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☐ Case Report ☐

A Case of Primary Bone Lymphoma Associated with Acquired Immunodeficiency Syndrome

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A 33-year old man with acquired immunodeficiency syndrome was admitted to Severance hospital following 1 year of diarrhea and 2 to 3 months of low sternal pain. The patient had progressive generalized lymphadenopathy for the previous 3 years. Whole body bone scan for evaluation of bone pain showed multiple abnormal hot uptakes at the low sternal body and T8 and T10 vertebra. Chest CT showed multifocal cortical erosion of the bone with soft tissue mass at the low sternal body and spine MRI showed multiple low-signal density in T1WI and high-signal density in T2WI at the T8 and T10 vertebral body. Biopsy was performed at the sternochondral junction and it showed high-grade malignant lymphoma of the large cell immunoblastic type. Immunostaining showed positive for the B-cell markers (CD79a and L26) and negative for the T-cell marker (UCHL1). Radiotherapy of 3,000 cGy was delivered to the sternum and vertebra. Since then, systemic chemotherapy with m-BACOD regimen (except dexamethasone) and anti-retroviral therapy with a combination of 3 drugs (didanosine, lamivudine, indinavir) has been performed. This is the first case report of primary bone lymphoma associated with acquired immunodeficiency syndrome in Korea.

Key Words: AIDS, primary bone lymphoma

Prior to the AIDS epidemic, the incidence of non-Hodgkin's lymphoma (NHL) was known to be increased in patients with congenital or acquired immunodeficiency, with the latter usually occurring as a consequence of immunosuppressive therapy used to prevent rejection following organ transplantation. However, HIV infection has now become the leading cause of acquired immunodeficiency since 1981, the first reported year of AIDS. The number of cases of malignant lymphoma and Kaposi's sarcoma has been rising steadily each year. The incidence of NHL in AIDS patients is approximately 5~10%, and the risk for developing NHL in AIDS is about 60~100 times greater than in the general population (Safai *et al.* 1992; Wang *et al.* 1995; Biggar and Rabkin, 1996). Histologically, the more common types of NHL seen in AIDS patients are high-grade immunoblastic or small non-cleaved cell. The mean age of patients with HIV-related NHL is 30~40 years of age, younger than in HIV-negative NHL patients whose mean age is 50~60 (Piras *et al.* 1996). Extranodal involvement is more frequent with an unusual location and the prognosis is poorer than in HIV-negative NHL. The incidence of bone lymphoma associated with AIDS is rare, approx-

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imately 1~5% of all AIDS-related NHL (Banerjee *et al.* 1992; Ackerman *et al.* 1994; Siskin *et al.* 1995). To the best of our knowledge, this is the first case of bone lymphoma associated with AIDS in Korea.

CASE REPORT

A 33-year-old man with acquired immunodeficiency syndrome was admitted to the Department of Internal Medicine of Yonsei Medical Center because of diarrhea for the previous year and low sternal pain for 2~3 months.

Three years prior to this admission, he had visited our hospital with the complaint of generalized lymphadenopathy. At that time, lymph node biopsy showed reactive B-cell hyperplasia without malignant cells, and serologic tests for EBV-IgM and anti-HIV antibody were positive. Thus the lymphadenopathy was thought to be due to progressive generalized lymphadenopathy (PGL) seen in HIV-infected patients.

He had been suffering from chronic diarrhea for about 1 year, and the diarrhea had been getting worse for the previous 2~3 months. Low sternal pain had also developed during the past 2~3 months. He had taken retonavir, a protease inhibitor as an anti-retroviral agent, by himself. He had been diagnosed with syphilis 8 years previously and chronic B-viral hepatitis 6 years before.

On admission, blood pressure was 90/60 mmHg, pulse rate 100/min, respiratory rate 22/min, and body temperature was 36.5°C. Severe direct tenderness on the low sternal area was noted and 0.5 cm-sized multiple lymph nodes were palpable in both inguinal areas.

