

Prognosis of AIDS-Related Systemic Non-Hodgkin Lymphoma Treated With Chemotherapy and Highly Active Antiretroviral Therapy Depends Exclusively on Tumor-Related Factors

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of Systemic AIDS-Related Lymphomas

Objectives: To assess complete remission (CR) and survival in patients with systemic AIDS-related non-Hodgkin lymphoma (ARL) receiving highly active antiretroviral therapy (HAART).

Methods: We analyzed the *Grupo de Estudio del SIDA* register of systemic ARL, which started in Jan 1994, to collect cases diagnosed at 15 institutions prospectively and with active follow-up every 6 months. The date of censorship for this study was March 2005.

Results: During the study period, 210 consecutive patients were diagnosed with ARL, with a median age 39 of years, 75.7% of whom were male, and with a median baseline CD4 count of 160 cells/ μ L. Histologic subtypes were diffuse large B-cell lymphoma (DLCL; n = 153 [72.9%]), Burkitt and atypical Burkitt/Burkitt-like lymphoma (BL; n = 40 [19.0%]), T-cell lymphoma (TC; n = 8 [3.8%]), and miscellaneous (n = 9 [4.3%]). Chemotherapy with or without other modalities was administered to 186 (88.6%) patients. In an intent-to-treat analysis of 184 patients who received at least 1 chemotherapy course with adequate follow-up to assess their response, 119 (64.7%) achieved CR, and the median length of survival (Kaplan-Meier analysis) was 52 months (95% confidence interval [CI]: 23 to 82 months). Factors independently associated with CR were histologic subtype and International Prognostic Index (IPI) score. Factors independently associated with improved overall length of survival (OS) were CR, low IPI score, and histologic subtype. The single

factor independently associated with disease-free survival was Ann Arbor stage.

Conclusions: In patients with ARL treated with HAART, CR was associated exclusively with tumor-related factors. The CR rate was poorer in patients with BL and TC subtypes and was inversely correlated with IPI score. OS was independently associated with CR, IPI score, and the histologic subtype.

Key Words: Burkitt lymphoma, highly active antiretroviral therapy, lymphoma, AIDS-related, lymphoma, large-cell, diffuse, lymphoproliferative disorders

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Systemic non-Hodgkin lymphoma was included in the list of AIDS-defining diseases in 1985.¹ Before the introduction of highly active antiretroviral therapy (HAART), AIDS-related non-Hodgkin lymphoma (ARL) was the second most frequent tumor after Kaposi sarcoma (KS) in HIV-infected patients. Its prevalence was 3% to 5%, and it caused 12% to 16% of deaths in these patients.^{2,3}

Shortly after the introduction of HAART, morbidity and mortality declined sharply among patients with advanced HIV infection.⁴ The incidence of KS and primary brain lymphoma also declined,⁵ although no substantial reductions in rates of systemic ARL were observed.^{6,7} Moreover, in the early years of HAART, the number of systemic ARL cases as an AIDS-defining condition increased in comparison with the pre-HAART era.^{8–10} Recent analysis of different cohorts has shown, however, that the incidence of systemic ARL among HIV-infected patients has decreased significantly since the introduction of HAART.^{11–13} In one study, the decreased incidence of ARL was associated with an overall decrease in the number of patients with low CD4⁺ cell counts, which suggests that the incidence of systemic ARL depends on the effectiveness of HAART in improving the immune status of the HIV-infected population.¹³

Before the introduction of HAART, treatment of systemic ARL was complicated by underlying immunosuppression, opportunistic infections, and poor bone marrow

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reserve. Consequently, the prognosis of these patients was poor.^{14–18} Several studies comparing outcomes of ARL before and after the introduction of HAART clearly reveal the beneficial effect of HAART on the response to chemotherapy in this type of tumor, however.^{19–24}

The response of systemic ARL to chemotherapy in patients receiving HAART is no longer determined by the fatal course of advanced and untreated HIV infection. For this reason, and to improve the care of HIV-infected patients with this severe complication, it is important to analyze the therapeutic response and prognostic factors of patients with ARL treated with HAART. In this report, we analyzed data from a large national register of patients with systemic ARL to assess survival, therapeutic response, and prognostic factors in patients with systemic ARL receiving HAART.

