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Case Report

Efficacy and Safety of Long Term Brentuximab Vedotin Therapy and Retreatment in an AIDS Patient Affected by Refractory/Relapsed Anaplastic Large Cell Lymphoma: Case Report and Literature Review

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Abstract

Lymphoma is the most common type of cancer in patients infected with HIV despite of the introduction of the antiretroviral therapy. Brentuximab Vedotin (BV) is an anti-CD30 antibody-drug conjugate, which has been approved for the treatment of relapsed or refractory Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL). However, fewer data are available on the role of the BV in the treatment of HIV-CD30+ lymphomas and of its impact on outcomes. We describe the first case of retreatment with BV in a HIV patient with ALCL, ALK- who relapsed after a complete response to a previous BV treatment.

Key words: *Anaplastic large cell lymphoma, HIV infection, Brentuximab vedotin.*

Introduction

Infection sustained by Human Immunodeficiency Virus (HIV) and the subsequent impairment of the immune system represent a major risk for developing lymph proliferative disorders like non Hodgkin lymphomas (NHL) [1], also after the introduction of the Highly Active Antiretroviral Therapy (HAART).

Diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma and primary lymphoma of the central nervous system are the most common histologic variants of NHL in this population, even if classical Hodgkin Lymphoma (cHL) is more frequent histology in the HAART era. Among the less frequent T-cell NHLs, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), cutaneous and systemic anaplastic large cell lymphoma (ALCL) ALK-negative seems to be the most common variants [2].

ALCL is a rare form of disease whose incidence does not exceed 12% of all cases of T-cell NHLs [3]; the expression of the CD30 antigen on the neoplastic cell surface makes it a potential target for the treatment with brentuximab vedotin (BV), an anti-CD30 humanized antibody drug conjugated. However, very few data are available regarding its efficacy and toxicity in the specific cohort of HIV patients treated with HAART.

We report a case of an ALCL, ALK- in a patient affected by acquired immuno-deficiency syndrome (AIDS) with progressive disease after the first-line chemotherapy who experienced a complete remission with BV monotherapy and obtained a second objective response to the retreatment with BV at the subsequent relapse.

Case report

A 49-years old woman was diagnosed with AIDS in November 2012, A3 according CDC categorization for HIV/AIDS. Her CD4 counts were 16 cells/μl and the HIV-RNA circulating copies were 12.540.000 IU/ml. She started HAART therapy with etravirine and tenofovir and lamivudine that resulted in a reduction of the viral load to undetectable levels and in a slightly improvement of CD4 counts with stable levels around 100 cells/μl. The HAART therapy was modified with raltegravir and etravirine and lamivudine in 2013 due to a new hospitalization for esophageal candidiasis.

In November 2014 she was admitted to our hospital for a wasting syndrome, esophageal candidiasis and lymphonodal swelling, the patient noticed also night sweats. At that moment, the CD4 counts were 123 cell/μL and the circulating HIV-RNA copies were undetectable. Based on onset of opportunistic infections and wasting syndrome the CDC classification was modified in C3. She performed a total body CT scan that showed the involvement of right cervical and supraclavicular lymphnodes, as well as mesenterial and left inguinal ones. Then, she performed a supraclavicular lymphnode biopsy which revealed a lymphomatous infiltration consistent with ALCL, ALK-. The neoplastic cells were positive for CD3, CD4+, CD30+, CD45+, Granzyme +, EMA+. The bone marrow biopsy was negative for neoplastic involvement. According to current guidelines, the patient started chemotherapy regimen with the cyclophosphamide, adriamycin, vincristine, etoposide, prednisone (CHOEP-scheme) which was continued for 4 courses.

