Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1662-18
Intern Med 58: 2387-2391, 2019
http://internmed.jp

【 CASE REPORT 】

Acute Promyelocytic Leukemia and HIV: Case Reports and a Review of the Literature

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Abstract:
Acute promyelocytic leukemia (APL) in human immunodeficiency virus (HIV)-infected individuals is very rare. There is currently no consensus regarding the use of anti-cancer drugs with highly active anti-retroviral therapy (ART) in these patients due to their small number. We herein report two cases of APL with HIV-infected patients. Both cases received all-trans-retinoic acid-containing chemotherapies and achieved complete remission. ART was continued throughout the treatment course. The clinical course of these cases suggests that it is preferable to perform standard chemotherapy for APL with ART if patients have an adequate performance status.

Key words: acute promyelocytic leukemia, human immunodeficiency virus

(Intern Med 58: 2387-2391, 2019)
(DOI: 10.2169/internalmedicine.1662-18)

Introduction

The introduction of highly active anti-retroviral therapy (ART) has dramatically improved the prognosis of human immunodeficiency virus (HIV)-infected patients, and a long-term survival can be expected even after the onset of acquired immunodeficiency syndrome (AIDS). Patients with a long treatment history, however, are at increased risk for developing cancer due to oncogenic factors, such as immune dysregulation status, chronic stimulation, direct viral pathogenicity, and long-term medication exposure. Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical carcinoma are considered AIDS-defining malignancies, and there is an increasing incidence of non-AIDS-defining malignancies as well, such as malignant melanoma, head and neck cancer, brain tumor, testicular tumor, lung cancer, stomach cancer, liver cancer, renal cancer, and anal cancer. With regard to hematologic malignancies, the frequency of lymphoid neoplasms is high, while that of myeloid neoplasms is much lower (1-5). A French cohort study showed that HIV-infected patients have an estimated two-fold higher risk for acute myeloid leukemia (AML) than the general population, and acute promyelocytic leukemia (APL) is rare (4-7).

To our knowledge, only seven cases of APL in the setting of HIV are reported in the literature (5). Because of the small number of reported cases of APL among HIV-infected patients, no guidelines outlining the therapeutic approaches in this situation have been published. Understandably, the myelosuppressive nature of both pathologies and their corresponding treatments poses a significant challenge to managing APL in these patients.

Recently, two HIV-infected patients with APL were treated in our hospitals. We herein report our two cases and discuss the therapeutic management with a review of the literature for patients with both APL and HIV.

Case Reports

Patient 1

A 32-year-old man was diagnosed with HIV-associated dementia and received ART. Because of the high viral load in the spinal fluid, darunavir (DRV) and abacavir (ABC)/lamivudine (3TC) were selected in consideration of their cerebrospinal fluid transferability. After 5 months, the labo-

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Received: June 8, 2018; Accepted: February 18, 2019; Advance Publication by J-STAGE: May 22, 2019
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ratory findings showed neutropenia [white blood cells (WBCs) 4,000/μL with 16% neutrophils and 68% blasts] and thrombocytopenia (platelets 2.2×10^4/μL). The prothrombin time (PT) was prolonged at 22.6 seconds, and the fibrinogen/fibrin degradation product levels were highly elevated with fibrinogen at 119 mg/dL. A smear preparation of his bone marrow revealed excessive promyelocytes with Auer rods, including Faggot cells. He was therefore diagnosed with APL.

At this time, he received ABC/3TC, DRV, and ritonavir (RTV); his HIV RNA was 75 copies/mL, and his CD4+ cell count was 38/μL, with no other infectious complications. He was treated with all-trans-retinoic acid (ATRA, 45 mg/m^2) only because of low compliance due to HIV-associated dementia. The increased APL cells (3,500/μL) led us to add chemotherapy with idarubicin (12 mg/m^2, 2 days) and cytarabine (100 mg/m^2, 5 days) from day 13. On day 14, he developed a fever and pleural effusion with an increased cardiothoracic ratio and was diagnosed with retinoic acid syndrome (8). We stopped the ATRA administration and added intravenously infused dexamethasone at that point. He developed bacterial pneumonia during the neutropenic period and received antibiotics, and his pneumonia improved with the recovery of leukocytes.