METHODS

The patients in this study came from the register of systemic ARL of the *Grupo de Estudio del SIDA* (GESIDA) of the *Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* (SEIMC), which started to collect cases diagnosed at 15 institutions in Spain prospectively in January 1994, with active follow-up every 6 months and information about survival, ARL status, and HIV status. At each institution, the research team was composed of at least a clinician and a pathologist who reviewed the tissue sections and classified the ARL according to the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues.²⁵

From 1994 through 2002, the information was collected on forms and sent by telefax or regular mail from each center to the GESIDA Clinical Trials Agency, where it was entered into a database. From 2002 to censorship, the information was entered directly into the database at each institution by means of an ad hoc online application that satisfied local requirements of data confidentiality.

For the purpose of this study (GESIDA 4003 Study), we analyzed the 210 patients with confirmed HIV infection and histologically proven systemic ARL who had been treated with HAART within the 6 months before and/or after the diagnosis of ARL. The date of censorship for this study was March 2005. For each patient, we extracted the following demographic and HIV data from the central database: age, gender, HIV transmission category, prior AIDS-defining conditions, baseline and nadir CD4⁺ cell counts, and baseline HIV viral load. We also recorded information about HAART, including type, date of initiation, and whether or not it was maintained during the treatment of non-Hodgkin lymphoma (NHL), and *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis. We also recovered the following ARL data: histology subtype, Ann Arbor stage, presence of B symptoms, number of extranodal sites involved, serum lactate dehydrogenase (LDH), bone marrow involvement, cerebrospinal fluid (CSF) involvement, and International Prognostic Index (IPI) score.²⁶ Treatment-related data were type of chemotherapy (if any), including the number of cycles and whether or not dose reduction was used. We also recorded the use of central nervous system (CNS) prophylaxis, radiotherapy, anti-CD20 monoclonal antibody (rituximab), and autologous stem cell

transplantation. The main outcome variables were complete remission (CR), defined as the lack of evidence of ARL lasting for at least 4 weeks; overall length of survival (OS), defined as the time from the diagnosis of ARL to death or to the date when the patient was last seen; and disease-free survival (DFS), defined as the period from CR to relapse.²⁷

Outcomes and prognostic factors of CR, OS, and DFS were assessed by an intention-to-treat (ITT) analysis of all patients who received at least 1 chemotherapy course. Univariate analysis of the association of the different variables with CR, OS, and DFS was performed by means of χ^2 , Student *t*, and Mann-Whitney *U* tests as appropriate. Prognostic factors of CR were identified by multivariate logistic regression analysis. OS and DFS were analyzed by Kaplan-Meier plots and Cox regression analyses.

RESULTS

A total of 210 patients with systemic ARL treated with HAART were included in the present study. The demographics and HIV-related characteristics are shown in Table 1. In brief, 76% of the patients were male, their median age was 39 years, 54% acquired HIV infection by intravenous drug use, 37% had had a prior AIDS-defining condition, the median CD4⁺ count at the diagnosis of ARL was 160 cells/ μ L, and the median HIV RNA viral load was 68,189 copies/mL. HAART and PCP prophylaxis details are shown in Table 1.

The predominant histologic subtype was diffuse large B-cell lymphoma (DLCL) in 73% of patients according to the morphology code of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (WHO ICD-O code 9680/3), followed by Burkitt and atypical Burkitt/Burkitt-like lymphoma (BL) in 19% (WHO ICD-O code 9687/3). Other data in relation to ARL, such as Ann Arbor stage and IPI score, are shown in Table 2.

Details of ARL treatment are shown in Table 3. A total of 186 (88.6%) of 210 patients received chemotherapy alone or in combination with another therapeutic modality such as radiotherapy, immunotherapy, or autologous stem cell transplantation. The most frequently used chemotherapy regimen was cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), followed by CHOP-rituximab and etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH). CNS prophylaxis was administered to 50% of the patients.

A total of 119 (64.7%) of 184 patients who received at least 1 chemotherapy course and adequate follow-up to assess response achieved CR. Of the patients who achieved CR, 19 (16.0%) relapsed a median of 9.9 months later (interquartile range [IQR]: 2.3–16.2 months). The median OS was 51 months (95% confidence interval [CI]: 19 to 83 months), and the 5-year OS was 46% (95% CI: 39% to 54%). The median DFS was not reached, and the 5-year DFS was 81% (95% CI: 67% to 95%).

