Raising Awareness of Non-Hodgkin Lymphoma in HIV-infected Adolescents: Report of 2 Cases in the HAART Era

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Summary: Human immunodeficiency virus (HIV) chronically infected patients are at increased risk of developing non-Hodgkin lymphoma compared with the general population. Highly active antiretroviral therapy has had a dramatic effect on the natural history of HIV infection, reducing the incidence of acquired immunodeficiency syndrome-related non-Hodgkin lymphoma and improving overall survival. However, problems related to adherence to treatment, frequently experienced during adolescence, may increase the risk of acquired immunodeficiency syndrome-related cancers. Optimizing highly active antiretroviral therapy and monitoring noncompliant patients with persisting HIV replication should be considered by physicians who take care of these patients. We herein report 2 cases of relapsed/progressive Burkitt lymphoma in HIV vertically infected adolescents.

Key Words: HIV-infected adolescents, non-Hodgkin lymphoma, Burkitt lymphoma, HAART adherence

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Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma (NHL) first described in African children 50 years ago.[1]

This malignancy has been classified in 3 clinical variants: endemic, sporadic, and acquired immunodeficiency syndrome (AIDS)-associated BL.[2]

Human immunodeficiency virus (HIV)-infected patients have a higher risk of developing NHL compared with the general population.[3] In particular, cumulative viral exposure has been strikingly related to development of BL.[4] Vertically HIV-infected children who have been highly treatment-adherent during the younger ages of their life frequently experience adherence problems during adolescence. Thus, HIV-infected adolescents may remain chronically exposed to high levels of HIV viremia, and this group has a high risk of developing NHL.

There are considerable differences between children and adults regarding the incidence, biology, treatment, and outcome of NHL. Adolescent patients form a separate group that falls between these categories. Although recent reports pay increasing attention to these patients,[5] the impact of adolescent age on the characteristics and outcome of NHL remains to be determined.

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We report here the last 2 cases of BL in HIV-infected adolescents observed in our center from 2007 to 2010.

CASE SERIES

Case 1

A 15-year-old boy vertically HIV infected, CDC B3 stage, presented a 1-month history of epigastric pain, lack of appetite, dysphagia, and tarry stools. The patient had experienced multiple antiretroviral (ARV) regimens always prescribed according to HIV genotyping. Nine months before admission he had started highly active antiretroviral therapy (HAART) based on darunavir, ritonavir, raltegravir, and maraviroc achieving undetectable viremia within 3 months.

Biological tests on admission revealed mild normocytic anemia—lactate hydrogenase (LDH) level 442 IU/L (normal values 100 to 420), $CD4^+$ cell count 762/mm^3 (33%), and viral load of < 50 copies/mL. Abdominal computed tomography (CT) showed multiple adrenal and pancreatic masses. Biopsy of an adrenal lesion revealed pathology consistent with BL according to WHO criteria. The cells were strongly positive for CD20 and CD79, and T-lymphocyte markers (CD3 and TdT) were negative. Tumor cells were negative for BCL-2 and Epstein-Barr virus (EBV) on in situ hybridization. Cytogenetic evaluation revealed a clone with (8;14) translocation. Without evidence of either central nervous system (CNS) or bone marrow involvement, stage IV according to Working Formulation was established. The patient started chemotherapy according to the Italian Association of Pediatric Hematology Oncology (AIEOP) protocol for NHL, which includes dexamethasone, ifosfamide, methotrexate, cytarabine, etoposide phosphate, vincristine, cyclophosphamide, daunomycin and intrathecal administration of prednisolone, cytarabine, and methotrexate, administered concomitantly with HAART. After 4 courses of chemotherapy, CT scan showed persistent adrenal and pancreatic masses. The fifth course of chemotherapy was administered with the addition of rituximab (375 mg/m^2). After completion of chemotherapy, with the support of pegfilgastrim, hematopoietic cells from the peripheral blood were collected by a single leukapheresis ($CD34^+$ 1.19×10^6). A repeat CT scan showed progression of lymphoma with increased dimensions of adrenal and pancreatic lesions. The biopsy of adrenal tissue demonstrated $CD20^+$ cells expression and the R-ICE salvage regimen (rituximab, ifosfamide, carboplatin, and etoposide) was started. Infectious complications during the antineoplastic treatment involved herpes zoster, BK virus isolated from the urine, *Stenotrophomonas maltophilia* in blood cultures and were treated with antibacterial and antiviral therapy. At the end of chemotherapy, instrumental tests showed a status of progressive disease with several spinal masses. Bone marrow aspirate and cerebrospinal fluid resulted positive for BL. The child died after 7 months from the diagnosis of lymphoma.

