Long-term follow up of patients with human immunodeficiency virus infection and advanced stage Hodgkin's lymphoma treated with doxorubicin, bleomycin, vinblastine and dacarbazine

In patients with human immunodeficiency virus (HIV) infection and advanced stage Hodgkin's lymphoma (HL), treatment with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and highly active antiretroviral therapy (ART) is feasible and effective, and the immunological response to ART has a positive impact on overall survival (OS) and event-free survival (EFS).[1] The ABVD schedule has similar efficacy but a more favorable toxicity profile in comparison with other schedules of chemotherapy.[2-4] Nevertheless, information is scarce about the long-term follow up of patients in complete response (CR), especially in terms of incidence of secondary malignancies or other non-acquired immunodeficiency syndrome (AIDS)-related events. We analyzed the long-term follow up of patients with HIV infection and advanced stage HL included in the study conducted by the Spanish GESIDA (Grupo de Estudio de SIDA) and GELCAB (Grupo Catalano-Balear para el Estudio de los Linfomas) Groups.

Sixty-two patients with HIV infection and advanced stage (III or IV according to the Ann Arbor staging system) HL receiving ABVD and concomitant ART were included in the study; 47 were on ART treatment at HL diagnosis and 15 beginning ART at the time of HL diagnosis. With a median 9-year follow up (range 1.1-15) of alive patients at the time of the original publication,[1] the 14-year OS (95%CI) probability was 65% (47-83%). Patients were on ART during chemotherapy and the entire follow up period. The following events were recorded in the 54 patients who achieved CR: relapse of the lymphoma, opportunistic infections (OI), and other malignancies. HIV viral load and CD4 lymphocyte count at the nearest time point to the event were also recorded. Comparison of these counts between patients with and without events was performed by the Mann-Whitney U-test for CD4 lymphocyte count and the χ^2 test for HIV viral load (categorized as negative or positive; >50 copies/mL). Cumulative probabilities of OI and secondary malignancies, as well as OS and EFS probabilities, were calculated by the Kaplan-Meier method. In patients with more than one event, the date of the first event was considered for analyses. This follow-up analysis was closed in July 2012.

At the time of the analysis, the median follow up of living patients was 9.84 years (range 1.13-15). Ten patients suffered from lymphoma relapse (one of them also had an OI), 5 patients had OI (tuberculosis n=1, *Pneumocystis jiroveci* pneumonia together with esophageal candidiasis and disseminated tuberculosis n=1, aspergillus and herpes zoster infection n=1, *Candida parapsilosis* pneumonia n=1 and non-identified cause n=1), and 3 patients presented with a secondary cancer (hepatocellular carcinoma n=1, rectal adenocarcinoma n=1, and prostate and colon adenocarcinoma n=1).

The median time of OI appearance was 0.35 years (range 0.11-5.07) and the cumulative probability of OI at 14 years was 10% (95%CI: 2-18%). For secondary malignancies, these values were 7.42 years (range 5.98-9.40) and 10% (95%CI: 0-22%). Fourteen patients died: 6 due to lymphoma relapse, 4 to OI, one to secondary cancer (hepatocellular carcinoma), and 3 to other causes (bacterial sepsis, sudden death and traffic accident). The 14-year OS actuarial probability for the cohort of 54 patients in first CR of the lymphoma was 65% (95%CI: 47-83%) (Figure 1A) and the EFS actuarial probability was 59% (95%CI: 44-74%) (Figure 1B). The 14-year OS actuarial probability for the whole series was 72% (61-83%), representing a 4% reduction in OS probability with respect to that observed in the original publication. Patients with events had significantly higher HIV viral load and lower CD4 lymphocyte counts compared with those without events (Table 1). Patients with OI had significantly lower CD4 lymphocyte

Table 1. Comparison of CD4 lymphocyte counts and HIV viral load in Hodgkin's lymphoma patients with events with those from patients who did not present any event.

	HIV viral load <50 copies/mL*	P	CD4 lymphocyte count (x10⁹/L) mean (SD)*	P
No event	26/31	0.034	612.22 (324.16)	0.021
Event	8/15		372.67 (350.26)	
Opportunistic infection	1/4		66 (31.27)	
Second cancer	3/3		679.67 (321.31)	
Lymphoma relapse	4/8		410.88 (345.90)	

+available in 46 patients; *available in 47 patients.