Univariate analysis showed that the variables associated with CR were histologic subtype (BL and T-cell [TC] vs. DLCL and miscellaneous), B symptoms, serum LDH greater than normal, Eastern Cooperative Group (ECOG) score, Ann Arbor stage, number of extranodal sites involved (0–1 vs. ≥ 2),

TABLE 1. Patient Characteristics and HIV-Related Data

Characteristic	N = 210 Patients
Age (y) (median, IQR)	39 (36–45)
Male gender	159 (75.7)
HIV acquired by IDU	113 (53.8)
Prior AIDS	78 (37.1)
CD4 ⁺ count at diagnosis, cells/μL (median, IQR)	160 (72–263)
Type of HAART	
PI-based	158 (75.2)
NNRTI-based	36 (17.1)
PI plus NNRTI-based	13 (6.2)
Triple NRTI	3 (1.4)
HAART during chemotherapy	160 (76.2%)
PCP prophylaxis	
Yes	182 (86.7)
No	28 (13.3)

IDU indicates intravenous drug use; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

and IPI score. Variables not associated with CR were age, gender, HIV transmission category, prior AIDS, baseline and nadir CD4⁺ cell counts, HIV viral load, PCP prophylaxis, bone marrow involvement, CSF involvement, presence of bulky tumor, radiotherapy, immunotherapy, and CNS prophylaxis.

TABLE 2. NHL-Related Data

NHL Characteristics	N = 210 Patients
Histology	
DLCL*	153 (72.9)
BL†	40 (19.0)
TC‡	8 (3.8)
Miscellaneous	9 (4.3)
Ann Arbor stage	
I	51 (24.3)
II	25 (11.9)
III	23 (11.0)
IV	108 (51.4)
Unknown	3 (1.4)
Bone marrow involvement	
Yes	56 (26.7)
No	130 (61.9)
Unknown	24 (11.4)
CNS involvement	
Yes	16 (7.6)
No	119 (56.7)
Unknown	75 (35.7)
IPI score	
0–1	79 (36.7)
2	47 (22.4)
3	47 (22.4)
4–5	37 (17.6)

*Morphology Code of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (WHO ICD-O code 9680/3).

†WHO ICD-O code 9687/3.

‡WHO ICD-O codes 9714/3, 97021/3, and 9705/3 (see reference 25).

TABLE 3. Details of NHL Treatment

NHL Treatment	No. (%)
Type of treatment	N = 210
Chemotherapy ± other modalities*	186 (88.6)
Radiotherapy and/or surgery	8 (3.8)
None	16 (7.6)
Chemotherapy regimen	N = 186
CHOP	131 (70.4)
CHOP + rituximab	14 (7.5)
EPOCH	13 (7.0)
Burkitt regimens	12 (6.4)
M-BACOD	5 (2.7)
Other	11 (5.9)
Dose reduction	N = 186
No	148 (79.56)
Yes	36 (19.35)
Unknown	2 (1.08)
CNS prophylaxis†	N = 186
Yes	93 (50.0)
No	93 (50.0)

*Radiotherapy (n = 25), immunotherapy (n = 12), and stem cell transplantation (n = 5).

†In most cases, 30 mg of cytosine arabinoside, 12 mg of methotrexate, and 20 mg of hydrocortisone.

Factors independently associated with CR by logistic regression analysis were histologic subtype and IPI score (see Table 4).

In March 2005, 13 (6.2%) patients had been lost to follow-up, 91 (43.3%) patients remained alive, and 106 (50.5%) patients had died: 71 (33.8%) as a result of ARL, 8 (3.8%) as a result of AIDS-related conditions, and 27 (12.9%) as a result of other conditions.

Univariate analysis showed that the variables associated with OS were histologic subtype, B symptoms, serum LDH greater than normal, performance status (ECOG score), Ann Arbor stage, IPI score, bone marrow involvement, and radiotherapy. Variables not associated with OS were age, gender, HIV transmission category, prior AIDS, baseline and nadir CD4⁺ cell counts, HIV viral load, PCP prophylaxis, number of extranodal sites involved, CSF involvement, presence of bulky tumor, immunotherapy, and CNS prophylaxis. Factors independently associated with OS, by Cox regression analysis, were CR, IPI score, and histologic subtype (Table 5; Figs. 1 and 2).