Case 2

A 15-year-old boy with vertically acquired HIV infection, CDC stage B3, with a very poor adherence to ARV treatment, presented a 6-month history of joint pain localized in hands and feet. During a previous hospitalization, skeleton x-ray and

autoantibodies were negative. Clinical examination showed left parietal and eyelid swelling and left exophthalmos. On admission, antiviral regimen included tenofovir, emtricitabine, atazanavir, ritonavir, saquinavir. Biological tests disclosed the following values: LDH 520 UI/L; $CD4^+$ cell count 105/mm^3 (5%); HIV viral load 66,000 copies/mL. Polymerase chain reaction detected the presence of 120,000,000 EBV blood copies/mL. Abdominal ultrasound and CT scan documented the presence of bulky enlarged lymph nodes at the celiac tripod, left renal hilum, and portal splenic mesenteric region. Skeleton x-ray showed osteolytic lesions at distal right radius and ulna and in frontal-parietal region. Magnetic resonance imaging confirmed signal alterations of the skull. Total-body bone scintigraphy revealed a higher fixation of radiocompound at the followed sites: skull, clavicles, ribs, metacarpal bones, right radius, femur, fibula, and upper tibia. Bone biopsy of right radius showed morphologic and histologic findings typical of BL. The cells were strongly positive for CD20 and CD79, and T-lymphocyte markers (CD3 and TdT) were negative. Cytogenetic test showed translocation (8;14). Bone marrow aspirate and CNS were negative for NHL and stage IV was established according to the Working Formulation. The patient started NHL treatment according to the AIEOP protocol with achievement of complete remission. After an interval of 2 years, the patient presented a relapse of BL with zygomatic localization. HAART at this time consisted of saquinavir, ritonavir, atazanavir, and abacavir/lamivudine. The HIV viral load and $CD4^+$ counts were < 50 copies/mL and 461 (21%), respectively. Polymerase chain reaction detected the presence of 974 EBV blood copies/mL. There was neither bone marrow nor CNS involvement. Salvage chemotherapy was begun according to the R-ICE protocol and 3 cycles were completed.

HAART was changed to ritonavir, darunavir, etravirine due to gastointestinal toxicity and maintained during the entire chemotherapy treatment period.

After completion of the last cycle of salvage chemotherapy and with the support of granulocyte-colony stimulation factor (G-CSF), hematopoietic cells from peripheral blood were collected by a single leukapheresis. High-dose therapy according to the BEAM regimen was started (carmustine/BCNU 300 mg/m^2 on day -7, cytarabine 100 mg/m^2 twice a day, and etoposide/VP-16 200 mg/m^2 on day -6 to -3, melphalan 140 mg/m^2 on day -2). Autologous transplantation with 15.3×10^6 $CD34^+$ cells/kg was performed on day 0. Renal toxicity manifested as proximal tubulopathy with hypophosphatemia and proteinuria requiring intravenous rehydration and electrolyte correction. Hematopoietic engraftment was attained on days $+12$ and $+22$ with $> 500/mm^3$ neutrophils and $> 20{,}000/mm^3$ platelets, respectively. Two days before transplantation, maraviroc was added to the patient's current ARV drugs, and it was continued until day $+60$. Clinical and radiologic evaluation demonstrated a continuous complete remission at $+13$ months.

DISCUSSION

Chronically HIV-infected patients are at increased risk of developing NHL as compared with the general population.[3] A recent study reported a decline of HIV-associated BL from 81 per 100,000 person-years in pre-HAART era (1980 to 1995) to 17 per 100,000 person-years in HAART era (1996 to 2007).[6]

Despite this progress, the incidence of AIDS-related NHL has been less dramatically reduced by HAART than that of others AIDS-related cancers.[3]

To date, it is widely accepted that the major risk factor for developing NHL and BL is represented by cumulative HIV viremia, defined as uncontrolled HIV replication during HAART, rather than the latest viral load, independently of $CD4^+$ cell count, as previously described.[4,7]

The development of lymphoma is often observed in a scenario of low adherence to treatment, which represents a relevant issue among young adults and adolescents. Adherence to drug treatment is often difficult in the pediatric population for reasons generally related to the developmental stage of the patient. In younger children, poor medication tolerability and palatability, lack of available liquid formulations for some medicines, hinder adherence. In the adolescent population, psychosocial factors contribute greatly to nonadherence to ARV therapy and often adolescents are given independence in taking medications despite not fully understanding their regimens.[8]

Furthermore, therapeutic options for vertically HIV-infected children, who enter into adolescence with a history of multidrug regimens, are limited to high pill burden.

The largest multicenter European study recently published by the COHERE group showed that the estimated cumulative proportion of children who had triple-class virologic failure by 5 years after anti retroviral therapy initiation was 12% and by 8 years was 20.3%. Noteworthy, older age (10 to 15 y) at the time of anti retroviral therapy initiation was associated with an increased risk of failure.[9] These results confirm the challenge of maintaining lifelong viral suppression in HIV vertically infected children.

Both our patients experienced multiple therapeutic regimens with poor adherence to treatment. One patient, who started HAART 9 months before BL diagnosis, presented undetectable HIV VL (viral load) despite earlier nonachievement of viremic control. The other case was characterized by suboptimal adherence and by uncontrolled HIV replication over time. Clinical and laboratory features are summarized in the (Table 1). Cumulative HIV viremia in both cases seems to be the main risk factor of lymphomagenesis even in these young patients.