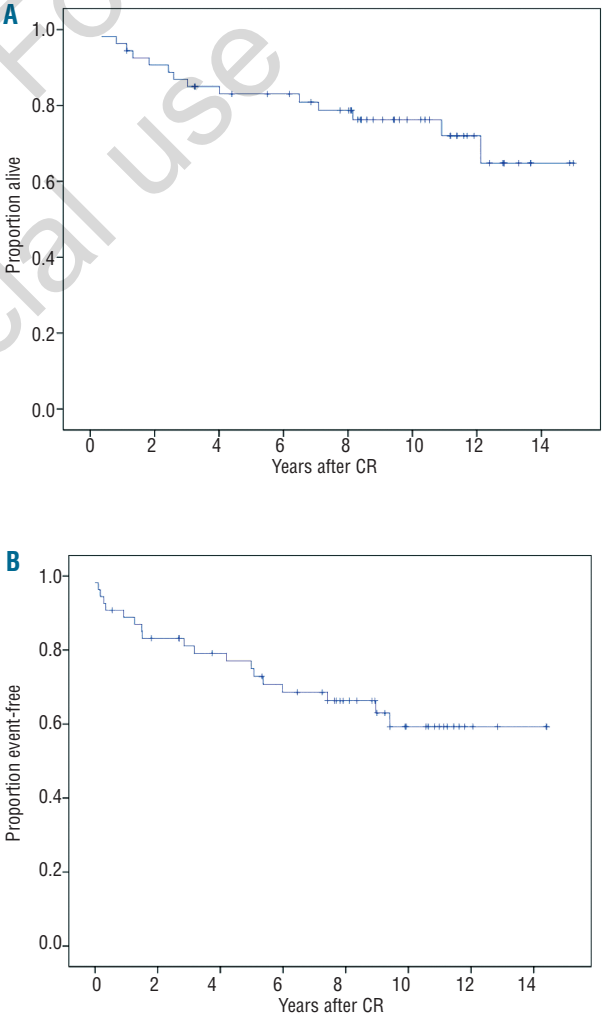

Figure 1. Overall survival (A) and event-free survival (EFS) probabilities of the 54 patients with Hodgkin's lymphoma who achieved complete response.

counts than those without events, whereas no significant differences in the CD4 counts were observed for the remaining events (secondary cancer and lymphoma relapse).

This long-term follow up study of HIV-infected patients with advanced stage HL treated with ABVD shows a remarkable frequency of OI and secondary cancers, the latter appearing later than OI. Of note, a significantly lower CD4 lymphocyte count and a higher viral load were observed in the group of patients with these events compared with those without these complications, although the difference was not statistically significant when OI were excluded.

The use of ART has improved the prognosis of HIV-infected patients with HL leading to an increase in survival, similar to that of the non-immunosuppressed patients in some cohort studies.[5-7] On the other hand, the incidence of non-AIDS-related malignancies has increased in the ART era.[8,9] However, information is scarce about secondary cancers in patients that have been successfully treated for lymphoma. Recently, Ribera *et al.*[10] reported the long-term follow up of a series of patients with HIV-related diffuse large B-cell lymphomas (DLBCL) treated in a phase II study with rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). In this study, a remarkable frequency of OI and secondary malignancies was observed, having a significant impact on the survival of patients. Patients with events (especially OI) had significantly lower CD4 lymphocyte counts compared with those without events. The impact of the concurrent use of rituximab on the onset of OI is uncertain. Similar to the data from the Ribera *et al.* study in HIV-related DLBCL, a significant frequency of OI and secondary cancers was also observed in our study in HIV-related HL, but the impact on OS was less evident. Patients with events had significantly lower CD4 lymphocyte counts and more frequent positive HIV viral loads compared to those without events. Two reasons may explain these findings: first, the lack of control of viral replication could increase the continuous activation of the lymphoid system, which is one of the features involved in AIDS-related lymphomagenesis; and second, the impaired immunosurveillance of the patients due to the low CD4 lymphocyte count could favour the onset of OI.[11] In addition, we can not exclude an influence of HBV/HCV co-infection or smoking on the results; risk factors which were not available in the database.

While the rate of non-AIDS-defining cancers remained stable during the pre-ART era, a significant increase has been observed for some cancers following the introduction of ART.[8-10] The remarkable frequency of non-AIDS-defining cancers observed in our cohort is consistent with these observations. Our data suggest that maintenance of the virological and immunological response to ART is essential to improve the long-term survival of patients with HIV-related HL.

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doi:10.3324/haematol.2012.079921

Key words: Hodgkin's lymphoma, HIV-related, long-term follow up, opportunistic infections, second cancers.

Funding: This work was supported by grants 36606/06 from FIPSE, and RD12-0036-0029 from RTICC, Instituto Carlos III, Spain .

Acknowledgments: the authors want to acknowledge the following physicians and institutions who participated in the study: Eugenia Abella, Hospital del Mar, Barcelona; Armando-López-Guillermo, Hospital Clínic, Barcelona; Javier Briones, Hospital de Sant Pau, Barcelona; M Jesús Tellez, Hospital Clínico San Carlos, Madrid; José Arribas, Hospital la Paz, Madrid; José López-Aldeguer, Hospital la Fe, Valencia; Vicente Pintado, Hospital Ramón y Cajal, Madrid; María Sepúlveda, Hospital Virgen de la Salud, Toledo; Jesús Santos, Hospital Virgen de la Victoria, Málaga; Julián Torre, Hospital Reina Sofía, Madrid; Esther Plensa, Hospital de Mataró, Mataró; José-Tomás Navarro, Institut Català d'Oncologia-Hospital Germans Trias I Pujol, Badalona.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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