

Results of treatment with doxorubicin, bleomycin, vinblastine and dacarbazine and highly active antiretroviral therapy in advanced stage, human immunodeficiency virus-related Hodgkin's lymphoma

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ABSTRACT

Background and Objectives

Although doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is considered the standard chemotherapy regimen for Hodgkin's lymphoma (HL), information on the results of this therapy in human immunodeficiency (HIV)-related HL is scarce. We analyzed the results of the ABVD regimen and highly active antiretroviral therapy (HAART) in patients with advanced stage, HIV-related HL.

Design and Methods

From January 1996 to December 2005, 62 HIV-infected patients with newly diagnosed HL were treated in 15 Spanish hospitals. Six to eight cycles of ABVD and HAART were planned. Response to chemotherapy, overall survival (OS) and event-free survival (EFS) were recorded.

Results

The median age of the patients was 37 years (range, 24-61) and 29 (47%) had a previously known diagnosis of acquired immunodeficiency syndrome. The median CD4 lymphocyte count at diagnosis was 129/ μ L (range 5-1,209). The histologic subtype of HL was nodular sclerosis in 17 patients (27%), mixed cellularity in 25 (41%), lymphocyte depletion in 10 (16%) and non-specified in the remaining 10 (16%). Twenty-one (34%) patients were in stage III and 41 (66%) in stage IV. The scheduled six to eight ABVD cycles were completed in 82% of cases. Six patients died during induction, 54 (87%) achieved a complete response (CR) and two were resistant. After a median follow-up of 39 and 47 months, 5-year EFS and OS probabilities were 71% (47-95) and 76% (65-87), respectively. An immunological response was observed in 24 out of 43 patients (56%) and a virological response in 27 out of 40 (68%). The immunological response to HAART had a positive impact on OS and EFS ($p=0.002$ and $p=0.001$, respectively).

Interpretation and Conclusions

In patients with advanced stage, HIV-related HL, treatment with ABVD together with HAART is feasible and effective. This supports the concept that patients with HIV-related HL should be treated in the same way as immunocompetent patients if HAART, adequate supportive therapy and anti-infectious prophylaxis are given concomitantly. An immunological response to HAART has a positive impact on OS and EFS.

Key words: Hodgkin's lymphoma, HIV-related, advanced stage, ABVD, HAART.

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Hodgkin's lymphoma (HL) is one of the most common non-acquired immunodeficiency syndrome (AIDS)-defining tumors in human immunodeficiency virus (HIV)-infected patients.¹ Its aggressive behavior includes unfavorable histological subtypes, advanced stage and extranodal involvement at diagnosis.²⁻⁶ Although in the era of highly active antiretroviral therapy (HAART) the incidence of non-Hodgkin's lymphoma (NHL) has declined according to several studies, this does not seem to be the case for HL. In recent years improvements have been observed in the survival of both patients with HIV-related NHL and those with HL.⁷⁻⁹ There are several possible reasons for these improvements. First, HAART increases CD4 lymphocyte counts and, concomitantly, reduces the risk of opportunistic infections; second, an improvement in the immunodeficiency status could prevent relapse of the lymphoma; and third, improvements in supportive therapy, e.g. the use of granulocyte colony-stimulating factor (G-CSF) together with chemotherapy, are useful for preventing hematologic toxicity and for avoiding a delay or reduction in doses of cytotoxic drugs. Nevertheless, the optimal approach for HIV-related HL in the HAART era is still unknown. Since 1996, several chemotherapy schedules (Stanford V,¹⁰ BEACOPP,¹¹ BEVEP),¹² given together with HAART and G-CSF, have been applied with encouraging results. Surprisingly, there is scarce information on the results of ABVD (considered the standard therapy for HL in non-immunocompromised patients) combined with HAART in HIV-related HL. In fact, in the HAART era only a small series of eight patients with HIV-related HL treated with ABVD (of whom only two received HAART concomitantly) has been published.¹³

The main objective of this retrospective study from the Spanish GESIDA (*Grupo Español de Estudio del SIDA*) and GELCAB (*Grup d'Estudi dels Limfomes de Catalunya i Balears*) groups was to analyze the results of the ABVD regimen plus HAART in a series of 62 patients with advanced stage HIV-related HL.

Design and Methods

From January 1996 to December 2005, 62 patients diagnosed with HIV-related HL in advanced stages (III and IV according to the Ann Arbor staging system)¹⁴ in 15 Spanish hospitals and treated with ABVD and HAART were retrospectively analyzed. These patients represent 76.5% (62 out of 81) of the cases of advanced-stage HL diagnosed in these institutions over the study period.

