Malignancies in HIV-Infected Children at Siriraj Hospital

KLEEBSABAI SANPAKIT, M.D.*,
WORAPANT KRIENGSUNTORNKIJ, M.D.*,
VORAVARN S. TANPHAICHITR, M.D., M.S.*,
GAVIVANN VEERAKUL, M.D.*,
KULKANYA CHOKEPHAIBULKIT, M.D.*,
CHULARATANA MAHASANDANA, M.D.*

Abstract

Background : Some malignancies such as Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) are one of the acquired immunodeficiency syndrome (AIDS) - defining illnesses. With the improving survival of patients with AIDS due to better prevention and treatment of infectious complications, there may well be an increase in AIDS-related malignancies.

Objective : To study malignancies in human immunodeficiency virus (HIV)-infected children in view of demographic data, HIV disease status, characters of malignancies, and treatment outcome.

Method : Retrospective study was performed in HIV-infected children with malignancies at Siriraj Hospital from January 1995 to October 2001.

Results : During the 6 year and 10 month period, there were 7 HIV-infected children (2 boys, 5 girls) with malignancies. Mean age at diagnosis of malignancies was 3 years 7 months (2 years 6 months - 5 years). Hepatomegaly and lymphadenopathy were the most common presenting symptoms. All patients had NHL stage III or IV. Burkitt's lymphoma was the predominant type. Six patients were treated with appropriate chemotherapy and one patient also received antiretroviral therapy. Only one patient with large cell lymphoma stage IV who received both antiretroviral and chemotherapy has survived to date. Five patients died during chemotherapy treatment and one patient died before receiving chemotherapy. Causes of death of these patients were infections. One of them with Burkitt's lymphoma stage III also had central nervous system (CNS) relapse at the time of death. Mean survival time after diagnosis with malignancies was 11 months (15 days - 3 years 1 month).

Conclusion : NHL is the most common malignancy in HIV-infected children at Siriraj Hospital. Age at presentation of NHL in these children is younger than their non-HIV counterpart. Outcome of treatment is poor. Adjustment protocol for treatment of malignancy in HIV-infected children combined with antiretroviral therapy for controlling HIV infection should be studied further.

Key word : Malignancies, Children, HIV Infection

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* Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Although childhood cancer seems rare, newly diagnosed patients in Thailand is approximately 1,200-1,500 cases per year (personal communication from Thai Pediatric Oncology Group meeting 2001). The etiologies of childhood cancer are mostly unknown but it is well demonstrated that immunodeficiency states increases the risk of cancer[1].

Human immunodeficiency virus (HIV) infection is one of the most common causes of acquired immunodeficiency states. The number of HIV-infected patients especially children is increasing. With improvement of healthcare, these children live longer and may be at risk of developing acquired immunodeficiency syndrome (AIDS) -related malignancy. The incidence of malignancy in these children was reported to be 0.5-4 per cent. The most common type has been non-Hodgkin's lymphoma (NHL) [2,3]. In patients with advanced HIV infection, the incidence of NHL is increased by approximately 100-360 fold[4]. The higher risk of HIV-infected patients to develop malignancy could be from suppression or loss of immune surveillance, cytokine dysregulations and concurrent infections with many potentially oncogenic viruses[5], especially Epstein-Barr Virus[6,7].

The authors reviewed HIV-infected children with malignancies at Siriraj Hospital to demonstrate the character of malignancies, HIV disease status, and treatment outcome.

PATIENTS AND METHOD

The medical records of all newly diagnosed pediatric HIV-infected patients with malignancies at Siriraj Hospital, Mahidol University, Bangkok, Thailand from January 1995 to October 2001 were retrospectively reviewed for demographic data, signs and symptoms at presentation, type and staging of malignancies, HIV disease status, treatment, complications, and outcome.

RESULTS

There were 7 HIV-infected children with malignancies during the 6 years and 10 months period. Two patients were boys and 5 were girls (boy:girl = 1:2.5). All patients acquired HIV infection from perinatal exposure. Age at presentation of malignancies was between 2 years 6 months to 5 years (mean 3 years 7 months). Clinical presentations are shown in Table 1.

