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RELAPSED NODULAR SCLEROSIS HODGKIN LYMPHOMA IN A PATIENT WITH HIV INFECTION

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Abstract: *In the combination antiretroviral therapy (cART) era, the incidence of Hodgkin lymphoma (HL) has not decreased, with some studies reporting it may have increased. The incidence of HL is approximately 10-fold higher in HIV-positive subjects. In this population, HL has a more aggressive behavior, including more advanced stage and extranodal involvement at diagnosis. Different chemotherapy regimens have been used, including ABVD, Stanford V and BEACOPP. The concomitant administration of chemotherapy and cART has been shown to have a favorable impact on clinical outcomes and overall survival. As a consequence, current recommendations suggest to treat HL in HIV-positive subjects similarly to uninfected ones and to give concomitantly cART and adequate supportive therapy.*

Here, we describe a case of nodular sclerosis HL in a patient with HIV infection, who achieved remission with ABVD chemotherapy, but unfortunately relapsed and died two years after the initial diagnosis.

KEY WORDS: *Hodgkin lymphoma, Extranodal involvement, Chemotherapy, Antiretroviral therapy, HIV.*

INTRODUCTION

The introduction of combination antiretroviral therapy (cART) has significantly reduced the incidence of AIDS-defining cancers[1-3]. In contrast, the incidence of Hodgkin lymphoma (HL), a non-AIDS-defining cancer, has not decreased[4-6], with some studies reporting it may have increased[7-9].

The incidence of HL is approximately 10-fold higher in the HIV-positive population[10]. HIV-related HL has unusual clinical and pathological characteristics. It commonly has a more aggressive behavior, including more advanced stage and extranodal involvement at diagnosis. Mixed-cellularity HL is the most common histological subtype. Bone marrow involvement is present in up to 50% of cases at diagnosis and Epstein-Barr virus (EBV) genome is usually found in the nucleus of Reed-Sternberg cells[2].

Optimal therapy for HIV-related HL has not been defined, although the combined use of chemotherapy and cART has significantly improved the overall survival (OS). Several chemotherapy regimens have been used, including ABVD, Stanford V and BEACOPP. For patients with relapsing or refractory HL, the use of high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) has been suggested as a salvage therapy[2].

Here, we describe a case of nodular sclerosis HL in a patient with HIV infection, who achieved remission with ABVD chemotherapy, but unfortunately relapsed and died two years after the initial diagnosis.

CASE REPORT

In 2012, a 56-year old HIV-positive man was admitted to hospital complaining of fever, night sweats and weight loss in the previous 6 months. The patient had

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been diagnosed with HIV infection in 1992 and had started antiretroviral therapy in 1995. He was taking darunavir, ritonavir, raltegravir and maraviroc, as he had developed resistance to several nucleoside and non-nucleoside reverse transcriptase inhibitors. His last CD4+ T-cell count was 173 cells/μl, with an undetectable HIV viral load. The patient had a history of hypertension, treated with candesartan, and syphilis. Laboratory results revealed severe anemia (hemoglobin 7.9 g/dl). A Computed Tomography (CT) scan showed multiple lymphadenopathies both above and below the diaphragm. A whole-body positron-emission tomographic (PET) scan confirmed increased 18F-fluorodeoxyglucose (FDG) uptake in several lymph nodes stations, in the lungs, liver and throughout the skeleton. Histological examination of a cervical lymph node revealed the presence of large nucleated Reed-Sternberg cells, who were positive for CD15 and CD30 and negative for CD20. On the basis of cell morphology and immunophenotype, a diagnosis of stage IVB nodular sclerosis HL was made. The patient was treated with six cycles of reduced dose chemotherapy (ABVD: doxorubicin, vinblastine, bleomycin and dacarbazine) and received supportive care with packed red cells and granulocyte colony-stimulating factor (G-CSF). He achieved and remained in remission for almost two years. However, in 2014 the patient started complaining of lumbar pain and fatigue. A relapse was suspected. A CT scan showed the presence of a thoracic paravertebral mass and the enlargement of lymph nodes since the last study. Salvage therapy with C-MOPP (cyclophosphamide, mechlorethamine, vincristine, procarbazine and prednisone) was started. Unfortunately, chemotherapy had to be suspended after two cycles, due to the development of severe pancytopenia and a sudden worsening of clinical conditions, which caused patient's death 28 months after the initial diagnosis.