The following clinical parameters were recorded in each patient: age, sex, risk activity (i.v. drug use, heterosexual activity, homosexual/bisexual activity), prior diagnosis of AIDS, time interval from diagnosis of HIV infection to HL, presence of B symptoms, complete blood cell counts, CD4 lymphocyte count, histologic subtype and extranodal involvement. HIV serology was assessed by enzyme-

linked immunoabsorbent assay and confirmed by western blot in all patients. The revised Centers for Disease Control (CDC) classification system for HIV infection was used for the diagnosis of AIDS.¹⁵ The viral load of HIV was measured in each participating center. The diagnosis of HL was performed by biopsy study in all cases and all were classified according to the World Health Organization (WHO) classification of neoplasms of the hematopoietic and lymphoid tissues in each center.¹⁶

HAART consisted of one or two protease inhibitors and two nucleoside reverse transcriptase inhibitors and was administered concomitantly with ABVD, following the recommendations of the GESIDA group.¹⁷ Patients received trimethoprim-sulfamethoxazole (160/800 mg) thrice weekly or aerosolized pentamidine (300 mg inhaled) as prophylaxis against *Pneumocystis jiroveci* infection. According to the policy of each center, six to eight cycles of standard ABVD therapy (doxorubicin 25 mg/m², bleomycin 10 mg/m², vinblastine 6 mg/m², dacarbazine 375 mg/m²), administered intravenously on days 1 and 15 (each cycle lasted 28 days), were planned to be administered. Patients received G-CSF (5 µg/Kg/day subcutaneous) during the ABVD treatment according to institutional practices. Involved field radiotherapy was given after chemotherapy if there was bulky disease at diagnosis or a residual mass after the completion of chemotherapy.

Complete response (CR) was considered as the lack of evidence of HL at the end of treatment lasting for at least 1 month after the completion of chemotherapy. Any other situation (partial response, stable disease or progression) was considered as therapeutic failure. Relapse was defined as the presence of HL in a patient who had been in complete remission for at least 2 months. Overall survival (OS) was considered as the period of time between the date of diagnosis and the date of death or the last follow-up of the patient. Event-free survival (EFS) was defined as the period between the date of CR, failure or death from any cause or last control in remission.¹⁸ There was considered to have been a virological response to HAART when the total HIV-1 RNA loads were below the limit of detection in serum (according to the reference level of each center) after being on HAART treatment for at least 6 months. An immunological response to HAART was considered to have occurred if there was an increase of CD4 lymphocyte counts over 100/mm³, and always over 200/mm³, after being on HAART treatment for at least 6 months.¹⁹ The chemotherapy schedule was considered to have been delayed when there was an over 10% delay in one or more cycles at any time throughout the chemotherapy program. Patients were regularly restaged every 3 months in the first year, every 6 months during the second year and once a year thereafter. This study was conducted according to the rules of good clinical practice of the GESIDA and GELCAB groups.

Statistical analysis

A descriptive analysis of the different variables was performed. Bivariate tests (Student's t-test, the Mann-Whitney U-test and variance analysis when appropriate) were used to compare quantitative variables, and the χ^2 or Fisher's exact test was employed to assess differences in proportions. All the comparisons were two-tailed. Actuarial curves for EFS and OS were plotted according to the Kaplan-Meier method²⁰ and were compared by the log-rank test.²¹ The statistically significant ($p < 0.05$) variables identified in univariate studies were included in multivariate analyses. A logistic regression model was used to identify predictive factors for achievement of CR and multivariate analyses for EFS and OS were performed using the Cox proportional hazard-regression model.²² Statistical analyses were carried out using the SPSS (Statistical Package for Social Sciences) package version 12 for Windows.

Table 1. Main characteristics of the HIV infection and HL in the 62 patients in the series.

HIV infection parameters	Number (percentage)
Risk activity (n=62)	
Intravenous drug use	33 (53)
Heterosexual	15 (24)
Homosexual/bisexual	13 (21)
Unknown	1 (2)
AIDS before HL (n=62)	29 (47)
CD4 lymphocyte count/ μ L at HL diagnosis* (n=62)	129 (5-1,209)
CD4 lymphocyte count <100/ μ L (n=62)	22 (35)
HIV viral load (copies/mL) at diagnosis* (n=62)	1,4 (0-3,9 \times 10 ⁵)
HIV viral load below the limit of quantification (n=62)	11 (20)
HAART at HL diagnosis (n=62)	47 (76)
HL characteristics	
Histologic subtype (n=62)	
Mixed cellularity	25 (41)
Nodular sclerosis	17 (27)
Lymphocyte depletion	10 (16)
Non-specified	10 (16)
ECOG score (n=53)	
0	6 (11)
1	25 (48)
2	17 (32)
3	4 (7)
4	1 (2)
B symptoms (n=62)	55 (89)
Bone marrow involvement (n=59)	33 (55)
Ann Arbor stage (n=62)	
III	21 (34)
IV	41 (66)

HIV: human immunodeficiency virus; *: median (range); HAART: highly active antiretroviral therapy; AIDS: acquired immunodeficiency syndrome; HL: Hodgkin's lymphoma; ECOG: Eastern Cooperative Oncology Group.