Most common signs and symptoms were hepatomegaly and lymphadenopathy. The duration of symptoms varied from one week to five months (mean 8.7 weeks) before the diagnosis of malignancy was made.

Characters of malignancy

All patients were diagnosed with malignant lymphoma (NHL type) either by lymph node or mass histology, ascitic fluid cytology, or bone marrow

Table 1. Presenting signs and symptoms of malignancies in pediatric HIV patients.

Signs and Symptoms	Numbers of patients	% of total patients
Hepatomegaly	5	71.43
Lymphadenopathy	5	71.43
Abdominal mass	3	42.86
Splenomegaly	3	42.86
Anemia	2	28.57
Weight loss	1	14.29
Fever	1	14.29
Mass at cheek	1	14.29
Mass at lip	1	14.29
Peritoneal effusion	1	14.29

examination. Three patients (42.9%) were in stage IV with bone marrow involvement in 2 patients and central nervous system (CNS) involvement in 1 patient and four patients (57.1%) had stage III disease. Summarized data of staging and pathology of NHL are shown in Table 2.

Type of lymphoma

From the pathological reports, 4 patients (57.1%) had small noncleaved cell type (Burkitt's lymphoma) (high grade), 2 (28.6%) had large cell type (intermediate grade), and one (14.3%) had unknown cell type due to extensive necrosis of the tumor.

HIV disease status

All patients had stage C3. Five patients had CD4 count with a result of less than 500 cells/mm^3 (<15%). One patient with CNS involvement at diagnosis and one patient with relapsed CNS disease had a CD4 count of 83 (3.77%) and 53 (4.3%) cells/mm^3 respectively.

Treatment protocol for lymphoma

Chemotherapy protocol for small noncleaved cell lymphoma stage III (SNC III) was modified from POG (Pediatric Oncology Group) protocol. Chemotherapy consisted of prednisolone, cyclophosphamide, vincristine, adriamycin, methotrexate and cytarabine with intrathecal methotrexate and cytarabine for a total of 8 months[8].

Chemotherapy protocol for small noncleaved cell lymphoma stage IV (SNC IV) was modified from LMB (lymphoma B) 89 protocol. The protocol consisted of reduction phase, induction phase, consolidation phase and maintenance phase. Chemotherapy was cyclophosphamide, vincristine, prednisolone, methotrexate, cytarabine, adriamycin and etoposide with intrathecal methotrexate, hydrocortisone and cytarabine for a total duration of 8 months[9].

Chemotherapy protocol for large cell lymphoma stage III (LCL III) was modified from BFM (Berlin-Frankfurt-Munster)-NHL protocol. Chemotherapy consisted of prednisolone, cyclophosphamide, ifosfamide, methotrexate, cytarabine, etoposide and doxorubicin with intrathecal methotrexate, cytarabine and hydrocortisone for a total duration of 6 months[10].

Chemotherapy protocol for large cell lymphoma stage IV (LCL IV) was modified from APO protocol (vincristine, adriamycin, prednisolone). The protocol consisted of induction, consolidation, CNS prophylaxis (intrathecal methotrexate and cranial irradiation) and maintainance phase for a total duration of 2 years. Chemotherapy was prednisolone, vincristine, adriamycin, 6-mercaptopurine, L-asparaginase and methotrexate[11].

Progression

Four patients were treated with chemotherapy protocol for small noncleaved cell and two

Table 2. Staging and pathology of non-Hodgkin's lymphoma in pediatric HIV infected patients at Siriraj Hospital.

Pathology	Stage	Numbers of patients	% of total patients
Small noncleaved cell	III	2	28.7
(Burkitt's lymphoma)	IV	2	28.7
Large cell lymphoma	III	1	14.2
	IV	1	14.2
Unknown cell type	III	1	14.2

patients received chemotherapy protocol for large cell lymphoma according to staging. Two patients with small noncleaved cell NHL (1 patient with stage III, 1 patient with stage IV) had pulmonary tuberculosis at the time of diagnosis of NHL. The patient with unknown cell type NHL died from *Klebsiella pneumoniae* sepsis before receiving chemotherapy. All patients except the one who died before receiving chemotherapy received trimethoprim/sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia. Only one patient with large cell lymphoma stage IV (bone marrow involvement) has survived up till now, 37 months after diagnosis. He was treated with chemotherapy protocol for large cell lymphoma and antiretroviral drugs (3 idovudine plus lamivudine while receiving chemotherapy and was changed to didanosine plus stavudine until the time of study). Chemotherapy had been completed for 13 months. The others did not receive antiretroviral therapy due to economic status or compliance problems. Five patients died during chemotherapy treatment from sepsis. Mean duration of survival after diagnosis of NHL was 11 months (0.5-37 months). Summarized data of patients are shown in Table 3.