After the fourth cycle, the disease evaluation performed with CT scan revealed the persistence of the supraclavicular lymphadenopathy and the onset of a new axillary lymphadenopathy. Despite the progression disease, the patient was not suitable candidate for more intensive second line therapy followed by autologous stem cell transplantation because of the persistence of wasting syndrome and of her body mass index which (BMI) were 15. For these reasons BV at dose of 1.8 mg/kg every 21 days was started. In May 2015, after 4 cycles of BV, a new disease evaluation with FDG-PET scan demonstrated a complete metabolic response (CMR). Considering the surprising and very fast response to the treatment and the slow improvement of the wasting syndrome, the patient continued on treatment with BV for a total of 16 courses. HAART with etravirine/lamivudine/ raltegravir was administered concurrently with the chemotherapy. She was also treated with prophylactic agents such as acyclovir for herpes simplex and zoster reactivation, fluconazole for fungal infection, sulfamethoxazole/trimethoprim for Pneumocystis Jiroveci and azithromycin for Mycobacterium Avium-Intracellulare Complex (MAC). The treatment was complicated by grade 4 asymptomatic neutropenia after the first cycle which not required dose delay or reduction. A secondary prophylaxis of neutropenia febrile with granulocyte colony stimulating factor (G-CSF) for 5 days for each cycle was started after the second course avoiding the occurrence of new side effects. Furthermore the BV therapy did not worse the antiretroviral associated neuropathy.

During this period, the patient obtained also an increase of BMI returning in a normal range. The virological assessment evaluated during the therapy showed an isolated viremic increase in March 2015 which was due to the incorrect assumption of antiretroviral drug; later, a correct adherence to the therapy guaranteed the negativity of quantitative plasmatic HIV-RNA determination assessed on April, June, November 2015 and January 2016. For the all treatment the CD4 counts did not exceed the 100/μL. At the end of treatment in January 2016, the final disease evaluation with PET scan confirmed the CMR and the patient showed a very good performance status with a BMI of 19.38.

In July 2016, after 5 months of observation, the patient presented a relapse of disease with the reappearance of the fever and axillary and supraclavicular lymphadenopathies. A total body CT scan confirmed these lymphadenopathies and revealed also the presence of pathologic abdominal lymph nodes. No bone marrow infiltration was detected by biopsy sample. Considering the good performance status of the patient at the relapse, she was considered eligible for a third line chemotherapy including the autologous stem cells transplantation. Then, she received three cycles of IGEV (Ifofosfamide, Gemcitabine, Vinorelbine) as salvage treatment. After the second cycle of IGEV a CD34-positive harvest of $3{,}0\times10^6$ cells/kg was obtained by G-CSF plus Plerixafor. A grade 4 neutropenia occurred after every cycle despite of the primary prophylaxis of the febrile neutropenia with G-CSF. A CT scan performed after the third cycle showed an increase of the diameter of lymph nodes and documented a progressive disease. According to the recent publication of Bartlett et al. [4] we decided to treat again our patient with BV. After only two cycles of BV the fever disappeared. A only drug related grade 3 anaemia occurred after the second cycle leading to blood transfusion and to reduce the next doses at 1.2 mg/kg. The third course was administered but the patient experienced a grade 4 fatigue and a peripheral motor neuropathy which led to a therapy delay. The CT scan performed after the fourth cycle revealed a very good partial response but the treatment was complicated by a back pain due to a vertebral fracture, therefore the patient discontinued the treatment on April 2017. She continued to remain in partial response until to June 2017 when she was hospitalized in another institution for a non neutropenic fever with septic shock and despite of a broad spectrum antibiotics was started, her condition worsened and she died several day later.

Discussion

The introduction of HAART improved the outcome of HIV infected patient affected by NHL. The control of HIV replication obtained with antiretroviral therapy allowed similar treatment approach as for HIV negative patients. Indeed the current guidelines for treatment of HIV associated lymphomas recommended that patients with HIV related lymphoma should usually be treated in an identical manner to HIV-negative patients [5]. The risk of HIV infected patients for developing a NHL varied during the decades according to the introduction of more effective therapies: in 2003, Biggar et al. reported a cumulative risk of 15% for T NHL in a cohort of 302.834 AIDS patients diagnosed between 1978 and 1996, before the introduction of the HAART [6]. More recently, a population based study of Gibson et al. demonstrated that HAART therapy reduced but not removed the risk for NHL development [2]. In particular for ALCL, an historical confront in HIV patients demonstrated a reduction of the standardized incidence ratio (SIR) which passed from 9 in the period 1996-2002 to 1.8 in the period 2003-2010 with an overall SIR of 14.2 compared to the general population. Interestingly, the authors reported an increased incidence of non AIDS-defining subtypes like marginal zone lymphoma, Waldestrom macroglobulinemia and T-cell NHL. In particular, the incidence of ALCL was reported to be higher during the AIDS period rather than in the HIV seropositive status only, suggesting the determinant role of the immune system in the control of this lymphoproliferative disorder [2].