Despite NHL diagnosis formally implies a progression of HIV disease according to CDC definition, both patients

TABLE 1. Summarizes Clinical and Laboratory Features

Features	Case 1	Case 2
Sex	M	M
Ethnicity	White	White
Age at HIV diagnosis (mo)	4	72
CDC before BL	B3	B3
HAART at BL diagnosis	TMC 114-RTV-RAL-MARA	TDF-FTC-ATZ-RTV-SAQUI
Time of HAART before BL (mo)	9	24
Age at lymphoma diagnosis (mo)	180	180
Presentation	Abdominal pain, nausea, vomiting	Joint pain
EBV	Negative	Positive
Viral load baseline (copies/mL)	49	66,000
$CD4^+$ baseline % (cells/mm^3)	33% (762)	5% (105)
Cumulative HIV viremia (mo)	120	96
Risk factor	Low adherence, cumulative viremia	Low adherence, cumulative viremia

ATZ indicates atazanavir; BL, Burkitt lymphoma; EBV, Epstein-Barr virus; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV, Human immunodeficiency virus; MARA, maraviroc; RAL, raltegravir; RTV, ritonavir; SAQUI: saquinavir; TMC 114, darunavir; TDF, tenofovir.

showed a good viremic control during chemotherapy and follow-up period, ensured by HAART coadministration. Patient 2, who performed transplantation, presented a rapid lymphocyte count recovery confirming as immune reconstitution after autologous stem cells transplantation in HIV-infected individuals is comparable to uninfected patients.[10] In HIV population, immune recovery after transplantation is influenced by viral-dependent factors, such as viral infection of bone marrow stromal cells, apoptotic and cytokine pathways.[11] Many studies focused on quantitative data, but the functional evaluation and protective role of reconstituted immune cells need to be investigated.

Treatment of such malignancy remains a major challenge even in this age group. In healthy adolescent population, survival rate reach values above 80%.[5] Mortality rate in vertically HIV-infected adolescents affected by NHL is not well defined. Most of the data present in the literature come from observational studies performed in developing countries where the quality of the data collected generally prevents a reliable estimate of the survival rate.[12]

HAART introduction along with improved supportive care allowed clinicians to explore dose-intensive approach in HIV-infected individuals with lymphoma.[13] Because many antineoplastic and ARV drugs are metabolized by the CYP system, their coadministration could result in drug accumulation leading to an increase in toxicity or decreased efficacy. As we described in our cohort, the previous treatment with tenofovir in association with a protease inhibitors in patient 2 could be the cause of the renal toxicity observed.[14]

Nevertheless different opinions are reported in literature; several studies confirmed that a combined administration of full-dose chemotherapy together with HAART is safe and improves survival outcomes similarly to non–HIV-infected individuals.[15–17] However, the optimal regimen for patients with AIDS BL has not yet been defined.

In our series, both patients received chemotherapy according to the AIEOP protocol for NHL with discordant results. One patient presented a progressive disease leading to death, whereas the other achieved complete remission and relapsed after 26 months. The optimal chemotherapeutic strategy for patients with relapsed/refractory AIDS-NHL has not yet been defined. R-ICE regimen is a commonly used salvage therapy because of the encouraging results in pediatric-relapsed NHL[18]; however, no prospective studies have been reported in HIV-infected patients.

Although the addition of rituximab to the chemotherapeutic regimen is a standard of care for immunocompetent patients with B-cell NHL,[19] its use is still debated in HIV-infected patients.[20,21] Recent data indicate that inclusion of rituximab in chemotherapy may be associated with an increased risk of infectious complications in HIV patients with severe immune impairment.[19] Despite these data, rituximab remains commonly used in HIV-infected patients without major side effects compared with HIV-negative population.[15]

In the HIV-negative setting, high-dose chemotherapy with autologous stem cell transplantation (ASCT) is the optimal therapy for relapsed Hodgkin and NHL.[22] Similarly, ASCT has resulted in a valid therapeutic option even in HIV-infected adults. Complete remission ranging from 48% to 90%, and overall survival ranging from 36% to 85% have been recently reported among HIV-infected adults over a long-term follow-up. Fatal toxic events at 3 months did not exceed 5%, which is not different compared with HIV-negative cases.[11] No definitive data have been published on pediatric population where experience is still limited. To date, only 2 cases of ASCT in children with lymphoma and HIV infection have been published.[23,24]

CONCLUSIONS

We herein reported 2 cases of relapsed/progressive BL in HIV vertically infected adolescents with different outcomes. HIV-infected adolescents are particularly vulnerable to specific adherence problems that expose them to increased risk of AIDS-related NHL. This should encourage physicians to optimize HAART regimens and to perform a careful monitoring of noncompliant patients with persisting HIV replications including psychological support.

To date, no standard second-line regimen has emerged for patients with relapsed or progressive AIDS-NHL. We used rituximab plus ICE regimen in both cases with different results. Considering the small number of patients and different outcomes, our experience precludes definitive conclusions about the efficacy of R-ICE regimen in AIDS-related BL.

Our second patient is the third case of pediatric HIV-related BL successfully treated with high-dose therapy including rituximab followed by ASCT described to date. Further studies are needed to validate this therapeutic strategy in HIV-related NHL.

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