Results

Patients' characteristics

Table 1 shows the main HIV infection-related characteristics and HL parameters of the patients of the series. The median age of the series was 37 years (range 24-61) and 54 of the patients (87%) were male. Twenty-nine of the patients (47%) had a previously known diagnosis of AIDS. The median time from diagnosis of HIV infection to HL was 5 years (range, 0-10). The most frequent risk activity for HIV infection was i.v. drug use. Most patients (75%) had been receiving HAART at the time of HL diagnosis for a median of 13 months (range, 1-109). However, the median CD4 lymphocyte count at the time of HL diagnosis was 129/ μ L (range, 5-1,209) and only 21/56 were in virologic response at diagnosis of HL. The most frequent HL subtype was mixed cellularity (41%). The HL subtype could not be assessed in ten patients because the diagnosis was made in extranodal sites. Forty-two percent of patients had an ECOG score \geq 2 and two thirds were in stage IV, with bone marrow involvement in 55% of patients.

Table 2. Treatment and response to therapy in the 62 patients in the series.

	Number of patients (percentage)
ABVD (6-8 cycles) completed	51 (82)
Involved field radiotherapy after ABVD	3 (5)
Resistance	2 (3)
Complete response	54 (87)
Relapse	6/54 (11)
Death	15
On induction	6*
Resistance	2°
Relapse	3
HIV	2
Other	
Traffic accident	1
Pneumonia	1
Median follow-up, months (range)	
EFS	39 (3-97)
OS	47 (4-107)
5-yr. EFS probability, % (95% CI)	71 (47-95)
5-yr. OS probability, % (95% CI)	76 (65-87)
Change in some of the antiretroviral agents of HAART	37 (60%)
Virologic response to HAART	27/40 (68%)
Immunologic response to HAART	24/43 (56%)

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; *: sepsis due *Candida parapsilosis* (1 patient), sepsis due *Staphylococcus epidermidis* (1 patient), unknown (1 patient), Hodgkin's lymphoma and human immunodeficiency virus-related events (3 patients); **: one patient was considered as resistant after having received five cycles, the other received the six scheduled cycles; HIV: human immunodeficiency virus; HL: Hodgkin's lymphoma; EFS: event-free survival; OS: overall survival; HAART: highly active antiretroviral therapy.

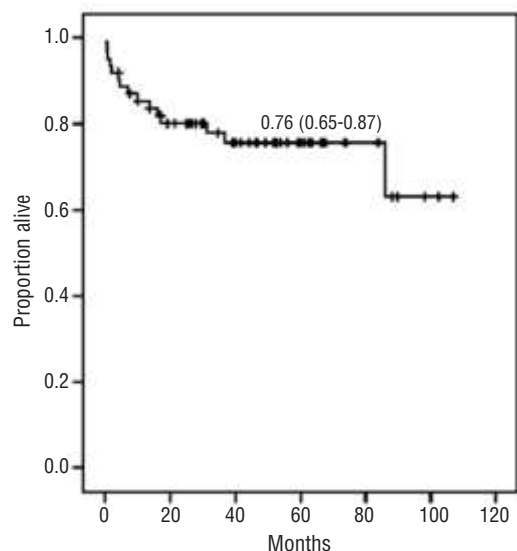


Figure 1. Overall survival of the 62 patients in the series.

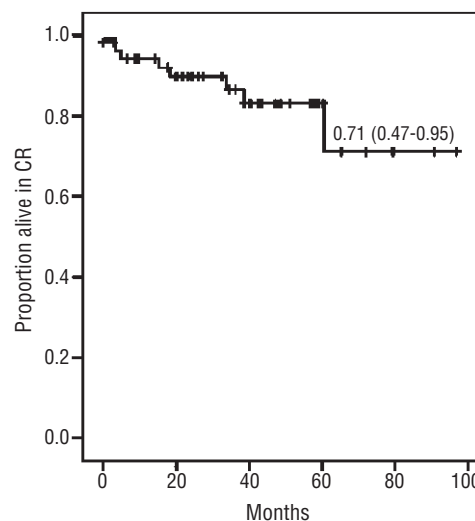


Figure 2. Event-free survival of the 54 patients in the series who survived induction therapy.

