stage HL who had a median CD4 lymphocyte count of 128/ μ l. CR was achieved in 56% and median survival was 19 months⁷⁵.

The poor therapeutic results of HL in HIV-infected patients can be explained by the same factors mentioned in the section on NHL, i.e., poor bone marrow reserve and base immunodepression. These factors make it difficult to administer chemotherapy and condition the appearance of opportunistic infections, which may be the cause of death in between 5% and 30% of cases^{82,83}.

As previously mentioned, there is very little information on the treatment of HL with chemotherapy and HAART⁸⁶. However, the experience accumulated with NHL allows us to hope that this therapeutic strategy can increase the percentage of CR and prolong survival.

TABLE 8. Diagnosis of extension of Hodgkin's lymphoma in HIV-infected patients

Anamnesis	B signs (any of the following in a period of $<$ 5 months) Fever Excessive night sweats Over 10% weight loss above 10%.
Physical examination	Palpable adenopathies (number, size and location) Hepatomegaly and splenomegaly Visible or palpable nodules or masses
Laboratory tests	Complete blood count Biochemical tests to determine LDH, β -2 microglobulin, transaminases, bilirubin, calcium, uric acid, serum proteins and immunoglobulins Serology: HBV, HCV, CMV, <i>Toxoplasma gondii</i> and <i>Varicella zoster</i> . Determination of HIV plasma viral load CD4 lymphocyte count
Histopathology	Aspiration and biopsy of bone marrow
Imaging techniques	Chest X-ray CT of neck, thorax, abdomen and pelvis Isotopic study with gallium-67 Occasionally: ultrasound, MR, PET

HBV: hepatitis B virus; HCV: hepatitis C virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus; CSF: cerebrospinal fluid; CT: computed tomography; MR: magnetic resonance; PET: positron emission tomography

TABLE 9. Characteristics, treatment and follow-up of 247 HIV-infected patients with Hodgkin's lymphoma in eight retrospective studies

	Italy (65)	France (66)	Spain (67)	Spain (75)	USA (82)	USA (68)	USA (69)	USA (85)
Number of patients	71	45	46	15	24	25	13	10
Median age	28	30	27	35	34	34	38	38
Stages III-IV (%)	80	75	89	73	92	74	92	90
B signs (%)	82	80	83	86	96	70	85	80
Previous AIDS (%)	16	11	7	20	0	22	46	30
No treatment	12	1	5	1	0	5	0	0
MOPP ± RT	22	13	6	4*	11	10	0	2
ABVD ± RT	5	14	4	2	5	1	0	0
MOPP + ABVD ± RT	19	14	21	7*	5	2	12	8
RT	7	5	3	1	0	6	1	0
Other chemo regimens	6	0	9		5	1	0	0
CR (%)	55	79	44	50	63	53	54	57
Median survival (months)	14	20	15	26	15	8	14	NR

MOPP: methochlorethamine, vincristine, procarbazine, prednisone; ABVD : doxorubicin, bleomycin, vinblastine, dacarbazine; RT: radiotherapy; CR: complete remission; NC: not collected. *Methochlorethamine was substituted by cyclophosphamide.

Practical recommendations for treatment

Advanced-stage disease

We understand as such stages III and IV and the existence of B signs, which make up more than 90% of cases in HIV-infected patients. In these cases the same regimens as in immunocompetent patients are recommended, such as ABVD (6 to 8 cycles) (AII). This regimen has several advantages: it does not contain glucocorticoids, it has a lower incidence of second neoplasias and lower gonadal toxicity. Furthermore, there is no cross-resistance between ABVD and MOPP (methochlorethamine, vincristine, procarbazine and prednisone) if a second therapeutic alternative is necessary. Other regimens that can also be used are MOPP or COPP derivatives (cyclophosphamide, vincristine, procarbazine and prednisone) or the MOPP/ABV mixed regimen^{81,75}. It is essential to guarantee adequate intensity of cytostatic doses, especially when there is frequent invasion of bone marrow.