He achieved complete remission (CR) at day 40. He was subsequently treated with ATRA and idarubicin or mitoxantrone as consolidation therapies according to the PETHEMA LPA 99 protocol (9). Out of consideration for the patient's safety, we treated him with consolidation therapy used for low-risk patients, although he was classified as an intermediate-risk patient according to the PETHEMA protocol due to his history of bacterial pneumonia during induction therapy and HIV-associated dementia, which made it difficult for him to manage his hygiene and other activities of daily living. In the neutropenic periods after chemotherapy, he had febrile neutropenia once during the three consolidation therapies. ART (ABC/3TC, DRV, and RTV) and prophylaxis for pneumocystis pneumonia and candidiasis were continued throughout the treatment course. He maintained CR and a stable state of HIV-associated dementia with low levels of HIV copies and no reactivation of cytomegalovirus. His clinical course is shown in Figure A.

Patient 2

A 46-year-old man diagnosed with HIV infection received ART with rilpivirine (RPV), emtricitabine (FTC), and tenofovir (TDF) 3 months after his diagnosis. He visited a clinic because of nasal bleeding 2 months after starting ART, and his laboratory studies indicated elevated WBC counts (10,000/μL) with 50% abnormal cells and decreased platelets (1.9×10^4/μL). He was referred to our hospital and diagnosed with APL based on bone marrow aspiration smear findings. At the diagnosis of APL, his HIV RNA was 325 copies/mL, and his CD4+ cell count was 264/μL, with no other AIDS-related complications. Because RPV requires food intake and has a lower antiviral efficacy and genetic barrier than integrase strand transfer inhibitor, RPV was changed to raltegravir (RAL) before chemotherapy was started (10). He was considered an intermediate-risk patient and treated with ATRA and idarubicin according to the PETHEMA/HOVON LPA2005 Protocol (11). He achieved CR at day 31 without severe complications. He was subsequently treated with ATRA and idarubicin or mitoxantrone as consolidation therapies under the same protocol. In the neutropenic periods after chemotherapy, he had febrile neutropenia twice during the three consolidation therapies. ART (RAL, FTC, and TDF) and prophylaxis against candidiasis were continued throughout the treatment course. Prophylaxis against pneumocystis pneumonia was also continued, although it was temporarily stopped at the end of the third consolidation therapy due to severe neutropenia. Because of liver dysfunction due to fatty liver (AST: 50-230 IU/L, ALT: 50-270 IU/L), he did not receive maintenance therapy, but he maintained CR and low levels of HIV copies. His clinical course is shown in Figure B.

Discussion

In the ART era, an improved survival after HIV infection has led to an increase in long-term morbidities, including cancer (2, 12). AML rarely occurs in HIV-infected patients, but the standardized risk ratio for AML is higher than that in the background population (4). Exposure to medications, including HIV nucleoside analogs and cytostatic agents, might also increase the risk of leukemic complications in HIV-infected patients (6). Furthermore, the high incidence of AML in two disorders associated with chronic T cell abnormalities - severe combined immunodeficiency and Wiskott-Aldrich syndrome - suggests that an immunodeficient state is associated with AML (6). In HIV-infected patients, AML is characterized by the predominance of FAB M2, M4, and M5 and an infrequency of M3, so-called APL (4-6). To our knowledge, only seven other cases of APL in the setting of HIV have been reported in the literature. These nine total cases including our own (4, 5, 13-17) are summarized in Table.

Most of the patients listed in the table had an intermediate risk according to the predictive model for the relapse-free survival for APL (8). This might be due to the early detection of a blood cell count abnormality in such patients due to regular doctor visits. This might be also due to a modification of the white blood cells and platelet counts owing to the administration of HIV therapeutic agents.

Regarding treatment, at least eight of the nine documented cases were treated with ATRA, either in combination with anthracycline or cytarabine or as the sole agent in induction. All eight cases achieved CR and remained alive during the observation period, and at least six of these cases received ART. ATRA induced terminal differentiation of malignant promyelocytes into mature neutrophils and produced CR in the treatment of APL. ATRA and chemotherapy resulted in a long-term survival, especially after adjusting for