Response to chemotherapy and survival

Table 2 shows the main results of ABVD therapy. Six cycles were given to 42 patients and eight cycles to 9. Treatment with the scheduled six to eight ABVD cycles was completed in 82% of patients. The reasons for not completing the scheduled treatment were toxic death in three patients, resistance in one, HL and HIV-related death in three and unknown in four patients (all were withdrawn from the protocol: one after receiving three cycles, one after receiving four cycles, and the other two after receiving five cycles). Of the 51 patients who completed the scheduled treatment, cycles had to be delayed in 21 (41%), mainly due to neutropenia. Of the eight patients in whom induction failed, three died in induction, two due to resistance to chemotherapy and three died due to HL and HIV-related infection (Table 2). Fifty-four of the 62 (87%) patients achieved a CR. G-CSF was given after ABVD chemotherapy to 10 out of 50 (20%) patients.

Figures 1 and 2 show the EFS and OS probabilities of the series. As can be seen, after a median follow-up of 39 and 47 months, 5-year (95% CI) EFS and OS probabilities were 71% (47%-95%) and 76% (65%-87%), respectively. Table 3 shows the results of the univariate analysis of prognostic factors for CR. In the present study a virological response was observed after completion of chemotherapy in 27 out of 40 (68%) evaluable patients and an immunological response in 24 out of 43 evaluable patients (56%). EFS and OS were better, although not statistically significantly so, in patients who had a virological response (5-year EFS probability of $69 \pm 31\%$ for non-responders versus $89 \pm 11\%$ for responders, $p=0.156$ and 5-year OS probability of $69 \pm 30\%$ for non-responders versus $88 \pm 12\%$ for respon-

ders, $p=0.385$), whereas immunologic response was associated with EFS and OS (Figures 3 and 4). Delays in administering the therapy did not have a significant impact on either EFS or OS.

Discussion

The results of this study show that the use of the standard ABVD therapy together with HAART is feasible in advanced stages of HIV-related HL and that the therapeutic response is similar to that observed in other studies using different multiagent schedules (Table 4). An immunological response to HAART had a positive impact on both EFS and OS. To the best of our knowledge, this is the largest series of patients with advanced stage HIV-related HL treated with ABVD together with HAART. The main limitation of this study is its retrospective and multicenter nature. For this reason, a selection bias cannot be ruled out (the patients analyzed represent 76.5% of the patients diagnosed in the participating centers) and the information on toxicity is limited.

Before the generalized use of HAART, the results of treatment of HIV-related HL were poor. Errante *et al.* conducted a randomized study applying full or dose-reduced schedules of EBV (epirubicin, bleomycin and vinblastine) together with zidovudine (given from the beginning of therapy or started after the third cycle) as antiretroviral therapy. The rate of opportunistic infection was significantly lower in patients receiving dose-reduced treatment, although OS remained unchanged.²³ The same Italian group conducted a prospective non-randomized trial adding prednisone to EBV (EBVP schedule) with zidovudine or dideoxinosyne as anti-

Table 3. Univariate analyses of prognostic factors for attaining complete remission.

Variable	Category	N	CR (%)	No CR (%)	p value
Age (years)	≥37	29	27	2	0.255
	>37	32	27	5	
Sex	Male	54	47 (87)	7 (13)	0.727
	Female	8	7 (88)	1 (12)	
Risk activity	Drug abuse	33	28 (85)	5 (15)	0.777
	Homosexual/bisexual	13	11 (85)	2 (15)	
	Heterosexual	15	14 (93)	1 (7)	
	Unknown	1	1 (100)	0 (0)	
AIDS before HL	Yes	29	24 (83)	5 (17)	0.282
	No	33	30 (91)	3 (9)	
Undetectable HIV VL (at diagnosis)	Yes	21	17 (81)	4 (19)	0.230
	No	35	32 (91)	3 (9)	
Histologic subtype	Mixed cellularity	25	23 (92)	2 (8)	0.438
	Nodular sclerosis	17	15 (88)	2 (12)	
	Lymphocyte depletion	10	9 (90)	1 (10)	
	Non-specified	10	7 (70)	3 (30)	
ECOG score	0	6	6 (100)	0 (0)	0.43
	1	25	20 (80)	5 (20)	
	2	17	16 (94)	1 (6)	
	3	4	4 (100)	0 (0)	
	4	1	1 (100)	0 (0)	
B symptoms	Yes	55	47 (85)	8 (15)	0.360
	No	7	7 (100)	0 (0)	
Extranodal involvement	<2	34	30 (88)	4 (12)	0.663
	≥2	17	15 (88)	2 (12)	
BM involvement	Yes	33	29 (88)	4 (12)	0.933
	No	26	23 (89)	3 (11)	
Stage	III	21	19 (91)	2 (9)	0.447
	IV	41	35 (85)	6 (15)	
G-CSF	Yes	10	9 (90)	1 (10)	0.603
	No	40	37 (93)	3 (7)	
Radiotherapy	Yes	3	3 (100)	0 (0)	0.681
	No	48	42 (87)	6 (12)	
HAART	Before HL	47	39 (83)	8 (17)	0.231
	During ABVD	14	14 (100)	0 (0)	
	After ABVD	1	1 (100)	0 (0)	
CD4 lymphocyte count/μL	<200	36	30 (83)	6 (17)	0.438
	>200	26	24 (92)	2 (8)	
	<100	22	17 (78)	5 (22)	0.096
	>100	40	37 (93)	3 (7)	
Virologic response	Yes	27	26 (96)	1 (4)	0.675
	No	13	13 (100)	0 (0)	
Immunologic response	Yes	24	24 (100)	0 (0)	0.442
	No	19	18 (95)	1 (5)	