Early-stage disease

This corresponds to stages IA and IIA with no voluminous illness, which occurs in fewer than 10% of cases in these patients. The recommended treatment is the same as in immunocompetent patients: four cycles of ABVD at full doses followed by involved-field radiotherapy (AII)⁸⁷.

Massive mediastinal involvement

This is an uncommon situation in these patients. Combined modality therapy with ABVD at 6 or 8 cycles and involved-field radiotherapy is recommended (as in advanced illness) (AII)⁸⁸.

Treatment of relapses

Before HAART, tumoral relapse was reported in more than 30% of patients who achieved CR. Treatment in these cases must be based on the same principles as in immunocompetent individuals: if the relapse occurs after the first year of CR, the same regimen of initial chemotherapy can be used although long-term survival is only 25% to 50% (AII). If there is good control of the HIV infection and there are no severe associated illnesses, the patient should be considered a candidate for auto-SCT (BII)⁵⁶. When the relapse takes place during the first year after CR, a chemotherapy regimen with no cross-resistance with the previous regimen should be chosen. If ABVD was used, MOPP or derivatives are possible (AIII). In these cases, the optimal strategy (if patient circumstances permit) involves achieving a second CR and later consolidating the treatment with auto-SCT (BII).

Treatment of resistant HL

There is no information on the ideal treatment of HIV-infected patients with HL who do not achieve CR after first line chemotherapy. In immunocompetent individuals, the possibilities of cure are minimal if SCT, which

achieves prolonged CR in 10%-20% of cases, is not used.

Hematopoietic growth factors

Their use is justified to guarantee adequate intensity of the chemotherapy dose^{75,85}. G-CSF is preferred for reasons already mentioned in the section on NHL.

Prophylaxis of opportunistic infections

The same recommendations as for NHL should be followed⁴⁸.

Administration of HAART during chemotherapy

There is very little data on the treatment of HL with chemotherapy and HAART⁵⁶. However, it would seem reasonable to follow the recommendations put forward in the section on NHL⁵⁴⁻⁵⁸.

AIDS-associated primary central nervous system lymphoma

PCNSL is a tumor limited to the craniospinal axis with no systemic involvement. Its incidence increased dramatically with AIDS although it later dropped drastically after the introduction of HAART^{89,90}. Most PCNSL are aggressive phenotype B NHL and the most frequent is the immunoblastic subtype^{91,92}. To date, the prognosis of these tumors without treatment has been very bad, with a median survival of 1 to 3 months. With specific treatment survival varies between 3 and 18 months. At present, there are two aspects of PCNSL which deserve consideration: the diagnostic procedure of choice after incorporation of new isotopic and molecular biology techniques and the most suitable antitumor treatment in the HAART era.

Clinical manifestations

PCNSL is usually present in patients with severe immunodepression with CD4 counts generally below 50/ μ l and in a third of the cases it is the AIDS-defining disease⁹⁵. Almost 50% of patients present non-focal encephalopathic symptoms. In the remainder, the initial symptoms are focal neurological deficits, stemming from intracranial hypertension, or seizures. Cerebellar symptomatology is less frequent and spinal cord alterations are exceptional.

Diagnosis

There is no specific sign or symptom of PCNSL and it is necessary to establish a differential diagnosis with other tumoral or infectious entities, especially with cerebral toxoplasmosis. When a patient with HIV infection presents neurologic symptomatology, neuroimaging together with CD4 count and serology for *Toxoplasma gondii* must be performed.

Cranial CT

This is the most common initial diagnosis technique, although it is sometimes not very sensitive. PCNSL images cannot be distinguished from those of toxoplasmosis in CT. In the first case, single, larger-sized lesions predominate. In general, these are necrotic masses, which are occasionally hemorrhagic, poorly delimited with irregular edges and a variable mass effect, peritumoral edema and contrast enhancement (50% in ring formation). Furthermore, the location of the lesions in the CNS does not allow PCNSL to be differentiated from cerebral toxoplasmosis. However, most PCNSL lesions (75%) are found in supratentorial structures. Lesions characteristically infiltrate deep in cerebral structures such as the periventricular regions, the thalamus, the basal ganglia and the corpus callosum. There may also be involvement of peripheral regions of the cerebral hemispheres^{94,95}.