BV is approved for the treatment of CD30 positive lymphomas (cHL, ALCL), but at the present time, few data are available regarding its use in HIV infected patients, because of a possible challenge may be represented by pharmacological interaction between BV and antiretroviral therapy. Regarding ALCL, in 2012 Pro et al. published the results of a phase II trial in which BV was administered in patients with relapsed/refractory ALCL; The authors reported an overall response rate (ORR) of 86% (57% CR and 29% PR) with a median duration of response of 12.6 months, but no mention was made regarding HIV patients included in this trial. It is remarkable that in this trial the use of BV cancelled the differences between ALK positive (which traditionally show a better outcome) and ALK negative patients; moreover the median duration of response of patients in CR treated with BV without stem cell transplantation (SCT) was similar to allogeneic SCT group [7]. More recently, BV was also tested in PTCL; in a phase I trial, the addition of BV to CHOP or CHP (without vincristine in order to minimize neurological toxicity) was safety and

showed a significant antitumor activity. At the present time, a phase III trial is comparing efficacy of BV plus CHP versus CHOP alone in CD30 positive T cell neoplasms (Clinical trial NCT01777152).

The exclusion of HIV infected patients from phase I-III trials of antineoplastic drugs gives few informations for clinicians who need to treat these forms of disease in this population. For this reason, there are few data about interaction of antiretroviral drugs and antineoplastic ones. If we consider the German guidelines [5], HAART should be maintained during chemotherapy and should be selected those compounds which demonstrated the lower interaction profile. Potential of interactions with increased toxicities appears to be higher with antiretroviral combinations that include strong enzyme inhibitors such as ritonavir-boosted protease inhibitors [8]. On the contrary, raltegravir undergoes glucuronidation and allows lower interaction with chemotherapy, based on these reasons our patient replaces tenofovir with raltegravir [9].

Recently, at the 57th Annual Meeting of the American Society of Hematolgy in Orlando, the AIDS Malingnancy Consortium (AMC) presented the results of the phase I portion of the first trial using BV with AVD in the upfront treatment of stage II-IV HIV-associated Hodgkin Lymphoma. Six HIV positive patients with untreated classical Hodgkin lymphoma (cHL) in advanced stage were enrolled. Five of the 6 patients had a negative PET/CT after two doses of BV and the 5 patients who completed the therapy, achieved a CR. The treatment was well tolerated and a phase II portion with 51 subjects to enroll is actively accruing in both the USA and France, in an AMC/LYSA collaboration, clinicaltrials.gov NCT01771107. The recommended Phase II dose is 1.2 mg/kg +AVD every other week [10]. Until major data from prospective clinical trial are available for the safety and efficacy of BV in HIV related lymphoma,only case reports and case series remain an important source of informations. We have found only two case reports described by Gandhi et al. They reported a first patient who had a relapsed ALCL after a previous diagnosis of cHL and a second one who had a relapsed advanced cHL. Both patients were treated with BV and experienced a rapid and complete remission with minimal toxicity, they remained in durable remission until the time of the publication in 2013 [11].

The safety profile of BV is now well described and it is mainly represented by neurological, haematological and pancreatic toxicity. Neuropathy remains a major problem also in patients treated with HIV infection and it may be caused both from antiretroviral drugs and HIV infection. In our patient during all the first treatment period, we did not observe any neurological as well as pancreatic toxicity. Regarding hematological toxicity, a neutropenia G4 was identified after the first cycle with BV but the use of secondary prophylaxis with G-CSF bypassed this potential side effect for all the further cycles of BV. We emphasize this, because the previous experience with chemotherapy and antiretroviral drugs demonstrated a higher incidence of haematological toxicity in HIV infected patients who received both antiretroviral and chemotherapy.