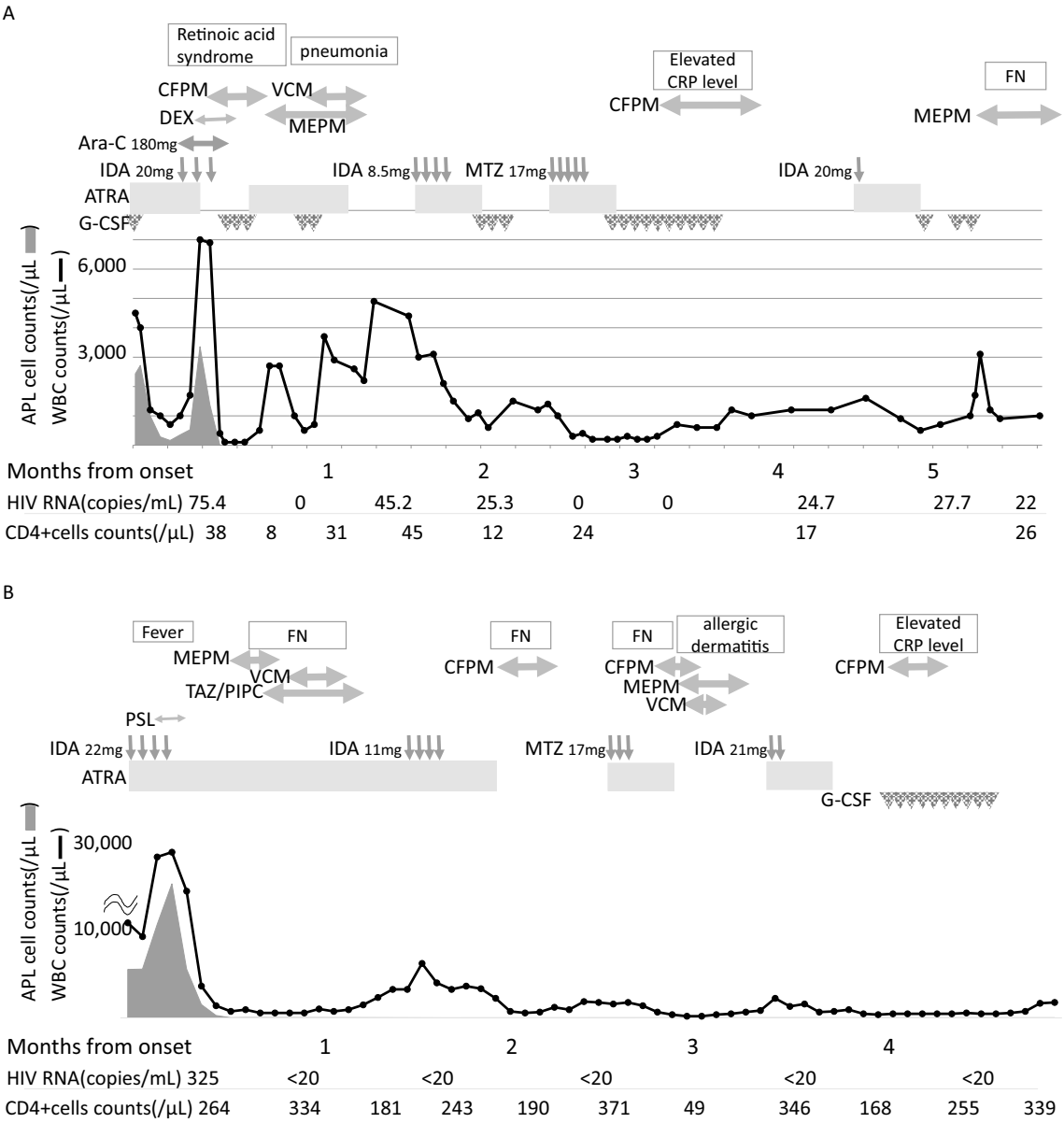

Figure. **Clinical courses of patients 1 (A) and 2 (B). ATRA: all-trans-retinoic acid, G-CSF: granulocyte-colony-stimulating factor, WBC: white blood cell, Ara-C: cytarabine, IDA: idarubicin, MTZ: mitoxantrone, DEX: dexamethasone, CFPM: cefepime, MEPM: meropenem, VCM: vancomycin, CRP: C-reactive protein, FN: febrile neutropenia, PSL: prednisone, TAZ/PIPC: tazobactam/piperacillin**

the risk categories and effects of front-line therapy in cases of newly diagnosed APL (9, 11, 18).