Laboratory findings were as follows : hemoglobin 14.0 g/dl, hematocrit 41.9%, WBC 4,500/μl(poly 51%, lymph 37.5%), platelet 230,000/μl, Na 132 mM/L, K 4.1 mM/L, Cl 110 mM/L, HCO_3 17 mM/L, calcium 8.6 mg/dl, phosphorous 6.2 mg/dl, total protein 9.2 g/dl, albumin 3.6 g/dl, globulin 5.6 g/dl, BUN 16 mg/dl, creatinine 1.3 mg/dl, AST 43 IU/L, ALT 57 IU/L, alkaline phosphatase 93 IU/L, LDH 160 IU/L, and β_2-MG was 6.9 μg/ml. Serologic tests for CMV and EBV antibodies were

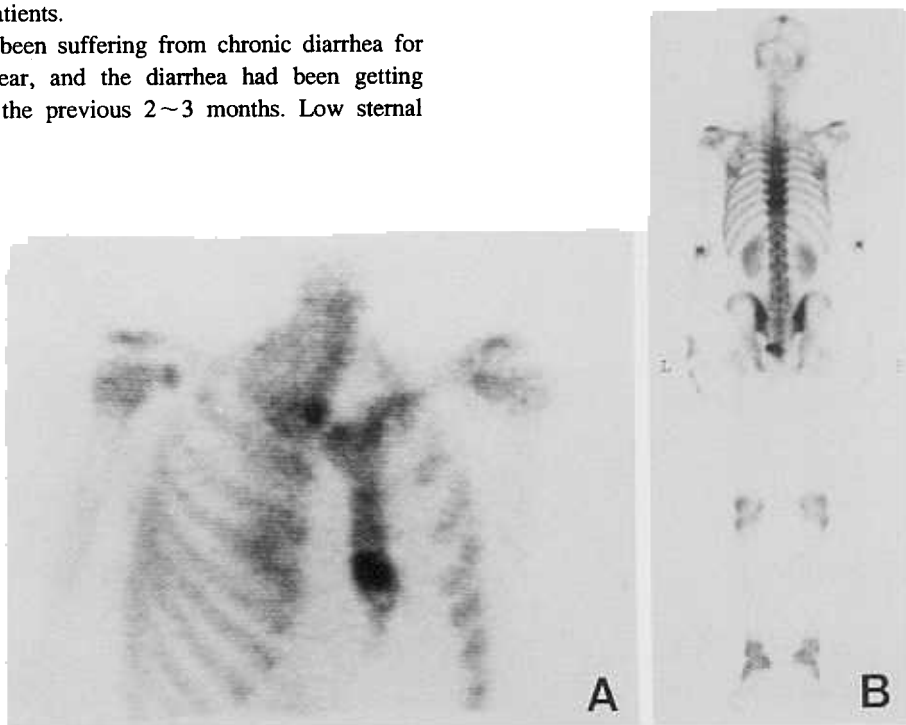

Fig. 1. Whole body bone scan showing hot uptake at the low sternal body(A) and T8 and T10 vertebral bodies(B)

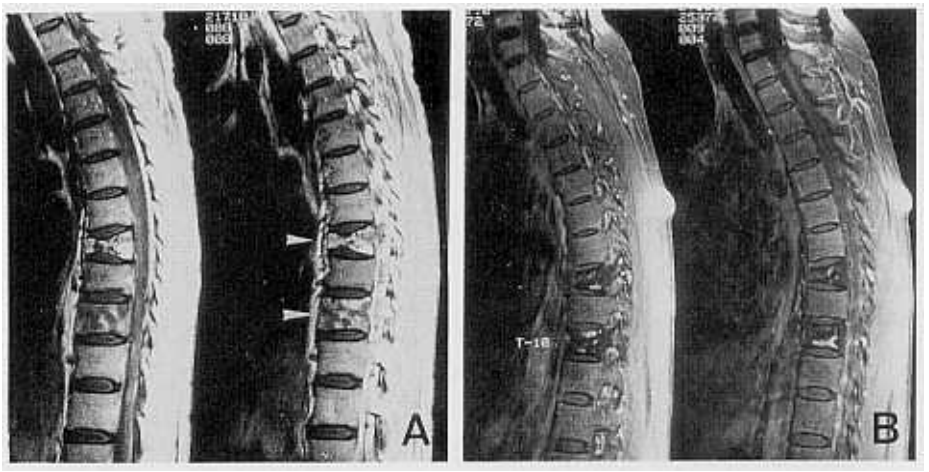

Fig. 2. Initial T-spine MRI showing heterogenously enhanced lesion by gadolinium injection at the T8 and T10 vertebra (A). After radiotherapy and the 3rd cycle of chemotherapy, follow-up MRI revealed possible fatty changes within the marrow space of T8 and T10 vertebral bodies, but there was still nodular and spotty enhancement after gadolinium injection (B).

negative. The percentage of CD4+ and CD8+ T lymphocytes was 5.5% and 55.3% of the total lymphocyte count, respectively, and the total number of CD4+ T lymphocytes was 93/μl. The HIV-RNA was 1,422 copies/ml and p24 antigen was positive.