DISCUSSION

With recent improvement in the treatment of HIV, these infected children are surviving longer. The current mean survival time of HIV-infected children is about 9-10 years[12]. Despite advances in antiretroviral therapy and in the treatment and prevention of opportunistic infections, oncological complications of HIV infection continue to occur and have become clinically significant[13]. Increased cancer risk is of particular concern and HIV-associated cancers have emerged as a leading cause of death among patients with AIDS[14]. The most frequent reported malignancy in HIV-infected children is NHL. The majority of these patients acquired the HIV infection vertically or from transfusion of blood and clotting factor concentrates[15]. The mean age at diagnosis of malignancy in the perinatal HIV-infected children has been reported at 35 months, with a range of 6 to 62 months[15].

In a previous report, most lymphomas in children with AIDS presented with fever, weight loss and extranodal site involvement with hepatomegaly, jaundice, abdominal distention, evidence of bone marrow involvement, or CNS symptoms from subarachnoid CNS involvement or an isolated primary

Table 3. Data of HIV-infected children with malignancies at Siriraj Hospital from January 1995 to October 2001.

Case	Pathology	Stage	CNS involvement	BM involvement	CD4 count♦ (cells/mm^3)	Concurrent infection♦	Antiretrovirus treatment	Chemotherapy protocol	Outcome	Duration of chemotherapy treatment
1	SNC	4	Yes	No	83	Pulmonary tuberculosis	No	SNC IV	Died, sepsis	3 days
2	SNC	3	No	No	ND	-	No	SNC III	Died, sepsis	3 months
3*	SNC	3	No	No	ND	Pulmonary tuberculosis	No	SNC III	Died, sepsis	10 months
4	NA	3	No	No	375	*Klebsiella pneumoniae sepsis*	No	NT	Died, sepsis	NT
5	LCL	3	No	No	285	-	No	LCL III	Died, sepsis	2 months
6	LCL	4	No	Yes	365	-	Yes	LCL IV	Survive	24 months (completed)
7	SNC	4	No	Yes	ND	-	No	SNC IV	Died, sepsis	2 months

SNC = small noncleaved cell or Burkitt's lymphoma, LCL = large cell lymphoma, NA = cell type can not be identified, ND = not done, NT = no chemotherapy treatment
* After treatment with chemotherapy for 8 months, this patient had CNS relapse. CD4 count at the time of relapse was 53 cells/mm^3.
♦ At the time of diagnosis of non-Hodgkin's lymphoma

intraparenchymal CNS lymphoma. Usually, they behave clinically aggressive and have diffuse (stage III or IV) disease at the time of presentation. HIV-associated NHL are predominantly high grade B cell tumors and t (8;14) is the most frequent translocation[15].

Pediatric patients with AIDS usually have CD4 lymphocyte counts of less than 50 cells/mm^3 at diagnosis of the malignancy[15,16]. Thus, a defective immune system seems to be important for the appearance of lymphoma. A study of adult AIDS patients with NHL found that a CD4 count of less than 50 cells/mm^3 correlated very strongly ($p = 0.0085$) with a higher rate of malignancy[17].

In the present study, all patients acquired HIV infection vertically and developed NHL at the mean age of 3 years 7 months; which was in the same age range previously reported[15]; however, younger than non-HIV infected patients in a previous study of childhood NHL at Siriraj Hospital (mean age at diagnosis 6 years 6 months), (unpublished data from a study of childhood NHL at Siriraj Hospital from 1994 to 1998 by Veerakul G et al.). The most common presenting symptom was hepatomegaly and lymphadenopathy. All had advanced disease (stage III, IV) and HIV stage C3. Small non-cleaved cells (Burkitt's lymphoma) were the predominant cell type. Two patients with a CD4 count of less than 100 cell/mm^3 had CNS involvement. These results support other studies in character of disease and in that the more immunocompromised, the more aggressive the malignant disease will be.