Univariate analysis showed that the following variables were associated with DFS: gender, B symptoms, Ann Arbor stage, extranodal sites, and IPI score. Variables not associated with DFS were age, HIV transmission category, prior AIDS, baseline and nadir CD4⁺ cell counts, HIV viral load, PCP prophylaxis, histologic subtype, serum LDH greater than normal, ECOG score, bone marrow involvement, CSF involvement, presence of bulky tumor, radiotherapy, immunotherapy, and CNS prophylaxis. The only factor independently associated with DFS, by Cox regression analysis, was Ann Arbor stage; the hazard ratio (HR) of relapse for Ann Arbor stages III through IV versus stages I through II was 6.0 (95% CI: 1.7 to 20.8).

TABLE 4. Factors Independently Associated With CR*

Variable	OR of Not Achieving CR	95% CI
Histologic subtype BL, TC	2.9	(1.3 to 6.6)
IPI score		
0-1	1	
2	3.8	(1.5 to 10.1)
3	5.8	(2.2 to 14.7)
4-5	15.8	(5.3 to 47.6)

*By ITT analysis of 184 patients who received at least 1 chemotherapy course and adequate follow-up to assess response.
OR indicates odds ratio.

DISCUSSION

This study reports the findings of a prospective cohort of 210 patients with ARL treated with HAART and cared for in 15 clinical centers in Spain. DLCL was the histologic subtype in 73%, and BL was the histologic subtype in 19%. In an ITT analysis of 184 patients treated with at least 1 chemotherapy course (CHOP in 70%) and with adequate follow-up to assess their response, the CR was 64.7%. The median OS was 51 months, and the 5-year predicted OS was 46%. The median DFS was not reached, and the 5-year predicted DFS was 81%. Outcome was associated exclusively with tumor-related factors. The CR rate was poorer in patients with BL and TC subtypes and was inversely correlated with IPI score. Factors independently associated with OS were CR, low IPI score, and histologic subtype. The only factor independently associated with DFS was Ann Arbor stage.

Before the introduction of HAART, the rate of CR in combination chemotherapy in ARL was approximately 50% and the median length of survival was only 5 to 9 months.¹⁴⁻¹⁸ These poor results were attributable to the high tumor burden, the ultimately fatal course of advanced and untreated HIV infection, the deleterious effects on host defense mechanisms of cytotoxic chemotherapy, and the poor bone marrow reserve characteristic of patients with AIDS. In a randomized clinical trial that compared low-dose versus standard-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) chemotherapy for ARL, the absolute CD4⁺ cell count was found to be the most important predictor of survival. In fact, when patients were grouped

TABLE 5. Factors Independently Associated With OS*

Variable	HR of Death	95% CI
IPI score		
0-1	1	Reference
2	1.5	(0.8 to 2.7)
3	4.4	(2.4 to 8.0)
4-5	3.4	(1.8 to 6.5)
No CR	17.7	(9.8 to 31.9)
Histologic subtype BL, TC	1.8	(1.2 to 2.9)

*By ITT analysis of 184 patients who received at least 1 chemotherapy course and adequate follow-up to assess response.

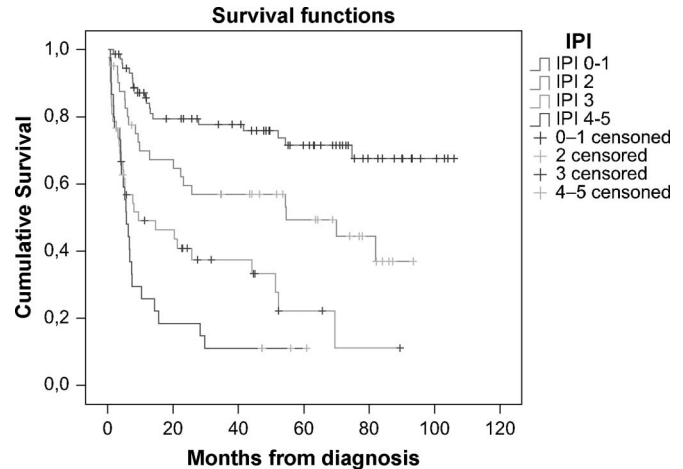


FIGURE 1. OS according to IPI score.

