Human immunodeficiency virus-related non-Hodgkin's lymphoma

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With the generalized use of highly active antiretroviral therapy (HAART) the survival of human immunodeficiency virus (HIV)-infected patients has increased dramatically. This has been due to decreases in the frequency of both opportunistic infections and some types of cancer, including HIV-related lymphomas.[1] Nonetheless, HIV-related lymphomas still constitute a major cause of death in HIV-infected patients. Most of these lymphomas are clinically aggressive monoclonal B-cell lymphomas, especially diffuse large B-cell lymphomas (DLBCL) and Burkitt's or Burkitt-like lymphomas (BL). Other much less frequent subtypes of HIV-related lymphomas include primary central nervous system (CNS) lymphomas, primary effusion lymphomas and plasmablastic lymphomas.

Several epidemiological studies performed in the United States and in Europe have confirmed a marked decline in the incidence of HIV-related lymphomas in the HAART era, which has been more dramatic for primary CNS lymphomas than for systemic non-Hodgkin's lymphomas. This favorable impact of HAART already became evident in the first months after initiation of HAART and has remained strong 10 years after the use of such therapy.[2] A clear relationship has been shown between the rise in CD4 lymphocyte counts and the decrease in the incidence of HIV-related lymphomas.[1] However, it has recently been found that the incidence of several non-AIDS-defining cancers, including Hodgkin's lymphoma, has increased in the HAART era. In one study that linked three cancer registries from the United States, non-AIDS-defining cancers accounted for 31.4% of cancers in HIV-infected individuals in 1991-1995 (pre-HAART era) compared to 58.0% in 1996-2002 (HAART era).[3] In another North American study comparing data from 54,780 HIV-infected people with data from 334,802,121 records from the Surveillance, Epidemiology and End Results (SEER) program, several non-AIDS defining cancers were significantly more frequent in the HIV-infected population than in the general population, Hodgkin's lymphoma being (standardized rate ratio –SRR- 14.7, CI 11.6-18.2) the third in risk after anal (SRR 42.9, CI 34.1-53.3) and vaginal cancers (SRR 21.0, CI 11.2-35.9).[4]

The clinical and biological heterogeneity of HIV-related lymphomas might reflect the existence of multiple pathogenetic pathways that have been only partially elucidated. In the presence of HIV-associated immunosuppression, continued antigen stimulation of B cells by the HIV infection itself and/or by other infective agents (Epstein-Barr virus, hepatitis C virus and others) seems to be critical for lymphomagenesis. This stimulation could lead to rearrangements in the immunoglobulin variable genes (*IGV*) that ultimately lead to the development and expansion of the lymphoma clone. In this issue of Haematologica Capello *et al.*[5] have shown that over 90% of HIV-related lymphomas (especially DLBCL and BL) had aberrant somatic hypermutation of *IGHV* genes, and a skewed *IGHV* repertoire was observed in specific clinicopathologic categories, supporting the hypothesis that both subtypes of HIV-related lymphomas originate from B cells that have terminated germinal center transformation. In contrast, some cases of primary CNS lymphoma were devoid of somatic hypermutation of the *IGHV* genes, suggesting that they may represent transformation of B cells experiencing preterminal germinal center-independent differentiation. The heterogeneous representation of the *IGHV* genes in HIV-related lymphomas may be related to specific pathways of antigen stimulation or to differences in host immune dysregulation and lymphoma histogenesis.[6]

There is evidence that the clinical spectrum of HIV-related lymphomas has changed in the HAART era. Extranodal disease at presentation is less frequent and, in general, the prognostic features of these lymphomas (assessed by the International Prognostic Index, IPI) are similar to those observed in non-immunosuppressed patients. Our group has recently shown a significant decrease in the frequency of leptomeningeal involvement at diagnosis in HIV-related lymphomas in patients receiving HAART.[7] Nonetheless, the clinicobiological characteristics of HIV-related lymphomas are not fully comparable to those observed in non-HIV-infected patients. It is of note that HIV-infected patients under HAART at diagnosis of non-Hodgkin's lymphoma usually have a better general status than patients with this lymphoma arising in the pre-HAART era and this feature has clear therapeutic implications.[8]