The chest X-ray was not remarkable. Whole body bone scan (WBBS) revealed hot uptake at the low sternal body and T8 and T10 vertebral bodies (Fig. 1). On magnetic resonance imaging (MRI) of the T-spine, T8 and T10 vertebrae were of low-signal intensity in T1- weighted image (T1WI) and high-signal intensity in T2-weighted images (T2WI) and heterogenously-enhanced by gadolinium enhancement (Fig. 2A).

Chest computed tomography (CT) revealed multifocal cortical erosion at the low sternal body combined with surrounding soft tissue mass (Fig. 3A). Excisional biopsy at the sternochondral junction was performed, and a diffuse large immunoblastic type of high-grade malignant lymphoma was suggested (Fig. 4A). Immunohistochemical staining using paraffin-embedded tissue demonstrated that the tumor cells expressed B-cell markers (CD79a) (Fig. 4B). The T- cell marker (UCHL1) was expressed only in reactive small lymphocytes. Bone marrow and CSF study were normal. The clinical stage was Stage IVAE.

Zidovudine (AZT) and ritonavir were initially used as anti-retroviral agents and the HIV-RNA count decreased from 1,422 to 971 and 866 copies /ml on serial samples obtained after a one-month interval. The CD4+ cell count was slightly increased from 144 to 176/μl. Radiotherapy of 3,000 cGy was delivered for 10 days to the low sternum and vertebra, respectively. After the radiotherapy, low sternal pain subsided and the surrounding soft-tissue mass disappeared, but a newly developed bilateral focal pleural thickening was noted at the posterior costal pleura at the level of the 10th rib (Fig. 3B). Furthermore, the patient took the anti -retroviral agents irregularly during the radiotherapy and the HIV-RNA count was elevated from 822 to 361,115 copies/ml and the CD4+ cell count decreased from 176 to 56/μl. After regularly taking anti-retroviral agents again, the HIV-RNA decreased to 147,145 copies /ml and the CD4+ cell count increased to 146/μl. But these drugs had to be stopped due to the elevation of transaminases. Thereafter, triple agents of didanosine (ddI), lamivudine (3TC), and indinavir were used as anti-retroviral therapy. The HIV-RNA decresead further to 13,029 copies/ml and the CD4+ cell count was 149/μl. For the treatment of NHL, a low-dose chemotherapy with m-BACOD regimen (MTX 200 mg/m^2, Bleomycin 4 U/m^2, Adriamycin 25 mg/m^2, Cyclophosphamide 300 mg/m^2, Vincristine 1.4 mg