according to the CD4⁺ cell count, longer survival was linked to higher CD4⁺ cell counts but not to the type of treatment.¹⁸

The introduction of HAART was a turning point in the management of ARL. To date, studies that have analyzed the effect of HAART on the response to chemotherapy of systemic ARL in patients with AIDS have shown a beneficial effect in terms of achievement of CR and in survival.¹⁹⁻²⁴ Some of these studies also analyzed prognostic factors for survival; variables associated with increased survival other than HAART have included full doses of chemotherapy,¹⁹ B symptoms,²² achievement of CR, prior AIDS and extranodal involvement,²⁰ and prior AIDS and bone marrow involvement.²¹ One article that specifically addressed prognostic factors in DLCL before and after HAART included 192 patients (120 before HAART and 172 after HAART); factors independently associated with decreased length of survival were increasing IPI scores and failure to attain CR, whereas a CD4⁺ count <100 cells/μL predicted shorter survival only in the pre-HAART era.²⁸

Nowadays, almost all patients with ARL receive HAART, and it is important to define the prognostic factors that are exclusive to this population. In this regard, our work clearly shows that CR and survival are no longer influenced by HIV-related factors; rather, they rely exclusively on tumor-related factors. Our data clearly show that the CR rate

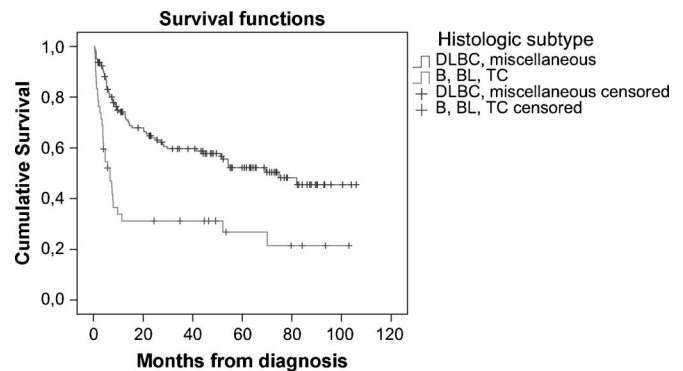


FIGURE 2. OS according to histologic subtype.

was poorer in patients with BL and TC subtypes and that it was inversely correlated with IPI score. We also found that OS was independently associated with CR, IPI score, and histologic subtype.

The IPI is a well established score for stratifying risk in DLCL among the general population.²⁶ Our study shows that the IPI can be used to define risk in ARL as it is used outside the context of AIDS. Other authors have also reported on the utility of this prognostic index for systemic ARL. In a single center study with 111 ARL patients treated with HAART and different chemotherapy regimens, the independent factors that predicted death were IPI score and CD4⁺ cell count.²⁹ In another study, IPI score was also independently associated with the failure to attain CR and decreased survival.²⁸ Interestingly, in the latter study, a CD4⁺ count <100 cells/ μ L predicted shorter survival only in the pre-HAART era.²⁸

The finding that treatment response is particularly poor for those patients with DLCL and an IPI score higher than or equal to 3 emphasizes the need to explore more effective treatments for these patients. Out of the context of AIDS, the addition of rituximab to standard chemotherapy has improved the response of DLCL.^{30,31} In HIV-infected patients with DLCL, the addition of rituximab probably improves the therapeutic response, although there are some caveats regarding its safety because of the increase in infectious complications, particularly in patients with profound immunosuppression.^{23,32} Another potential approach for patients with systemic ARL of the DLCL subtype and poor prognostic factors is the use of autologous stem cell transplantation, a procedure that has been found to be feasible, safe, and efficacious in this setting.³³⁻³⁶

An important issue in the HAART era is the appropriate management of patients with BL. As our study shows, the prognosis of patients with this histologic subtype is worse than that of patients with DLCL, an observation found by other authors. For example, in a clinical trial that compared reduced CHOP versus full-dose CHOP in which all patients also received HAART, patients with BL had a lower likelihood of achieving CR than patients with DLCL, independent of whether full-dose or reduced CHOP was used.³⁷ In another study that analyzed outcomes in a large cohort of patients with AIDS-related BL and DLCL treated with CHOP or M-BACOD in the pre-HAART versus HAART eras, the overall median survival in the pre-HAART era was similar for both groups, whereas in the HAART era, it was significantly worse in patients with BL.³⁸ In that study, failure to attain CR and a CD4⁺ count <100 cells/mm³ independently predicted poor survival in the pre-HAART era. The BL subtype and no attainment of CR were independent poor prognostic factors in the HAART era, however.³⁸