Regarding infectious complications, during the first treatment we did not identify any adverse events, although CD4 counts during all the treatment period remained around 100 cells/μl, the quantitative HIV circulating RNA was always negative during the same period.

We demonstrated also that the retreatment with BV in patients with relapsed ALCL has still antitumor activity. Bartlett et al demonstrated in an open-label multicentre study, the antitumor activity of the retreatment with BV in 68% of relapsed HL or ALCL previously treated with BV [4]. The estimated median time for responding patients was 9.5 months. The rates of AEs were generally very similar to those reported in the pivotal phase 2 trials [7]. However peripheral motor neuropathy was seen higher in the retreatment than in the pivotal study. In our patient, we obtain a second very good partial response with the disappearance of the systemic symptoms and the reduction of the lymphadenopathies but unfortunately the retreatment led to more severe adverse events than in the previously primary treatment. We can explain these severe adverse events with the HIV infection status and the combination HAART and immunotherapy that could be more toxic.

Conclusions

To our knowledge this is the first case report with a patient with relapsed HIV associated ALCL retreated with BV. The progress in clinical and pharmacological research revolutionized the outcome of HIV patients with lymphomas but the toxicity remains a major problem so far. The introduction of novel less toxic drugs, as BV in HIV patients should be a future challenge in terms of evaluation of the efficacy and feasibility therefore new prospective clinical trials are expected with this population. Our experience demonstrated both efficacy and safety of BV in an HIV selected patient and that an early retreatment, even if in advanced progressive disease, seems to be associated with a clinical objective response. However, during BV retreatment these patients should be followed very closely for peripheral motor and sensorial neuropathy and for infectious complications. The confirmations of our data in major cohorts of patients are needed for overpass traditional concern about treatment of HIV infected patients.

References

1. Centers for Disease Control and Prevention (1987) Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. Council of State and Territorial Epidemiologists; AIDS Program, Center for Infectious Diseases. *MMWR Morb Mortal Wkly Rep.* 36: 1S–15S.
2. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA (2014) Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. *AIDS* 28: 2313–2318. [crossref]
3. William BM, Armitage JO (2013) International analysis of the frequency and outcomes of NK/T-cell lymphomas. *Best Pract Res Clin Haematol* 26: 23–32. [crossref]
4. Bartlett, et al. (2014) Retreatment with brentuximab vedotin in patients with CD30-positive hematologic Malignancies. *Journal of Hematology & Oncology* 7: 24
5. Hentrich M, et al. (2014) Therapy of HIV-associated lymphoma recommendations of the oncology working group of the German Study Group of Physician in Private Practice Treaning HIV-Infected Patients (DAGNÄ), in cooperation with the GermanAIDS Society (DAIG). *Ann Hematol* 93: 913–21.
6. Biggar RJ, Engels EA, Frisch M, Goedert JJ (2001) AIDS Cancer Match Registry Study Group, Risk of T-cell lymphomas in persons with AIDS. *J Acquir Immune Defic Syndr* 26: 371-376. [crossref]

7. Pro B, et al. (2012) Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol* 30: 2190–6.

8. Ezzat HM, et al. (2012) Incidence, predictors and significance of severe toxicity in patients with human immunodeficiency virus-associated Hodgkin lymphoma. *Leuk Lymphoma* 53: 2390–2396

9. Kassahun K, et al. (2007) Metabolism and disposition in humans of raltegravir (MK-0518), an anti-AIDS drug targeting the human immunodeficiency virus 1 integrase enzyme. *Drug Metab Dispos* 35: 1657–63.

10. Rubistein PG, et al. (2015) AMC-085: A Pilot Trial of AVD and Brentuximab Vedotin in the Upfront Treatment of Stage II-IV HIV-Associated Hodgkin Lymphoma. A Trial of the AIDS Malignancy Consortium. *Abstr at 57th ASH Meeting, Blood* 126: 1526

11. Gandhi M, Petrich A (2014) Brentuximab vedotin in patients with relapsed HIV-related lymphoma. *J Natl Compr Canc Netw* 12: 16–19. [crossref]

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