Therapy for adults with HIV infection and systemic NHL has resulted in a poor rate of success with short survival time after diagnosis despite intervention. Most chemotherapy regimens resulted in a median survival of only 5-6 months, with death often caused by intercurrent opportunistic infections[18, 19]. The number of pediatric AIDS patients treated for lymphoma is too small to make any conclusion. There is a report of cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine and prednisolone plus intrathecal methotrexate and/or cytarabine providing durable remission[15]. CNS lymphomas are a greater challenge because of delayed diagnosis in most cases and the poor outcome from treating these patients[20]. Data from several studies indicated that intrathecal therapy is essential even for those without evidence of meningeal or CNS mass lesions at diagnosis of NHL because of the high incidence of subsequent CNS disease[15,21]. Radiation therapy may be a helpful adjunction for those with CNS involvement. Chemotherapy can result in dose-limiting cytopenia and an increased risk of opportunistic infection. Survival rate of patients depends on several HIV-related factors such as performance status, history of AIDS before diagnosis of lymphoma, and CD4 cell count[22,23].

In the present study, mean survival time after diagnosis with NHL was 11 months. Six of seven cases died from sepsis before or during treatment with chemotherapy. Only one patient who was diagnosed with intermediate grade large cell lymphoma stage IV with bone marrow involvement is still alive to date. He was treated with chemotherapy for large cell lymphoma stage IV and antiretroviral drugs. His malignancy-free-survival is at least 13 months after completion of chemotherapy. Concomitant antiretroviral therapy may be an important part of cancer treatment protocol because therapy for cancer will be beneficial to the child if the clinical manifestations of HIV infection can be controlled during the iatrogenic immunosuppression state from chemotherapy. The hematopoietic growth factors could diminish the problems of neutropenia and infection. They may also allow maintaining the dose intensity of chemotherapy that is necessary to cure the malignancy. Supportive care for patients undergoing chemotherapy is also important including *Pneumocystis carinii* or fungal prophylaxis and maintaining adequate nutritional status since the treatment of these patients is often complicated by multiple HIV associated organ dysfunctions as well as drug interactions and infectious complications secondary to severe immunosuppression[24].

The treatment of cancer in pediatric AIDS has been progressing in large part. Preliminary results with dose-intensive, but brief chemotherapy regimens have been encouraging[5,25]. An earlier report suggested that highly active antiretroviral therapy (HAART) resulted in a decreased incidence of lymphoma, and that patients with systemic lymphoma who were treated with HAART had a better prognosis[26].

In summary NHL, B cell type is the most frequent malignancy in children with HIV infection. The mean age of onset of lymphoma in these patients is younger than in non-HIV infected patients. Degree

of immunosuppression (CD4 count) is related to the aggressiveness of the malignancy. Lymphoma itself and also the treatment could lead to more immunodeficiency and increased risk of infection leading to a poor survival rate in these patients. The use of antiretroviral therapy to control HIV infection during treatment with chemotherapy should be considered. Progress in the treatment of HIV-related malignancies is needed to improve the survival of these patients.

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มะเร็งในผู้ป่วยเด็กที่ติดเชื้อเอ็ชไอวีในโรงพยาบาลศิริราช

กลีบสไบ สรรพกิจ, พ.บ., กวิวัณณ์ วีรกุล, พ.บ.*, วรพันธ์ เกรียงสุนทรกิจ, พ.บ.*, กุลกัญญา โชคไพบูลย์กิจ, พ.บ.*, วรวรรณ ตันไพจิตร, พ.บ., วท.ม.*, จุฬารัตน์ มหาสันทนะ, พ.บ.**