DISCUSSION

HIV-infected subjects with HL tend to present with advanced stage disease. In fact, at the time of diagnosis up to 90% of patients have stage III/IV disease, with frequent involvement of extranodal sites and high prevalence of B symptoms[11].

The relationship between HL and the magnitude of immune suppression is complex. The risk of developing HL seems greater among patients with moderate immune suppression. In the United States HIV/AIDS Cancer Match study, patients with a CD4+ T-cell count of 150-199 cells/μl were at higher risk of developing HL in comparison to those with severe immune suppression[9]. This observation may reflect the fact that a certain level of immune competence seems important for the proliferation of malignant cells. In fact, in HL tissues the majority of cells are benign lymphocytes, histiocytes, plasma cells and eosinophil granulocytes, which provide crucial antiapoptotic and proliferative signals to Reed-Sternberg cells[12].

Before the introduction of cART, patients often received suboptimal chemotherapy regimens. As a consequence, response to treatment was poor and OS significantly shorter than uninfected subjects. With the availability of effective and tolerated antiretroviral drugs, as well as better supportive care, the use of intensive chemotherapy protocols has become feasible in the setting of HIV infection. It was recently shown that the prognosis for HIV-related HL has become similar to that observed in HIV-negative HL. In one study[13], HIV status did not affect OS: in fact, 5-year OS was 81% for HIV-positive subjects and 88% for HIV-negative ones. Both groups received ABVD chemotherapy. The optimal chemotherapy regimen has not been defined. Spina et al[14] reported that the use of the Stanford V regimen was associated with complete remission in 81% of patients. After a median follow up of 17 months, 33 out of 59 patients were alive and disease-free. Although 69% of patients completed treatment without dose reduction or delay in chemotherapy administration, 78% of subjects developed grade 3 and 4 neutropenia. In another small study[15], the use of the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) in 12 patients (5 of whom were on antiretroviral therapy) was associated with a 100% complete remission rate but a high incidence of opportunistic infections. ABVD is considered the standard regimen for HL in HIV-negative patients. As for HIV-infected subjects, in a recent multicenter Spanish study[16], 62 HIV-positive patients with advanced HL received six to eight cycles of ABVD together with cART. 20% of patients also received G-CSF. The complete remission rate was 87%, which was similar to the response rate observed with the Stanford V regimen. Of importance, the authors found that immunological response to cART was associated with a better OS and event-free survival. For patients with relapsing or refractory disease, the association of high-dose chemotherapy and HSCT has been suggested as a feasible salvage option[17,18].

CONCLUSIONS

It is currently recommended to treat HIV-related HL with the same regimens used in HIV-uninfected patients and to give concomitantly cART and adequate supportive therapy. Randomized con-

trolled trials are needed to compare the efficacy and tolerability of different chemotherapy regimens and to better assess the interaction between chemotherapy and antiretroviral drugs.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