Cranial MR

MR is more sensitive than CT for detection of small lesions and defines lesions located in the leptomeninges or in the spinal cord better. However, cranial MR studies have not shown greater specificity than cranial CT for the definitive diagnosis of PCNSL.

In recent studies with dynamic MR for the evaluation of gadolinium uptake velocity in certain cerebral lesions, it has been observed that PCNSL uptake kinetics in T1 sequences is faster and more intense (up to three times) than that of toxoplasmosis. Another diagnostic method, not yet widespread, is MR spectroscopy (MRS), which allows us to compare the spectrum of the lesion with that of healthy tissue, by identifying peaks of biochemical metabolites characteristic of certain illnesses. Undoubtedly, these techniques will improve the future diagnostic yield of MR^{96,97}.

Cranial PET and SPECT

Nuclear medicine techniques such as SPECT (single photon emission CT) with thallium 201 and PET (positron emission tomography) obtain better specificity for establishing a differential diagnosis. Studies of SPECT with thallium 201 carried out in patients with PCNSL show an uptake of lesions owing to an active transport of thallium 201 within neoplastic cells. This is not the case in cerebral toxoplasmosis. The limitations of SPECT with thallium 201 are that it does not detect lesions under 6 mm, leptomeningeal lesions, or those close to the base of the cranium or the cranial vault. Furthermore, glucocorticoids can stabilize uptake of thallium. SPECT has 75% sensitivity and 97% specificity. The authors believe that a positive SPECT would be indicative of an early stereotactic brain biopsy. Other studies have improved the diagnostic yield of the technique using evaluation of the early or late uptake and calculation of the thallium retention index^{98,99}. PET is a technique which uses metabolites such as 18 fluoro-deoxy-D-glucose (FDG), which is taken up by the cells with greater metabolic activity and a higher consumption of energy, such as tumoral cells, thus allowing differentiation between tumoral and infectious processes. PET seems to have a sensitivity of 89% and 100% specificity^{100,101}.

Analysis of CSF

Analysis of CSF can assist in the diagnosis of PCNSL, and should therefore be carried out, as long as it does not represent a risk to the patient. When there is meningeal or periventricular involvement, tumor cells can be identified in CSF in up to 20% of cases. Immunohistochemical techniques, in situ hybridization or polymerase chain reaction (PCR) can show neoplastic monoclonal lymphocyte populations and EBV genome sequences in the nucleus of these cells. These techniques have a sensitivity of 100% and a specificity of 98%⁹⁹. Some studies have observed a good diagnostic correlation between stereotactic brain biopsy and PCR for EBV in CSF¹⁰⁵. Semiquantitative PCR for EBV has also been used to monitor the response to treatment¹⁰⁴.

Stereotactic brain biopsy

Stereotactic brain biopsy, when carried out by experienced teams, has a high rate of defi-

nitive histological diagnoses (96%) and very few complications^{105,106}. This diagnostic technique should be carried out where possible.

Practical recommendations

HIV-infected patients with space-occupying lesions in the CT or MR must have *Toxoplasma* serology and a CD4 count. Several situations may be advanced.

1. If there is only one lesion or *Toxoplasma* serology is negative, a SPECT or PET should be carried out. In the absence of contraindications, a lumbar puncture test should be performed with examination of cerebro-spinal fluid by cytocentrifugation and PCR for EBV. In general, positive isotopic techniques should accelerate the performance of a biopsy, although the total of positive tests which indicate PCNSL (including cytology and/or PCR) may obviate brain biopsy in some cases. It is important to remember that when diagnosis is uncertain, empirical antitoxoplasma therapy must be administered.
2. When there are many lesions and *Toxoplasma* serology is positive, empirical antitoxoplasma therapy must be administered for two weeks. If, after this period, there is resolution or improvement of symptoms and it can be radiologically verified that the size of the lesions has decreased, a diagnosis of cerebral toxoplasmosis may be assumed. Otherwise, a stereotactic brain biopsy must be performed as soon as possible. This procedure is justified by the fact that, on the one hand, toxoplasmosis is the most common brain lesion in AIDS patients, curable in more than 75% of cases and, on the other, a delay in diagnosis of PCNSL can negatively influence the response to therapy and the survival of the patient.