The improvement in the clinical condition of patients with HIV-related lymphomas and the adequate control of opportunistic infections by HAART has led many groups to use the same therapies for these lymphomas as those employed for non-Hodgkin's lymphomas arising in non-immunosuppressed patients. In DLBCL the most frequently employed regimens are CHOP[9] and the infusional regimens EPOCH[10] and CDE. Although in some studies[10] HAART was interrupted during chemotherapy, the concomitant administration of HAART has proven to be feasible. However, the hematologic toxicity of zidovudine, the neurological toxicity of didanosine, zalcitabine and estavudine, as well as the potential nephrotoxicity of tenofovir and indinavir must be considered. It is also important to evaluate the pharmacokinetic interactions between cytotoxic and antiretroviral drugs. In addition, the frequent changes in the drugs included in HAART regimens and the inclusion of new antiretroviral drugs in HAART schedules whose potential interactions with chemotherapeutic agents are still unknown should also be taken into

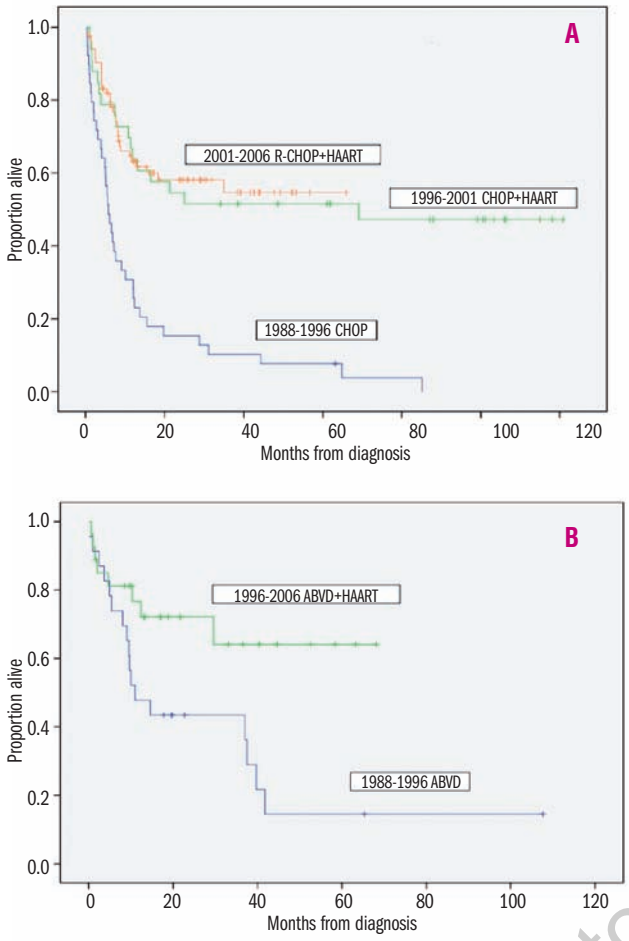

Figure 1. Evolution of the therapy and outcomes of patients with HIV-related non-Hodgkin's lymphomas (A) and Hodgkin's lymphoma (B) in Spain before and after the widespread use of highly active antiretroviral therapy.

account. The results of the combination of full dose chemotherapeutic regimens and HAART have improved the response rate and the survival of patients with HIV-related lymphomas (Figure 1). In two comparative studies, the prognosis of patients with HIV-related lymphomas was similar to that observed in non-immunosuppressed patients with non-Hodgkin's lymphoma of the same histological type.[11,12] The main prognostic factors for these patients were the IPI score and the CD4 lymphocyte count at the time of diagnosis.[13] In addition, it is of note that chemotherapy and concomitant HAART do not cause prolonged suppression of lymphocyte subsets[14] and, most importantly, that the immmunological response to HAART has a positive effect on the survival of these patients.[15]

Treatment of patients with HIV-related BL has evolved from reduced-dose or CHOP-like chemotherapy regimens with resultant poor clinical outcomes to more Burkitt-oriented short, intensive multiagent chemotherapy including fractionated cyclophosphamide, high-dose methotrexate and cytarabine. The widespread use of HAART has overcome much of the reluctance to pursue intensive regimens in AIDS-related BL. Specific therapies for these patients have included CODOX-M/IVAC,[16] LMB86[17] and ALL3/97.[18] Although these regimens have been associated with significant toxicity in HIV-related BL, they have resulted in an improvement in the response rate and in the survival probability of up to 50%. In the ALL3/97 study, no significant differences were observed in the survival of patients with HIV-related or unrelated BL.[18] Again, patients with an immunological response to HAART had a better prognosis than those who did not take or did not respond to HAART.