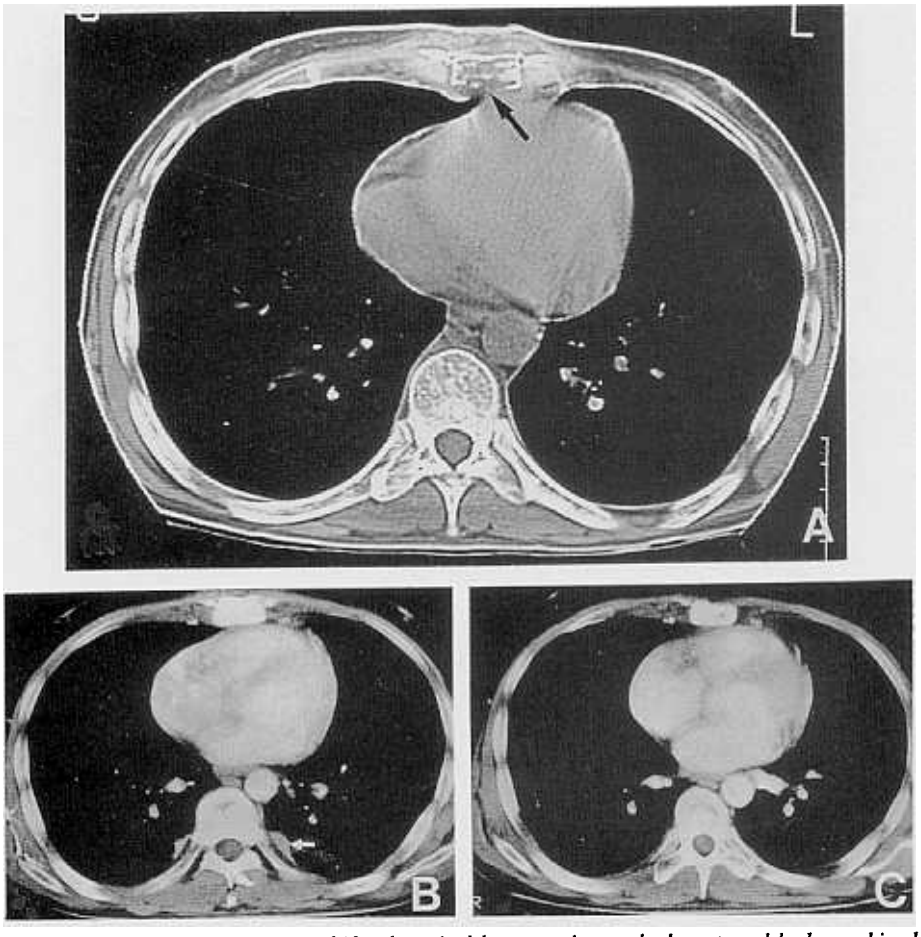

Fig. 3. *Chest CT scan showing multifocal cortical bony erosion at the low sternal body combined with surrounding soft-tissue mass (A). Focal pleural thickening was noted at the posterior costal pleura after radiotherapy (B). Previously-destructed sternal lesion and focal pleural thickening were improved after 3rd cycle of chemotherapy (C).*

/m^2, Dexamethasone 3 mg/m^2) was started. Dexamethasone was not included in the m-BACOD regimen because the patient had chronic B-viral hepatitis. CNS prophylaxis with Ara-C was not done because the CSF and the bone marrow findings were normal. Among the triple anti-retroviral agents, only didanosine was skipped during anti-cancer chemotherapy due to the possibility of enhancing neurotoxicity when vincristine was administered. Three cycles of chemotherapy with continuous use of the anti-retroviral agents were performed without side effects, except for neutropenia after the 3rd cycle. G-CSF was used during neutropenia after the 3rd cycle. The CD4+ cell count increased to 220/μl and the HIV-RNA decreased to less than 250 copies/ml. Follow-up chest CT scan showed that the previously-noted sternal destruction and focal pleural thickening at the posterior costal pleura were improved (Fig. 3C). Follow-up MRI revealed somewhat increased signal intensity within the marrow space of the T8 and T10 vertebral bodies suggesting possible fatty changes. However, after gadolinium injection, there was still nodular and spotty enhancement within the marrow space (Fig. 2B). Considering all objective and clinical findings described above, this patient showed partial remission. Fig. 5 shows the inverse relationship between CD4+ cells and HIV-RNA during anti-retroviral therapy.

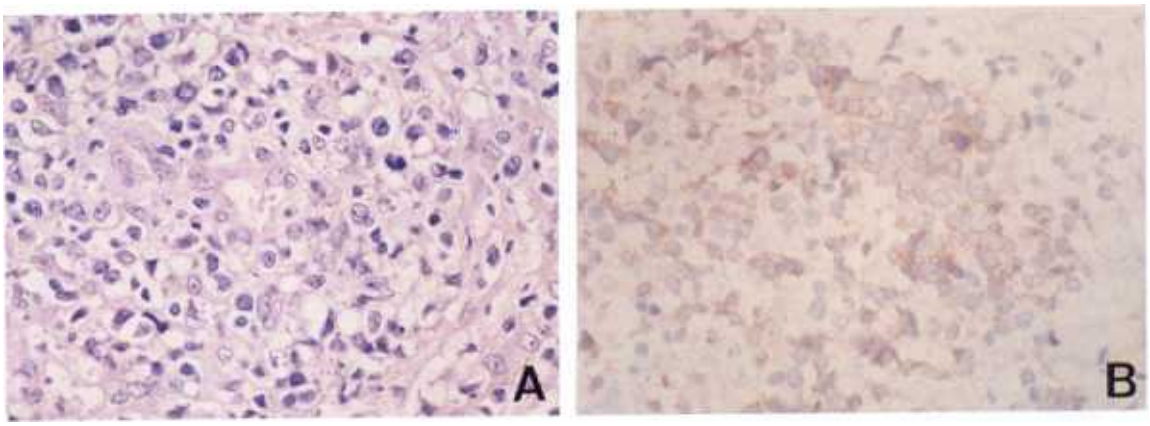

Fig. 4. A) Excisional biopsy at the sternochondral junction showing diffuse proliferation of large pleomorphic cells. B) Immunohistochemical staining using paraffin-embedded tissue demonstrating cytoplasmic positivity of tumor cells to the B-cell marker (CD79a).