CR: complete remission; AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; HL: Hodgkin's lymphoma; VL: viral load; ECOG: Eastern Cooperative Oncology Group; BM: bone marrow; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; G-CSF: granulocyte colony-stimulating factor; HAART: highly active antiretroviral therapy.

retroviral therapy together with G-CSF. In this case, 74% of the patients achieved a CR. However, the relapse rate was high (38%) and the median survival was 16 months, with OS probability of 32% and disease-free survival probability of 53% at 36 months.²⁴ In the era of HAART, several prospective studies have analyzed the feasibility and results of multiagent chemotherapy in HIV-related HL given concomitantly with HAART. The regimens studied include Stanford V,¹⁰ BEACOPP¹¹ and VEBEP.¹² All have proven to be feasible and highly effective in HIV-related HL. Spina *et al.* evaluated the feasibility and the results of the Stanford V¹⁰ regimen and, more recently, the VEBEP schedule.¹² The Stanford V schedule showed high hematologic toxicity

(78% of patients developed grade 3 or 4 neutropenia), although 69% of patients were able to complete the treatment without a reduction or delay in doses. An International Prognostic Score (IPS)²⁵ higher than 2 was associated with poor OS and freedom from progression. The 3-year disease-free survival and OS were 76% and 83%, respectively. In the VEBEP study, preliminary data showed a high percentage of CR (75%) with a low relapse rate (10%), moderate toxicity and excellent overall and disease-free survival probabilities (86% and 90% at 2 years, respectively). Hartmann *et al.*¹¹ reported on a small series of 12 patients treated with the BEACOPP regimen, five of whom were on antiretroviral therapy (in the five patients recruited before 1997, anti-

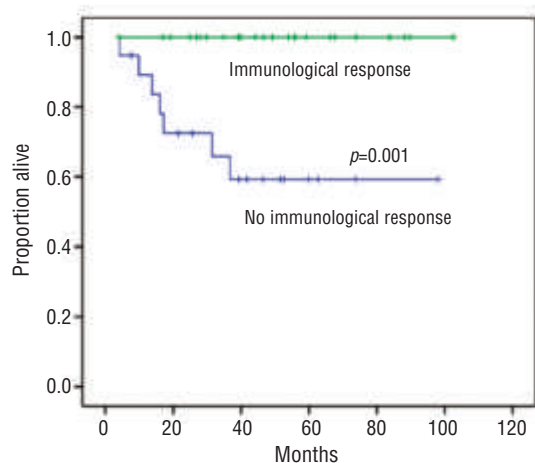


Figure 3. Overall survival probability according to the immunological response.

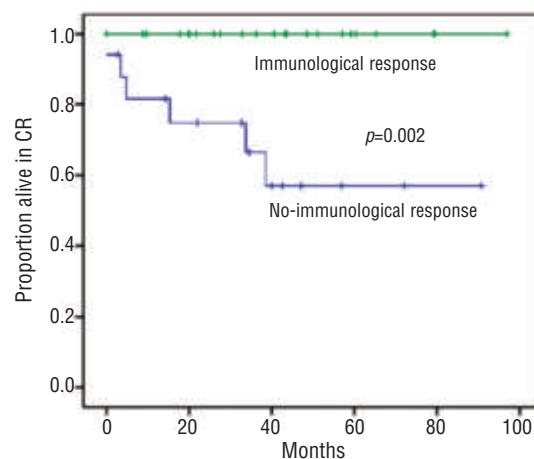


Figure 4. Event-free survival probability according to the immunological response.

retroviral therapy was discontinued during chemotherapy). All patients achieved a CR and eight patients were able to complete the treatment. Hematological toxicity was frequent (grade 3-4 neutropenia in 75% of patients). Three out of the 12 patients died within the study period.

