Research Letters

Challenges to Treatment of Leukemia in HIV-positive Children

Summary

We describe the challenges to treatment of leukemia in three cases of human immunodeficiency virus (HIV)-infected children with multiple infections and complications. Two of the three patients had acute myeloid leukemia and the other one acute lymphoblastic leukemia. Two of the patients were known with HIV infection; the third was diagnosed on admission. All patients received antiretroviral therapy with standard doses of lamivudine, stavudine and efavirenz or lopinavir/ritonavir. All three were diagnosed with Mycobacterium tuberculosis on one or more occasions: pulmonary or miliary involvement or tuberculous meningitis. One patient developed spinal paraplegia and needed an urgent laminectomy. Later he recovered almost completely. The interaction between antiretroviral and antituberculosis treatments combined with chemotherapy, antibiotics and supportive care is not known. Despite the severity and the complexity of several associated diseases, the outcome of the patients was rewarding and encouraging.

Key words: leukemia, HIV, infection, children, Africa.

Introduction

Leukemia is the most common childhood malignancy in South Africa; human immunodeficiency virus (HIV)-positive children may also be affected. We describe three HIV-infected children treated for leukemia, tuberculosis (TB) as well as multiple infections and the challenges raised by their treatment.

Case 1

A 5-year and 7-month-old HIV-infected boy was referred to the oncology service because of extreme pallor and petechiae. Two months before referral, he had been diagnosed with pulmonary TB and stage 3 HIV disease [1]. His CD4 count was \(407 \times 10^9/l\) and the viral load was \(1400\) RNA copies ml\(^{-1}\).

He had pancytopenia with 74% blasts on the peripheral smear. A bone marrow examination indicated acute myeloid leukemia (AML) M3 with fluorescence in situ hybridization for t(15;17)-positive. The patient received chemotherapy according to the acute myeloid leukemia-Berlin Frankfurt Munster (AML-BFM) 2004 protocol, with all-trans retinoic acid and antiretroviral therapy (lamivudine, stavudine and efavirenz), while anti-TB treatment continued.

Six days later, the patient reported severe back pain losing overnight, both ambulation and continence, due to a flaccid paraplegia with L2 sensory level. Emergency magnetic resonance imaging revealed the presence of a large soft tissue collection that originated from the psoas muscle, extending into the spinal canal at levels L1–2. An emergency L1–L3 decompression laminectomy was performed. The biopsy confirmed leukemic infiltrates.

With continued chemotherapy, within 1 week, he regained bladder and bowel control while grade 2/5 power was noted bilaterally.

While on treatment he had frequent systemic infections and developed allergic reactions, most probably related to some of the numerous drugs administered.

In spite of the tortuous course of his management, a year after completion of chemo- and anti-TB therapies the child remains in complete remission, virally suppressed, immune reconstituted and neurologically intact.

Case 2

A 9-year-old HIV-infected girl presented with a 2-week long history of cough, fever, poor appetite and a 4-day history of left-sided weakness. She had been diagnosed with stage 4 HIV infection at the age of 3 years and was commenced on highly active antiretroviral therapy (HAART)—lamivudine, stavudine and efavirenz—at the age of 6 years. Her previous history depicted a long battle with TB, being treated three times previously. At presentation she was marasmic and stunted, weighing just 59% of the expected weight for age and measuring only 84% of the expected height for age [2] with signs of chronic lung disease and a left hemiplegia.

Contrasted computed tomography revealed a right-sided basal ganglia infarction and magnetic resonance T2 Fluid-Attenuated-Inversion-Recovery (FLAIR) showed a large hyperintense lesion extending from the basal ganglia to the centrum semiovale on the right. The lesions were deemed to be in keeping with HIV encephalopathy. The initial full blood count showed a white cell count of \(45 \times 10^9/l\), a severe anemia (hemoglobin of \(4.7\ g/dl\)) and a platelet count of \(47 \times 10^9/l\). The peripheral smear showed 88% blasts, with Auer rods. The diagnosis of AML was confirmed on bone marrow aspiration and trephine biopsy. Empiric anti-TB treatment was started considering the child’s immune deficiency state and previous history of repeated TB infections. Viral load was...
undetectable. Shortly after admission, the patient developed varicella-zoster (VZ) infection with pneumonia.

The chemotherapy (AML-BFM 2004 protocol) was started after the infectious episode. Anti-TB treatment, *Pneumocystis* prophylaxis (trimethoprim–sulfametoxazole) and HAART were continued.

The child achieved remission following the induction phase of the protocol but unfortunately relapsed on maintenance.

**Case 3**

A 2-year and 8-month-old boy presented with a short history of pallor and right-sided artralgia. Ten months previously, he had been treated for TB pneumonia but the child’s mother discontinued his treatment once he showed clinical improvement. He was diagnosed later as HIV-positive (CD4 count 16%).

Physical examination revealed an acutely ill, pale child with generalized lymphadenopathy, hepatosplenomegaly and a painful right knee joint. Radiographs showed bilateral knee effusions and periosteal reactions. Cerebrospinal fluid analysis revealed 110 lymphocytes, no polymorphs, protein of 3.52 g l\(^{-1}\) and cerebrospinal fluid (CSF) glucose of 3.4 mmol l\(^{-1}\). No acid-fast bacilli were seen on microscopy but the child was restarted on anti-TB treatment for presumed TB meningitis. The joint lesions were also attributed to TB. Shortly thereafter the patient contracted a VZ infection from his mother.

The bicytopenic blood picture and the joint lesions prompted the performance of a bone marrow aspiration and biopsy. The results indicated a pre-B lymphoblastic leukemia and the cytospin of the CSF was highly suggestive of meningeal infiltration. HAART was initiated (lamivudine, stavudine and lopinavir/ritonavir) and chemotherapy was started according to the acute lymphoblastic leukemia-Berlin Frankfurt Munster (ALL-BFM) 95 standard risk protocol.

Six months after the start of intensive chemotherapy, the HIV viral load was undetectable and almost 6 years after the diagnosis of ALL, the child remains in remission.

**Discussion**

The multiple challenges to the treatment in this series originated from: the TB co-infection; the high incidence of opportunistic infections during chemotherapy; the differential diagnosis of neurological signs and the potential for drug interactions. Further, there are no guidelines on adapted chemotherapy protocols, reduced intensity protocols and specific therapy duration or for bone marrow transplant.

All reported children received TB treatment, antiretroviral treatment, chemotherapy, antiemetics and pneumocystis prophylaxis concurrently. Often antimicrobials, antifungals, antipyrexial medication and analgesia were added according to the local protocol. In some instances most of these drugs were used concurrently. Only another study describes the association of AML in a 7-year-old HIV-positive child with a poor outcome.

The controversial relationship between the curative treatment of leukemia in children with HIV and TB remains debatable as it is not yet agreed if they should be treated with reduced intensity protocols, receive granulocyte colony stimulating factor (GCSF) or be offered bone marrow transplants (BMTs). In countries with limited resources, GCSF is not in the protocols and BMT is not an option in the treatment of leukemia. BMT could be considered if the patient has an HLA compatible, HIV-negative sibling.

**Conclusion**

We conclude that HIV-infected children could be treated successfully for leukemia on full-intensity chemotherapy protocols and that the numerous complications, mostly infectious, should be treated immediately.

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