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Leukocytopenia due to Zidovudine- and Nevirapine-Containing Regimens in Elderly Patients with HIV Infection

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Leukocytopenia was observed in three cases among 17 HIV-1-infected patients receiving regimens containing both zidovudine (ZDV) and nevirapine (NVP) (Table). Common features included the occurrence of leukocytopenia within 5 weeks of treatment, good response to granulocyte-colony stimulating factor (G-CSF), and the advanced age of the patients. In two of the patients, leukocytopenia was absent during regimens containing either ZDV or NVP alone.

Case 1: A 48-year-old HIV-1-infected homosexual man commenced highly active antiretroviral therapy (HAART) with ZDV/NVP/lamivudine (3TC) on January 11, 1999. Two weeks later, the dose of NVP was raised to 400 mg/day. At that time, WBC was 3,800/ μ l, CD4 count 263/ μ l, and viral load 700 copies/ml. On February 13, 1999, day 33 of the therapy, he developed diarrhea, fever (40°C), and impetigo on his back. As leukocytopenia (240/ μ l; neutrophil 0%) was noted, he was hospitalized. HAART was stopped immediately, and subcutaneous administration of G-CSF at a dose of 300 μ g daily was started. Both pyrexia and diarrhea improved within 9 days. WBC recovered to 6,200/ μ l within 3 days. A new regimen containing stavudine (d4T)/NVP/3TC was then begun. No further episodes of leukocytopenia occurred subsequently.

Case 2: A 68-year-old HIV-1-infected homosexual man was admitted to our hospital due to the onset of *Pneumocystis carinii* pneumonia (PCP) on September 16, 1999. After treatment of PCP, he commenced HAART, which included ZDV/NVP/nelfinavir on November 19, 1999. At that time, WBC

was 3,500/ μ l, CD4 count 2/ μ l, and the viral load 610,000 copies/ml. Twenty-three days later, his body temperature rose to 39°C. As WBC decreased to 200/ μ l, HAART was stopped. Subcutaneous administration of G-CSF at 300 μ g daily was initiated on December 12. The nadir WBC was 70/ μ l (neutrophil 1%) on December 16. Although WBC recovered to 2,070/ μ l and body temperature returned to normal on December 22, the patient died of disseminated candidiasis on February 3, 2000. In this case, transient thrombocytopenia with a nadir count of 5,000/ μ l was observed on December 18.

Case 3: A 50-year-old HIV-1-infected hemophiliac had been treated with ZDV/didanosine (ddI) since 1996; ritonavir/saquinavir (RTV/SQV) were added to the regimen in January 1999. Although he showed an excellent response to this regimen, achieving suppression of viral load to below quantifiable levels and an elevation of the CD4 count to more than 500/ μ l, he complained of exacerbation of hemophiliac arthritis associated with more frequent bleeding episodes after adding RTV/SQV. Therefore, RTV/SQV were replaced by NVP at 200 mg/day on January 18, 2000, and the dose of NVP was increased to 400 mg/day on February 6. However, WBC declined from 4,900/ μ l to 1,000/ μ l (neutrophil 50%) on February 10. HAART was stopped, and G-CSF was given subcutaneously for 4 days at a dose of 150 μ g daily. WBC recovered to 5,500/ μ l on February 15. Twenty days later, HAART was re-initiated with d4T/3TC/efavirenz. No further episodes of leukocytopenia were experienced.

The incidence of AIDS and mortality due to AIDS have

Table. Three cases of leukocytopenia caused by ZDV- and NVP-containing regimen

case	age (year)	prior regimen	drug other than ZDV/NVP	WBC (μ l)		days after commencement	alternative therapy
				before	nadir (neutrophil %)		
1	48	none	3TC	3,800	240 (0%)	33	d4T/3TC/NVP
2	68	none	NFV	3,500	70 (1%)	23	none
3	50	ZDV/ddI/RTV/SQV	ddI	4,900	1000 (50%)	24	d4T/3TC/EFV

ZDV: zidovudine, NVP: nevirapine, 3TC: lamivudine, d4T: stavudine, NFV: nelfinavir, ddI: didanosine, RTV: ritonavir, SQV: saquinavir, EFV: efavirenz

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been declining markedly in the era of HAART, which includes the use of two nucleoside reverse-transcriptase inhibitors (NRTIs) and an HIV-specific protease inhibitor (PI). However, adherence to these regimens is often difficult because of the large number of pills, side effects, and drug-drug interactions related to PIs. Furthermore, reports of unexpected serious side effects in patients exposed to PIs over a long period are increasing in number. In particular, metabolic disturbances such as increased levels of cholesterol or triglycerides and insulin-resistant diabetes in association with abnormal fat redistribution, which is referred to as lipodystrophy syndrome (1), have been observed. Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) are advantageous due to the lower burden of pills and fewer drug-drug interactions compared with PI. Therefore, HAART consisting of 2 NRTIs and 1 NNRTI is being prescribed as initial therapy in treatment-naïve patients, and 'switch therapy' with NVP in place of PIs is being prescribed for patients with long-term sustained viral suppression (2). Leukocytopenia caused by ZDV was reported soon after its approval (3). However, there has been little information regarding myelotoxicity caused by antiretroviral regimens containing NVP in adults. At our hospital, 44 patients have been treated with NVP-containing regimens since 1997. Seventeen underwent regimens containing NVP and ZDV. As described above, 3 out of 17 patients (17.6%) developed leukocytopenia 3-5 weeks after the commencement of antiretroviral therapy. In cases 1 and 2, regimens including ZDV and NVP were introduced as the first antiretroviral therapy, resulting in leukocytopenia. In case 1, ZDV was replaced by d4T, while 3TC and NVP were not changed in the second regimen, this patient had no further episodes of leukocytopenia. Although case 3 had been treated with ZDV/ddI since 1996, he had never developed leukocytopenia until dual-PIs were changed to NVP. These observations appear to indicate that leukocytopenia by ZDV might be intensified by NVP.

Toxic hepatitis and Stevens-Johnson's syndrome have been reported as serious adverse events associated with NVP. However, in previous studies of NVP in combination with ZDV, serious leukocytopenia has not been reported among the more than 400 participants studied (4). In our cases, the patients were relatively older. If advanced age is a predisposing factor for leukocytopenia, this will have clinical relevance.

Lipodystrophy syndrome can cause cardiovascular complications (5). Therefore, older patients should likely be given PI-sparing regimens to avoid complications. Our observations appear to suggest that the myelotoxicity of ZDV can be exacerbated by NVP. It may therefore be important to be aware of this potential side effect, especially during the first 5 weeks of therapy in elderly patients.

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