The clinical characteristics of the patients in the present series are comparable to those of patients included in these previously mentioned trials (Table 4). It is of note that patients from our study were more immunocompromised at the time of HL diagnosis than in the other studies, despite the fact that 76% of them were receiving HAART. The median CD4 lymphocyte count was 125/ μ L and only 37% of patients had a viral load below the limit of quantification at the time the HL was diagnosed. Nonetheless, 82% of the patients were able to complete the planned treatment. A similar CR rate (87%) was found in our study, which compares with 81% and 75% observed in the studies of the Stanford V¹⁰ and VEBEP¹² regimens, respectively. The percentage of relapses was higher among patients treated with the VEBEP regimen (38% versus 11% in our study). While 69% of patients completed the treatment plan without any reduction or delay in the Stanford V trial and 5 out of 12 did so in the BEACOPP study,¹⁰ chemotherapy was delayed in 41% of the patients in our retrospective study. With respect to OS, our results are similar to those of the above mentioned studies. Regarding prognostic factors, an IPS higher than 2 was associated with poor OS and freedom-from-progression rates in the Stanford V regimen. Unfortunately, the retrospective and multicenter nature of our study did not enable evaluation of the potential prognostic impact of the IPS in our series.

The influence of HAART on the outcome of HIV-related lymphomas has been studied by some groups. In non-Hodgkin's lymphoma, Oriol *et al.*²⁶ demonstrated better OS in HIV-infected patients treated with a specif-

Table 4. Studies in patients with HIV-associated Hodgkin's lymphoma treated with chemotherapy and HAART.

Regimen (reference)	Stanford V ⁹	BEACOPP ¹⁰	VEBEP ¹¹	ABVD (Present study)
Number of patients	56	12	28	62
Median age, yr. (range)	38 (28-64)	33 (22-49)	39 (NS)	37 (24-61)
Stages III-IV(%)	71	92	71	100
B symptoms (%)	74	83	NS	89
Median CD4 lymphocyte counts/ μ L (range)	238 (32-1,008)	205 (110-1,020)	257 (44-589)	129 (5-1,209)
Median HIV RNA/mL (range)	3,400 (60-455,000)	16,846 (0-1,086,398)	9,402 (89-500,000)	14,000 (0-39,000)
Known HIV infection(%)	20	25	32	47
HAART at diagnosis	yes	yes	yes (25% patients)	yes
G-CSF	yes	yes	NS	20% patients
Complete response (%)	81	100	75	87
Survival probability, %(years)	51 (3)	NA	86 (2)	76 (5)

Stanford V: doxorubicin, vinblastine, meclizetamine, etoposide, vincristine, bleomycin and prednisone; BEACOPP: cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisone, bleomycin and vincristine; VEBEP: epirubicin, cyclophosphamide, vinorelbine, bleomycin and prednisone; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; HIV: human immunodeficiency virus; HAART: highly active antiretroviral therapy; G-CSF: granulocyte colony-stimulating factor; NS: not specified; NA: not applicable.

ic Burkitt's lymphoma protocol, especially if they had a virological response to HAART, and Navarro *et al.*²⁷ reported a better CR rate and better overall and disease-free survival in diffuse large-B cell lymphoma when treated with CHOP concomitantly with HAART. In the latter study, patients in virological response to HAART (15 out of the 25 evaluable cases) had a better survival. In the HIV-HL setting, two studies have evaluated the impact of the response to HAART given together with chemotherapy. Firstly, our group reported a series of 45 patients in whom the CR rate, OS and disease-free survival were significantly better in patients taking HAART than in patients who were not, but the influence of the response to HAART was not evaluated.⁷ The second study, conducted by Hoffmann *et al.*,⁸ analyzed the impact of HAART on survival in 57 HIV-related HL patients treated with different chemotherapy schedules, including ABVD. The factors independently associated with better OS were the virological and/or immunological response to HAART, together with complete remission attainment and age less or equal to 45 years. Virological response was analyzed as a marker of response to HAART in most of the studies previously mentioned, thereby demonstrating that this response influences OS and EFS. Nevertheless, response to HAART can also be evaluated in terms of immunological response, although there are few data on the impact of this type of response in HIV-related lymphomas. Our study focused on both issues, immunological and virological responses. To the best of our knowledge, this is the first study demonstrating that immunological response is associated with a better OS and EFS in the HL setting. In addition, virological response was associated with a better, albeit not statistically significantly improved, EFS and OS. The reasons for the favorable impact of HAART response on survival in AIDS-related HL and NHL are speculative. However, control of viral replication could decrease the continuous activation of the lymphoid system, which is one of the features involved in AIDS-related lymphomagenesis.²⁸ On the other hand, the improved immunological status, demonstrated by a sustained increase in CD4 lymphocyte counts could control the re-emergence of malignant lymphoid clones.