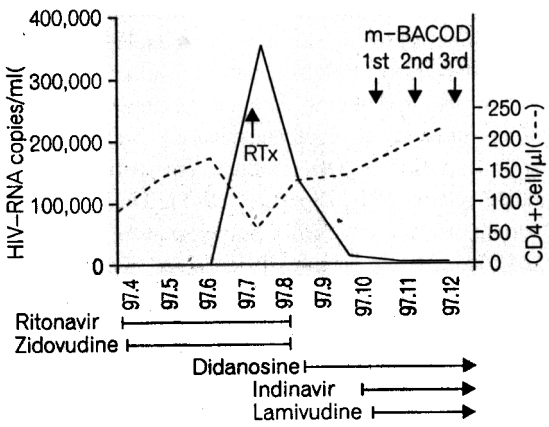

Fig. 5. Interval changes in the CD4+ cell count (dotted line) and HIV-RNA during antiretroviral therapy

DISCUSSION

Overall, approximately 5~10% of all HIV-infected individuals will develop NHL (Safai *et al.* 1992; Wang *et al.* 1995; Biggar and Rabkin, 1996), and two cases of AIDS-related lymphoma were previously reported in Korea. One was AIDS-related NHL on the palate and the other was AIDS-related primary CNS lymphoma (Jeong *et al.* 1995; Lee *et al.* 1996). The incidence of AIDS-related NHL may substantially increase with improved supportive care and an increased average life-span for HIV-infected individuals. This may be due to the use of newer and possibly more effective anti-retroviral agents and improved means of treating and prophylaxing the various opportunistic infections associated with the disease. Additionally, some cases of NHL have remained dormant while the patients were still alive with AIDS and then were discovered only at the postmortem examination. Therefore, the actual incidence of AIDS-related NHL is probably underreported (Safai *et al.* 1992).

Sixty-five percent of patients with AIDS-related NHL are of high-grade histology, with a nearly equal number of large-cell immunoblastic and small noncleaved-cell (Burkitt's) types (Sandler and Kaplan, 1996a). This is in sharp contrast to HIV-negative individuals where only 10 percent of cases are high grade. Most AIDS-related lymphomas possess a B-cell phenotype and relatively few express T-cell antigens or both B- and T-cell antigens (Wang *et al.* 1995; Biggar and Rabkin, 1996; Sandler and Kaplan, 1996b). Extranodal involvement is more common and approximately 75% of patients have advanced (stage III/IV) disease. Extranodal sites of the disease can involve nearly any part of the body, with the most common locations being the CNS (30%), bone marrow (25%), gastrointestinal tract (20%), and liver (12%). But the bone lymphoma associated with AIDS is very rare and just a few cases of AIDS-related bone lymphoma have been

reported worldwide (Banerjee *et al.* 1992; Steinback *et al.* 1993; Ackerman *et al.* 1994; Siskin *et al.* 1995). The most common presentations of AIDS -related NHL are systemic B symptoms (fever, night sweats, and weight loss), which occur in about 80~90% of cases. Twenty-two percent of NHL patients have progressive generalized lymphadenopathy (PGL) (Safai *et al.* 1992) and this patient may have had PGL 3 years before. However, the clinical significance of PGL is unclear.

Major factors which consistently emerge as being indicative of a particularly poor prognosis in AIDS -related lymphoma in multivariate analyses include: (1) a CD4 count of less than 100/μl; (2) a poor performance status (Karnofsky Performance Status <70%); (3) a prior AIDS-defining opportunistic infection; and (4) a lymphomatous bone marrow involvement (Sparano, 1995). Other minor factors include advanced stage, high-grade histology, systemic B-symptom, bulky tumor mass, extranodal involvement, a high serum LDH level before therapy, absence of complete remission after therapy, and more dose-intensive regimens (Wang *et al.* 1995). This patient did not have any other poor prognostic factors except a low CD4+ cell count (93/μl) and a high-grade histology.