REFERENCES

1. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD; HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006; 43: 27-34.
2. Pinzone MR, Fiorica F, Di Rosa M, Malaguarnera G, Malaguarnera L, Cacopardo B, Zanghì G, Nunnari G. Non-AIDS-defining cancers among HIV-infected people. Eur Rev Med Pharmacol Sci 2012; 16: 1377-1388.
3. La Ferla L, Pinzone MR, Nunnari G, Martellotta F, Lleshi A, Tirelli U, De Paoli P, Berretta M, Cacopardo B. Kaposi's sarcoma in HIV-positive patients: the state of art in the HAART-era. Eur Rev Med Pharmacol Sci 2013; 17: 2354-2365.
4. Clifford GM, Rickenbach M, Lise M, Dal Maso L, Battegay M, Bohlius J, Boffi EL, Amari E, Karrer U, Jundt G, Bordoni A, Ess S, Franceschi S; Swiss HIV Cohort Study. Hodgkin lymphoma in the Swiss HIV Cohort Study. Blood 2009; 113: 5737-5742.
5. Polesel J, Franceschi S, Suligoi B, Crocetti E, Falcini F, Guzzinati S, Vercelli M, Zanetti R, Tagliabue G, Russo A, Luminari S, Stracci F, De Lisi V, Ferretti S, Mangone L, Budroni M, Limina RM, Piffer S, Serraino D, Bellù F, Giacomin A, Donato A, Madeddu A, Vitarelli S, Fusco M, Tessandori R, Tumino R, Piselli P, Dal Maso L; Cancer and AIDS Registries Linkage Study Cancer; AIDS Registries Linkage Study, Lise M, Zucchetto A, De Paoli A, Intrieri T, Vattiato R, Zambon P, Puppo A, Patriarca S, Tittarelli A, Autelitano M, Cirilli C, La Rosa F, Sgargi P, Di Felice E, Cesaraccio R, Donato F, Franchini S, Zanier L, Vittadello F, Vercellino PC, Senatore G, Contrino ML, Antonini S, Palombino R, Maspero S, La Rosa MG, Camoni L, Regine V. Cancer incidence in people with AIDS in Italy. Int J Cancer 2010; 127: 1437-1445.
6. Bedimo R, Chen RY, Accortt NA, Raper JL, Linn C, Allison JJ, Dubay J, Saag MS, Hoesley CJ. Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989-2002. Clin Infect Dis 2004; 39: 1380-1384.
7. Powles T, Robinson D, Stebbing J, Shamash J, Nelson M, Gazzard B, Mandelia S, Møller H, Bower M. Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. J Clin Oncol 2009; 27: 884-890.
8. Simard EP, Pfeiffer RM, Eengels EA. Cumulative incidence of cancer among individuals with acquired immunodeficiency syndrome in the United States. Cancer 2011; 117: 1089-1096.
9. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006; 108: 3786-3791.
10. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007; 370: 59-67.
11. Carbone A, Gloghini A, Serraino D, Spina M. HIV-associated Hodgkin lymphoma. Curr Opin HIV AIDS 2009; 4: 3-10.
12. Gloghini A, Carbone A. Why would the incidence of HIV-associated Hodgkin lymphoma increase in the setting of improved immunity? Int J Cancer 2007; 120: 2753-2754.
13. Montoto S, Shaw K, Okosun J, Gandhi S, Fields P, Wilson A, Shanyinde M, Cwynarski K, Marcus R, De Vos J, Young Am, Tenant-Flowers M, Orkin C, Johnson M, Chilton D, Gribben JG, Bower M. HIV Status does not influence outcome in patients with classical hodgkin lymphoma treated with chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine in the highly active antiretroviral therapy Era. J Clin Oncol 2012; 30: 4111-4116.
14. Spina M, Gabarre J, Rossi G, Fasan M, Schiantarelli C, Nigra E, Mena M, Antinori A, Ammassari A, Talamini R, Vaccher E, Di Gennaro G, Tirelli U. Stanford V regimen and concomitant HAART in 59 patients with Hodgkin disease and HIV infection. Blood 2002; 100: 1984-1988.
15. Hartmann P, Rehwald U, Salzberger B, Franzen C, Sieber M, Wöhrmann A, Diehl V. BEACOPP therapeutic regimen for patients with Hodgkin's disease and HIV infection. Ann Oncol 2003; 14: 1562-1569.
16. Xicoy B, Ribera JM, Miralles P, Berenguer J, Rubio R, Mahillo B, Valencia ME, Abella E, López-Guillermo A, Sureda A, Morgades M, Navarro JT, Esteban H; GESIDA Group; GELCAB Group. Results of treatment with doxorubicin, bleomycin, vinblastine and dacarbazine and highly active antiretroviral therapy in advanced stage, human immunodeficiency virus-related Hodgkin's lymphoma. Haematologica 2007; 92: 191-198.
17. Gabarre J, Marcelin AG, Azar N, Choquet S, Lévy V, Lévy Y, Tubiana R, Charlotte F, Norol F, Calvez V, Spina M, Vernant JP, Autran B, Leblond V. High-dose therapy plus autologous hematopoietic stem cell transplantation for human immunodeficiency (HIV)-related lymphoma: results and impact on HIV disease. Haematologica 2004; 89: 1100-1108.
18. Re A, Cattaneo C, Michieli M, Casari S, Spina M, Rupolo M, Allione B, Nosari A, Schiantarelli C, Vigano M, Izzi I, Ferremi P, Lanfranchi A, Mazzuccato M, Carosi G, Tirelli U, Rossi G. High-dose therapy and autologous peripheral blood stem cell transplantation as salvage treatment for HIV-associated lymphoma in patients receiving highly active antiretroviral therapy. J Clin Oncol 2003; 21: 4423-4427.