In spite of the fact that ABVD is considered the standard therapy for HL, there is surprisingly little information on its use in HIV-related HL. In the pre-HAART era, the results of the therapy of HIV-related HL with ABVD and G-CSF were disappointing, with less than a 50% CR rate, a median survival of only 1.5 years and a high rate of life-threatening neutropenia and opportunistic infections, as reported by Levine *et al.*²⁹ More recently, the addition of HAART and G-CSF to ABVD produced

encouraging results in a small series of eight patients, all of whom had responses, who had a median survival of 43.5 months, as reported by Gastaldi *et al.*¹³ In our study, treatment with ABVD was given concomitantly with HAART in all patients and 20% also received G-CSF. Eighty-two percent of the patients completed the scheduled six to eight cycles. The induction mortality rate was only 10% and there was a low number of HIV-related deaths. The CR rate was high (87%) and only six (11%) patients relapsed, thus confirming the efficacy of ABVD in these patients. Our results of ABVD therapy in the HAART era confirm that HAART plays an important role in the management of HIV-related HL, as has been observed in previous studies.^{7,8}

In conclusion, ABVD together with HAART is feasible and highly active in patients with advanced stage HIV-related HL with a similar efficacy to that observed in other chemotherapy schedules. This supports the concept that patients with HIV-related HL should be treated in the same way as non-immunocompromised patients if HAART and adequate supportive therapy and anti-infectious prophylaxis are given concomitantly. Improvement in the response to HAART is essential to achieve maximum benefits from the treatment of HIV-related HL.

Appendix

The following institutions and investigators participated in the study: Germans Trias i Pujol. Badalona (B Xicoy, JM Ribera, JT Navarro, M Morgades, JL Mate), General Universitario Gregorio Marañón. Madrid (P Miralles, J Berenguer, J Cosín, JC López), 12 de Octubre. Madrid (R Rubio, F Pulido, V Moreno, C Cepeda), Carlos III. Madrid (ME Valencia, V Moreno, J González), Universitario de San Carlos. Madrid (MJ Téllez, J Vergas, V Estrada, V Roca), La Paz. Madrid (ML Montes, JR Arribas, J. Gonzalez-Garcia), La Fe. Valencia (J Lacruz, J López, M Salavert), Virgen de la Victoria. Málaga (J Santos, R Palacios, M Márquez), Virgen de la Salud. Toledo (MA Sepúlveda), Reina Sofía. Córdoba (J de la Torre, A Rivero, M García), Ramón y Cajal. Madrid (V Pintado, A Antela, L Patier), del Mar. Barcelona (E Abella), Clínic. Barcelona (A López-Guillermo), Sant Pau. Barcelona (A Sureda), Mataró. Mataró (LI Rodríguez).

Authors' Contributions

BX and JMR were primarily responsible for the evaluation of the data and the design of the paper. Both authors contributed equally to this work. BM and MM analyzed the data. The remaining authors (PM, JB, RR, MV, JN, EA, AL, AS) qualified for authorship according to the WAME criteria, reported on the patients and followed them clinically. These contributions explain the order of the authors.

Conflicts of Interest

The authors reported no potential conflicts of interest.