Except in primary CNS disease, local therapies are not usually beneficial, and combination chemotherapy is generally recommended (Levine *et al.* 1991; Wang *et al.* 1995). In a HIV- infected patient, aggressive combination chemotherapy is likely to exacerbate the immunodeficient state, resulting in an increased risk of opportunistic infection and myelosuppression, thus potentially-shortening survival (Kaplan *et al.* 1989; Sparano, 1995). In general, the complete response rates in HIV-infected patients are lower than those for non-HIV-infected patients. Less than 10% of patients survive beyond 2 years and the median survival time is less than 12 months. Furthermore, among patients who died following therapy for AIDS-related NHL, approximately 75% had active lymphoma at the time of death, and relapsed or refractory lymphoma was the primary cause of death in approximately 33% (Sandler and Kaplan, 1996b).

An AIDS Clinical Trial Group (ACTG) studied to directly compare low-dose m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) versus standard-dose m-BACOD with GM-CSF. No differences were observed between the two treatment groups with respect to complete response (50% vs. 46%), relapse after CR (19% vs. 23%), time to progression (22 weeks vs. 28 weeks), and overall median survival (31 weeks vs. 34 weeks). The only difference between the two groups was in their toxicity profiles (Sandler and Kaplan, 1996b). Therefore, this trial suggested that low-dose therapy with its reduced toxicity profile may be a better choice for the severely immunocompromised AIDS patient. Even though a low-dose m-BACOD regimen was used in this patient, grade 4 neutropenia was developed after the 3rd cycle of chemotherapy and G-CSF was used.

There have been relatively few advances over the last 10 years in the development of experimental treatments for AIDS-related NHL. Some are chemotherapy-based regimens, others are antibody-mediated, whereas others use immune-modulators (Sandler and Kaplan, 1996b). Sparano evaluated the efficacy and toxicity of 96-hour continuous intravenous infusion of cyclophosphamide, doxorubicin, and etoposide (CDE regimen) in patients with AIDS-related NHL (Sparano, 1995). Thirteen of 21 patients (62%) achieved a complete response and 5 (24%) achieved a partial response. The median survival in this study was 21 months. MGBG (methyl-glyoxal-bis guanylhydrazone) interferes with polyamine biosynthesis and it has been shown to be active in a variety of malignancies. Because of its long half-life, its ability to permeate the blood -brain-barrier, and its lack of marrow toxicity, MGBG is thought to be an excellent agent for the treatment of relapsed or refractory AIDS-related NHL. Topoisomerase-1 inhibitors, immune modulators like interleukin-2 and anti-interleukin-6, immunotoxin therapy like anti-CD19, and cellular adoptive immunotherapy using EBV-specific T cells are currently being tried (Sandler and Kaplan, 1996b).

Whether to administer anti-retroviral therapy concurrently with chemotherapy, following the completion of chemotherapy, or not at all, and with which anti-retroviral agent, are important questions that have not been systematically studied. One study suggested that the combination of chemotherapy with zidovudine may result in excessive myelotoxicity (Errante *et al.* 1994). Didanosine and

zalcitabine, on the other hand, are more suitable candidate drugs to combine with chemotherapy because of their lack of myelosuppressive effects, but they must be used cautiously when given concurrently with vincristine because of their potential neurotoxicity (Kahn *et al.* 1992). In this patient, didanosine was skipped during anti-cancer chemotherapy due to the possibility of enhancing neurotoxicity. Recent data from the ACTG clinical trial in Kaposi's sarcoma, however, indicate that neurotoxicity is not significantly enhanced when vincristine is administered with either didanosine or zalcitabine (Sandler and Kaplan, 1996b). Therefore, with the exception of zidovudine, most anti-retroviral agents can probably be safely administered with anti-cancer chemotherapy.

Lymphoma occurs in all population groups at risk for HIV, in all age groups and in diverse geographic regions. The prevalence of AIDS-associated malignant lymphoma will increase during the next few years in Korea and NHL may be one of the leading causes of death among patients with AIDS in the future. Recently, however, anti-retroviral therapy with triple agents is very effective in reducing the HIV-RNA load and therefore the prognosis of AIDS-related NHL will be better.

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