In the general population, the standard regimens for DLCL have had poor results with BL subtypes. Nevertheless, experience over the last 3 decades with regimens that include non-cross-resistant cytotoxic agents and with intensive CNS penetration and intrathecal prophylaxis, such as cyclophosphamide, doxorubicin, and high-dose methotrexate (CODOX-M) alternating with ifosfamide, etoposide, and high-dose cytarabine (IVAC),³⁹⁻⁴¹ hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD),⁴² and others,⁴³ has resulted in a marked improvement in the prognosis

of BL in HIV-negative patients. The results of recent studies suggest that the addition of the monoclonal antibody rituximab may increase the efficacy of these regimens without increasing toxicity.⁴⁴

There are no well-designed clinical trials on such treatments for BL in patients with HIV infection, although in the HAART era, these patients may benefit from these intensive regimens. To date, few studies have explored the efficacy and safety of intensive chemotherapy regimens for the treatment of BL in HIV-infected patients. Cortes et al⁴⁵ investigated the use of the hyper-CVAD regimen in 13 HIV-infected patients with BL, 9 of whom also received HAART. The CR rate was 92%, although the median length of survival was only 12 months. It is noteworthy that 6 of 7 patients who received HAART were alive and in CR after a median of 29 months, whereas the 4 patients who did not receive HAART subsequently died. Toxicity in patients with HIV was similar to that reported in non-HIV-infected patients treated with the same regimen. In a second study, the clinical outcome of an intensive regimen (CODOX-M/IVAC) in 14 HIV-infected patients with BL was compared with the clinical outcome of 24 concomitantly treated HIV-negative patients with BL. CODOX-M/IVAC was associated with improved DFS in all patients, particularly those with high-risk factors. Of note, HIV-positive patients tolerated chemotherapy well, with rates of bone marrow suppression and infectious complications similar to those of HIV-negative patients.⁴⁶ In a third study carried out in Spain in 53 adult BL patients treated with the Programa para el Estudio de la Terapéutica en Hemopatía Maligna-Acute Lymphoblastic Leukemia Protocol 3/97 (PETHEMA-LAL3/97) regimen, 14 (28%) of whom were infected with HIV, there were no differences in CR rates between HIV-negative (77%) and HIV-positive (71%) patients, and the OS of HIV-negative and HIV-positive patients did not differ significantly.⁴⁷ In a follow-up analysis to elucidate the role of HAART in the survival of HIV-infected patients included in the PETHEMA-LAL3/97 protocol, patients receiving HAART seemed to have a slightly better DFS than those who were not.⁴⁸ All these studies show the feasibility of chemotherapy regimens for the treatment of BL in individuals with HIV infection.

We can draw several conclusions that are relevant for clinical practice. First, in ARL patients treated with HAART, the therapeutic response depends exclusively on tumor-related factors and not on HIV-related factors. Second, the IPI should be used to define risk in ARL as it is used outside the context of AIDS. Third, treatment response is particularly poor for those patients with DLCL and an IPI score higher than or equal to 3 and for those patients with BL. These findings emphasize the need to explore more effective treatments for these groups of patients.

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APPENDIX

Other members of the GESIDA register of systemic AIDS-related lymphomas include the following: Site Principal Investigators—M. L. Montes, J. Torre-Cisneros, V. Boix, F. Gutiérrez, G. Peralta, and M. A. Sepúlveda; and Associated Investigators—A. Antela, J. R. Arribas, J. Arrizabalaga, E. Bernal, C. Cepeda, J. Cosín, H. Esteban, V. Estrada, M. García-Lázaro, J. González-García, J. González-LaHoz, J. C. López Bernáldo-de-Quirós, J. López-Aldeguer, M. Marquez, J. L. Mate, J. Menárguez, E. Merino, V. Moreno, V. Moreno-Celda, M. J. Muruzábal, J. T. Navarro, J. I. Olalla, R. Palacios, J. L. Patier, J. Portilla, F. Pulido, A. Rivero, M. Salavert, D. Serrano, J. Vergas, and M. A. Von Wichmann.