Mimicking non-Hodgkin's lymphoma in non-immunosuppressed patients, the next step was to use immunochemotherapy for both AIDS-related DLBCL and BL. Three phase II trials with chemotherapy (CHOP in two trials[19,20] and CDE in one[21]) and rituximab have shown that immunochemotherapy with concomitant administration of HAART is feasible, safe and effective, with complete responses in more than 70% of patients and survival probabilities ranging from 65% to 75%. However, from the data of these phase II trials it is difficult to determine the contribution of rituximab to the overall efficacy. The only comparative trial published to date, the AMC-10 trial,[22] which compared the CHOP regimen with or without rituximab, showed a not statistically significant trend for a better response rate (57.6% *vs.* 47%) in the rituximab-CHOP (R-CHOP) arm, which did not translate into better survival, at least in part because of the excess number of infectious deaths in that arm (14% *vs.* 2%). Nevertheless, even in moderately immunosuppressed patients (i.e., those with a CD4 lymphocyte count over 100/μL) no significant benefits in terms of survival were observed in the R-CHOP arm. The inclusion of a high number of severely immunosuppressed patients in that trial could explain the inferior results with respect to those from the three aforementioned phase II trials, since in some studies the CD4 lymphocyte count is a poor prognostic factor in patients with HIV-related lymphomas treated with CHOP-like chemotherapy in the HAART era.

Some groups have explored the combination of rituximab and specific chemotherapeutic regimens in AIDS-related BL. The Spanish PETHEMA, GELTAMO GELCAB and GESIDA groups have recently analyzed the results of the protocol B-ALL/NHL2002 (developed by the German Multicenter Adult Lymphoblastic Leukemia Group) in patients with HIV-related or unrelated BL or leukemia.[23] The response rate was similar in the two groups of patients (84% *vs.* 88%), as was the 2-year overall survival (73% *vs.* 82%). However, in spite of similar hematologic toxicity, HIV-infected patients had higher incidences of grade 3-4 mucositis and severe infectious episodes. Overall, these results were better than those previously achieved in BL with specific chemotherapy without rituximab. If confirmed in larger trials, specific chemoimmunotherapy could become the standard treatment for HIV-related BL provided that the management of the short-term toxicity of the regimen (particularly myelosuppression, mucositis and neutropenia-related infections) is adequate.

The changes in the therapeutic approach to HIV-related lymphomas in the HAART era have also

involved patients with relapsed or refractory disease. Again mimicking the therapeutic options for non-immunosuppressed patients, second-line chemotherapy regimens followed by autologous stem cell transplantation have been increasingly employed in HIV-infected patients. Several uncontrolled studies from European and North American groups and from the European Group for Bone and Marrow Transplantation (EBMT) registry have shown that the procedure is feasible and safe.[24] Collection of peripheral blood stem cells was adequate with mobilization procedures including preferentially chemotherapy and granulocyte colony-stimulating factor, the conditioning regimen was well tolerated, the numbers of days to platelet and neutrophil engraftment were similar to those usually observed in non-immunosuppressed patients and the frequency of both opportunistic and non-opportunistic infections and transplant-related mortality were acceptable. Administration of HAART during the autologous transplantation was strongly recommended to control the HIV load. As expected, the results of autologous stem cell transplantation were better in patients in first or second complete or partial response than in those with chemorefractory lymphomas. The EBMT Working Party on Lymphomas has recently completed a case-controlled study comparing the results of autologous stem cell transplantation in HIV-infected versus non-infected patients. The preliminary results show that except for a slight increase in transplant-related mortality in HIV-infected patients, there was a similar survival after stratification of patients according to the histology of the lymphoma and disease phase at the time of transplantation. On the other hand, case reports and small series suggest that allogeneic transplantation for patients with HIV-related lymphomas merits further investigation in the setting of appropriately designed studies.