ภูมิหลัง : มะเร็งบางชนิดเช่น Kaposi's sarcoma มะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin เป็นลักษณะทางคลินิกอย่างหนึ่งของโรคเอดส์ ปัจจุบันการรักษาและป้องกันการติดเชื้อแทรกซ้อนในผู้ป่วยที่ติดเชื้อเอ็ชไอวีดีขึ้นทำให้ผู้ป่วยมีชีวิตยืนยาว ดังนั้นอัตราการพบโรคมะเร็งในผู้ป่วยโรคนี้จึงสูงขึ้น

วัตถุประสงค์ : เพื่อที่จะศึกษาลักษณะของโรคมะเร็งที่พบในผู้ป่วยเด็กที่ติดเชื้อเอ็ชไอวี และผลของการรักษาในโรงพยาบาลศิริราช

วิธีการ : เก็บข้อมูลย้อนหลังผู้ป่วยเด็กที่ติดเชื้อเอ็ชไอวีและเป็นโรคมะเร็งในโรงพยาบาลศิริราชระหว่างเดือนมกราคม พ.ศ. 2537 ถึงเดือนตุลาคม พ.ศ. 2543

ผลการศึกษา : ในช่วงเวลา 6 ปี 10 เดือนดังกล่าว มีผู้ป่วยเด็กที่ติดเชื้อเอ็ชไอวีและเป็นโรคมะเร็งทั้งหมด 7 ราย (ชาย 2 ราย, หญิง 5 ราย) อายุเฉลี่ยที่ได้รับการวินิจฉัยโรคมะเร็งคือ 3 ปี 7 เดือน (2 ปี 6 เดือน ถึง 5 ปี) อาการแสดงแรกรับที่พบมากที่สุดคือ ตับโตและต่อมน้ำเหลืองโต ผู้ป่วยทุกคนได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin ระยะที่ 3 หรือ 4 โดยเป็นชนิด Burkitt's lymphoma มากที่สุด ผู้ป่วย 6 รายได้รับการรักษาด้วยยาเคมีบำบัดและ 1 รายได้รับยาต้านไวรัสเอ็ชไอวีร่วมด้วย ในจำนวนนี้มีเพียงรายเดียวที่ยังมีชีวิตอยู่จนถึงปัจจุบัน ผู้ป่วยรายนี้ได้รับการรักษาด้วยยาเคมีบำบัดและยาต้านไวรัสเอ็ชไอวี ผู้ป่วย 5 รายเสียชีวิตระหว่างการรักษาด้วยยาเคมีบำบัด 1 รายเสียชีวิตก่อนที่จะเริ่มให้ยาเคมีบำบัด สาเหตุของการเสียชีวิตในผู้ป่วยคือการติดเชื้อ มีผู้ป่วย 1 รายที่เป็น Burkitt's lymphoma stage III และเสียชีวิต ผู้ป่วยรายนี้มีการกลับเป็นซ้ำของโรคที่ระบบประสาทร่วมด้วย ระยะเวลาเฉลี่ยที่ผู้ป่วยมีชีวิตอยู่หลังจากวินิจฉัยโรคมะเร็ง คือ 11 เดือน (15 วัน ถึง 3 ปี 1 เดือน)

สรุป : มะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin เป็นมะเร็งชนิดที่พบบ่อยที่สุดในผู้ป่วยเด็กที่ติดเชื้อเอ็ชไอวีในโรงพยาบาลศิริราช อายุเมื่อมีอาการของโรคมะเร็งต่อมน้ำเหลืองน้อยกว่าผู้ป่วยโรคนี้ที่ไม่ได้ติดเชื้อเอ็ชไอวี ผลการรักษาโรคมะเร็งในผู้ป่วยกลุ่มนี้ยังไม่ดีนัก ดังนั้นการปรับยาเคมีบำบัดที่ใช้ในการรักษารวมทั้งการใช้ยาต้านเชื้อเอ็ชไอวี เพื่อควบคุมโรคเป็นสิ่งที่น่าจะต้องทำการศึกษาต่อไป

คำสำคัญ : มะเร็ง, เด็ก, เอ็ชไอวี

กลีบสไบ สรรพกิจ, กวิวัณณ์ วีรกุล, วรพันธ์ เกรียงสุนทรกิจ, กุลกัญญา โชคไพบูลย์กิจ, วรวรรณ ตันไพจิตร, จุฬารัตน์ มหาสันทนะ
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* ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700