Treatment

Radiotherapy

Radiotherapy has been the treatment of choice for PCNSL although, as previously indicated, results have not been good as there is usually local relapse of the tumor. The optimal dose of radiotherapy for the treatment

of PCNSL in AIDS patients is not well established. Some authors feel that the response to treatment does not depend so much on the dose of radiotherapy administered as on the general health status of the patient. In a patient with a generally acceptable status and immunological condition that is likely to improve with antiretroviral treatment, radical treatment may be attempted. In these cases, if there is only one lesion, it is considered suitable to begin by irradiating a holocranial volume (4,000 cGy in fractionation schedules of 200 cGy) and to proceed to irradiation of the tumor with the same fractionation schedule up to a dose of 5,000-5,400 cGy. If on the other hand there are several lesions, 4,000-4,600 cGy can be administered to the whole holocranial mass, with fractionation schedules of 180-200 cGy/day. In patients having poor general status or irreversible immunological alteration, palliative therapy on the holocranial mass with doses of 3,000 cGy in 10 fractions would be appropriate¹⁰⁷.

Chemotherapy

The poor response to radiotherapy has led to consideration of other forms of treatment. Various studies with PCNSL using combined radiotherapy and chemotherapy have been carried out on non-HIV-infected patients¹⁰⁸⁻¹¹¹. In general, a prolonged median survival is obtained with such a combined modality therapy. The most commonly used drugs are methotrexate and/or cytosine arabinoside combined with glucocorticoids. The current trend in the treatment of this tumor in non-HIV-infected patients is the use of systemic chemotherapy to avoid the neurotoxicity of chemoradiotherapy, reserving radiotherapy for salvage therapy of tumor relapse^{112,115}.

There is very little information on combined modality therapy in patients with PCNSL and AIDS. In one study, a discreet improvement in survival was observed with methotrexate, thiotepa and procarbazine followed by radiotherapy (3,000 to 4,400 cGy), although most patients had responded to chemotherapy before starting radiotherapy¹¹³. Information on treatment with chemotherapy only is very scarce. In one prospective study, 15 patients were treated with high doses of methotrexate (3 g/iv every 14 days, maximum 6 cycles), salvage with folinic acid, glucocorticoids and G-CSF¹¹⁴. Median survival (290 days) has been the longest reported to date. However, this study was

later questioned since not all diagnoses were confirmed by histology¹¹⁵.

Finally, it is worth mentioning a study carried out on the basis of the apoptosis inducer effect of zidovudine in B-cell lines infected by EBV, an effect which is boosted by ganciclovir. Five patients were treated with zidovudine, ganciclovir and interleukin 2. Response was good in four cases with survival of up to 22 months¹¹⁶.

Highly active antiretroviral therapy

As previously mentioned, HAART has modified the natural history of AIDS-associated PCNSL, by acting prophylactically on the development of the tumor. There are some data that suggest a beneficial therapeutic effect of HAART on established PCNSL. For example, in a recent report, significantly higher survival was observed in patients with PCNSL treated with radiotherapy and HAART than in historic controls who had received radiotherapy only¹¹⁷. There have even been reports of cases of remission of PCNSL with HAART associated or not with a short cycle of glucocorticoids^{118,119}.

Practical recommendations

Any HIV-infected patient with PCNSL should receive HAART (AII). Those in good health and in whom immunological improvement with antiretrovirals is possible should consider themselves eligible for some of the regimens of chemotherapy designed for this tumor. Depending on the response to chemotherapy, radiotherapy should be evaluated as adjuvant therapy or as a rescue therapy after progression or relapse. If the patient's clinical and immunological situation is poor, radiotherapy is still a powerful therapeutic weapon to palliate the symptoms. In some cases this allows radiological and clinical responses which prolong survival and improve quality of life (BII).

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