References

- Frish M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;4:1736-45.
- Hartmann P, Rehwald U, Salzberger B, C Franzen, V Diehl. Current treatment strategies for patients with Hodgkin's lymphoma and HIV infection. *Expert Rev Anticancer Ther* 2004;4:401-10.
- Rubio R. Hodgkin's disease associated with human immunodeficiency virus infection. A clinical study of 46 cases. Cooperative Study Group of Malignancies Associated with HIV infection of Madrid. *Cancer* 1994; 73:2400-7.
- Andrieu JM, Roithmann S, Tourani JM, Levy R, Desablens B, Le Maingnan C, et al. Hodgkin's disease during HIV Infection: the French registry experience. French Registry of HIV-Associated Tumors. *Ann Oncol* 1993;4:635-41.
- Ames ED, Conjalka MS, Goldberg AF, Hirschman R, Jain S, Distenfeld A, et al. Hodgkin's disease and AIDS. Twenty-three new cases and a review of the literature. *Hematol Oncol Clin North Am* 1991;5:343-56.
- Ree HJ, Strauchen JA, Khan AA, Gold JE, Crowley JP, Kahn H, et al. Human immunodeficiency virus-associated Hodgkin's disease. Clinicopathologic studies of 24 cases and preponderance of mixed cellularity type characterized by the occurrence of fibrohistiocytoid stromal cells. *Cancer* 1992;69:1614-21.
- Ribera JM, Navarro JT, Oriol A, López-Guillermo A, Sureda A, Abella E, et al. Prognostic impact of highly active antiretroviral therapy in HIV-related Hodgkin's disease. *AIDS* 2002;16:1973-76.
- Hoffmann C, Chow KU, Wolf E, Faetkenheuer G, Stellbrink HJ, van Lunzen J, et al. Strong impact of highly active antiretroviral therapy on survival in patients with human immunodeficiency virus-associated Hodgkin's disease. *Br J Haematol* 2004;125:455-62.
- Tirelli U, Vaccher E, Rossi G, Schiantarelli C, Fasan M, Spina M. Hodgkin's disease and HIV infection (HD-HIV) in pre- and post- HAART era: the GICAT (Italian Cooperative Group on AIDS and tumors) experience in 139 patients. *Blood* 2005; 106:415a[abstract].
- Spina M, Gabarre J, Rossi G, Fasan M, Chiantarelli C, Nigra E, et al. Stanford V and concomitant HAART in 59 patients with Hodgkin's disease and HIV infection. *Blood* 2002;100:1984-88.
- Hartmann P, Rehwald U, Salzberger B, Franzen C, Sieber M, Wöhrmann A, et al. BEACOPP therapeutic regimen for patients with Hodgkin's disease and HIV infection. *Ann Oncol* 2003;14:1562-9.
- Spina M, Rossi G, Antinori A, Allione B, Fasan M, Rizzardini G, et al. VEBEP regimen and highly active antiretroviral therapy (HAART) in patients with HD and HIV Infection (HD-HIV). *Blood* 2005; 106:100a [abstract].
- Gastaldi R, Martino P, Gentile G, Picardi V, De Propios MS, Pirillo MF, et al. Hodgkin's disease in HIV-infected patients: report of eight cases usefully treated with doxorubicin, bleomycin, vinblastin and dacarbazine (ABVD) plus granulocyte colony-stimulating factor. *Ann Oncol* 2002;13:1157-60.
- Carbonne PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. *Cancer Res* 1971;31:1860-61.
- Centers for Disease Control "1993 revised classification system for HIV infection and expands surveillance case definition for AIDS adolescents and adults": *MMWR* 1992;41:1-18.
- Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November, 1997. *J Clin Oncol* 1999; 17: 3835-49.
- Miralles P, Rubio C, Berenguer J, Ribera JM, Calvo F, Díaz-Mediavilla J, et al. Recomendaciones de GESIDA/Plan Nacional sobre el Sida sobre el diagnóstico y tratamiento de los linfomas en pacientes infectados por el virus de la inmunodeficiencia humana. *Med Clin (Barc)* 2002;118:225-36.
- Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trial in acute myeloid leukemia. *J Clin Oncol* 2003;21: 4642-9.
- Antinori A, Cingolani A, Alba L, Ammassari A, Serraino D, Ciancio BC, et al. Better response to chemotherapy and prolonged survival in AIDS-related response to highly active antiretroviral therapy. *AIDS* 2001;15:1483-91.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958;53: 457-81.
- Peto R, Pike MC. Conservatism of the approximation $\Sigma(O-E)^2/E$ in the log-rank test for survival data or tumor incidence data. *Biometrics* 1973;29:579-84.
- Cox DR. Regression models and life tables. *J Roy Statist Soc* 1972;3:187-200.
- Errante D, Gabarre J, Ridolfo AL, Rossi G, Nosari AM, Gisselbrecht C, et al. Hodgkin's disease in 35 patients with HIV infection: an experience with epirubicin, bleomycin, vinblastine and prednisone chemotherapy in combination with antiretroviral therapy and primary use of G-CSF. *Ann Oncol* 1999; 10: 189-95.
- Errante D, Tirelli U, Gastaldi R, Milo D, Nosari AM, Rossi G, et al. Combined antineoplastic and antiretroviral therapy for patients with Hodgkin's disease and human immunodeficiency virus infection. A prospective study of 17 patients. The Italian Cooperative Group on AIDS and Tumors (GICAT). *Cancer* 1994;73:437-44.
- Hasenclever D, Diehl V, for the International Prognostic Factors Project on Advanced Hodgkin's disease. A prognostic score for advanced Hodgkin's disease. *N Engl J Med* 1998;339:1506-14.
- Oriol A, Ribera JM, Brunet S, Esteve J, Potro E, Abella E, et al. Influence of highly active antiretroviral therapy in the outcome of AIDS-related Burkitt's lymphoma or leukaemia. Results of the PETHEMA-LAL3/97 study. *Haematologica* 2005;90:990-2.
- Navarro JT, Ribera JM, Oriol A, Romeu J, Sirera G, Mate JL, et al. Favorable impact of virological Response to HAART on survival in patients with AIDS-related lymphoma. *Leuk Lymphoma* 2002; 43:1837-42.
- Gaidano G, Carbone A, Dalla-Favera R. Pathogenesis of AIDS-related lymphomas. *Am J Pathol* 1998; 152:623-30.
- Levine AM, Li P, Cheung T, Tulpule A, Von Roenn J, Nathwani BN, et al. Chemotherapy consisting of doxorubicin, bleomycin, vinblastine and dacarbazine with granulocyte-colony-stimulating factor in HIV-infected patients with newly diagnosed Hodgkin's disease : a prospective, multi-institutional AIDS clinical trials group study (ACTG 149). *J Acquir Immune Defic Syndr* 2000; 24:444-50.