In recent years, particularly after the widespread use of HAART, significant advances have been made in the management of HIV-related lymphomas. The results of the therapy have improved dramatically (Figure 1) and are currently almost identical to those attained in non-immunosuppressed patients if adequate supportive therapy is given. It is conceivable that these patients will further benefit from the present and future advances in the therapy of lymphomas to the same degree as the remaining patients. Many of these advances will come from basic and translational research. Research on the mechanisms utilized by lymphomas in immunodeficient individuals (that presented in the article by Capello *et al.*[5] in this issue of the journal is a good example) may have applications in lymphomas in other situations of immunosuppression and even in those arising in immunocompetent patients.

The use of HAART has provided a perhaps more important advantage beyond reducing viral load: a significant decrease in the incidence of HIV-related lymphomas. This decrease has been most evident in the subtypes of HIV-related lymphomas with the poorest prognosis such as primacy CNS lymphomas, which, at present, are only exceptionally observed in patients responding to HAART. Improvement in antiretroviral therapy could contribute to further decrease the incidence of HIV-related lymphomas by completely instead of partially restoring immunosuppression. Adequate collaboration between oncologists, hematologists and specialists in HIV disease is, therefore, mandatory. Ultimately, the eradication of HIV disease, ideally by prevention, albeit currently very difficult at a global level, will definitively solve the problem of HIV-related lymphomas. A Spanish saying states: *Muerto el perro se acabó la rabia* [kill the dog, kill the rabies].

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Cardiovascular disease after hematopoietic cell transplantation – lessons learned

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Hematopoietic cell transplantation (HCT) has now become the treatment of choice for a large number of malignant and non-malignant diseases.[1] It is quite clear that unless effective targeted therapy becomes available, HCT will continue to be offered as a curative therapeutic modality to patients diagnosed with a variety of malignant and non-malignant disorders. Among those who survive the first 2 years, nearly 80% of allogeneic HCT recipients[2,3] and 70% of autologous HCT recipients[4] are expected to become long-term survivors, with an attendant growth in such survivors. Due to improvements in survival rate, major issues for patients undergoing HCT have expanded to include the care and management of survivors, prevention of adverse outcomes, and maintenance of a good health-related quality of life. Some of the well-described complications in this population include subsequent malignancies, cataracts, pulmonary complications, endocrine dysfunction, osteonecrosis, chronic kidney disease, and impairment in functional status due to persistent, chronic graft-versus-host disease (GVHD).[5-7] Details regarding cardiovascular dysfunction after HCT are now emerging.[8-10]

In this issue of the journal, Tichelli *et al.* publish the results of their retrospective study designed to describe the magnitude of risk of and associated risk factors for the development of arterial events after allogeneic HCT.[10] The events of interest include coronary artery disease, cerebrovascular disease and peripheral artery disease. They report that the cumulative incidence of arterial events at 15 years is 6%, and identify older age at the time of HCT and presence of pre-established cardiovascular risk factors (diabetes, obesity, dyslipidemia, arterial hypertension) as being associated with an increased risk of these outcomes.

In a recent study, we used a nested case-control study design to examine the independent role of pre-HCT exposure to therapeutic agents, transplant-related conditioning and co-morbidities in the development of congestive heart failure (CHF) after HCT.[8,9] We identified pre-HCT exposure to anthracyclines and the presence of post-HCT co-morbidities as being associated with delayed CHF after HCT.

The best-described therapy-related late cardiac complications include valvular dysfunction, conduction abnormalities, pericarditis, and cardiomyopathy.[11-13] Arterial complications can occur as a result of damage to the entire vascular system and include coronary artery disease, cerebrovascular disease, and peripheral artery disease.[14,15] While the latency period for many of these diseases can be short, survivors often do not have clinical evidence of disease until several years following HCT.[14-16] As with most other complications observed after HCT, cardiovascular complications following HCT are due, in part, to the treatment prior to, during, and following HCT.

Age at therapeutic exposure, gender, and past medical history are important considerations when identifying the potential risk of long-term cardiovascular disease. The cardiotoxic potential of many anti-neoplas-