Arsenic trioxide (ATO) induces differentiation and causes apoptosis of promyelocytes in APL and is effective as a single agent in patients with relapsed APL. Recently, it has also been shown to be effective in patients with newly diagnosed APL as induction therapy (19, 20). There are no reports of the use of ATO in HIV-infected patients, but ATO might be valuable as a therapy for those with such comorbid conditions, although it should be used with caution.

The administration of a non-Boost integrase inhibitor prevents the interaction of ART with many medicines, leading to fewer adverse events and making it easier to manage the treatment of cases with comorbidities. This allows such patients to receive almost the same treatment as patients without HIV. Regarding patients with comorbidities that started to receive ART prior to the era of HIV integrase inhibitors, they can be switched to a non-Boost integrase inhibitor based on the results of drug resistance tests. This is recommended because, in such cases, adverse drug interactions and the patient's dietary intake are not a major concern (10, 21, 22). When the comorbidity is AML, ART should be continued without interruption; however, temporary interruption is unavoidable if adherence is decreased due to a mucosal disorder. Hematopoiesis may be insufficient, especially in AIDS patients and those with a history of AZT use, and myelosuppression may be more likely to occur, so patients must be carefully screened for opportunis-

Table. Seven Previously Documented Cases and Our Two Cases of Acute Promyelocytic Leukemia with HIV Infection.

Age(years)/ Sex (references)	Time between HIV and APL diagnosis	ART	WBC Platelets($\times 10^4$) counts/(μL)	Risk group*	CD4+ cell counts (/μL) HIV RNA (copies/mL)	Induction	Consolidation	Maintenance	Treatment outcome	Alive/ dead	Observation period
30/Male (13)	2 years	ND	4,800 0.2	intermediate	240 ND	ATRA	DNR Ara-C MTZ	ND	CR	Alive	8 months
22/Female (14)	ND	ND	16,000 3.0	high	ND ND	ND	ND	ND	Not reached CR	ND	ND
36/Male (4)	0	ND	4,000 ND	low or intermediate	400 ND	ATRA	ND	MTX 6-MP	CR/Relapse at day 303	Dead	350 days
27/Male (15)	8 years	IDV 3TC ZDV	8.00 1.9	intermediate	356 undetectable	ATRA IDA Ara-C	High dose Ara-C	ATRA MTX 6-MP Maintenance therapy interrupted due to liver dysfunction	CR	Alive	40 months
46/Female (16)	2 years	EFV TDF 3TC	5,090 0.15	intermediate	>500 <50	ATRA IDA	ATRA IDA MTZ	ATRA MTX 6-MP	CR	Alive	21 months
35/Male (17)	10 years	D4T LPV	1,600 2.8	intermediate	184 <50	ATRA IDA	ATRA	ND	CR	Alive	14 months
43/Female (5)	0	ATV TVD RAL	40,700 1.5	high	118 >500,000	ATRA IDA	ATRA IDA MTZ	ATRA MTX 6-MP	CR	Alive	8 months
32/Male (our case)	5 months	ABC/3TC DRV RTV	4,000 2.2	intermediate	38 75.4	ATRA IDA Ara-C	ATRA IDA MTZ	ATRA MTX 6-MP	CR	Alive	38 months
46/Male (our case)	5 months	RAL FTC TDF	10,000 1.9	intermediate	264 325	ATRA IDA	ATRA IDA MTZ	Impossible due to liver dysfunction	CR	Alive	30 months

* The risk group indicates the predictive model for relapse-free survival in reference 8.

ATV: atazanavir, TVD: tenofovir/emtricitabin, RAL: raltegravir, IDV: indinavir, 3TC: lamivudine, ZDV: zidovudine, EFV: efavirenz, TDF: tenofovir, D4T: stavudine, LPV: lopinavir, ABC: abacavir, DRV: darunavir, RTV: ritonavir, FTC: emtricitabine, ATRA: all-trans-retinoic acid, Ara-C: cytarabine, MTZ: mitoxantrone, MTX: methotrexate, 6-MP: mercaptopurine, CR: complete remission, ND: not described

tic infections.

We need reasonably objective criteria to assess the comorbid status of HIV disease in chemotherapy for AML, including APL. The main elements of this are the HIV viral loads, sensitivity of the virus to available antiretroviral drugs, CD4+ cell counts, and history of AIDS-related complications (1). Another report indicated that AML in AIDS-free HIV-infected patients with CD4+ cell counts above 200/μL and a good performance status should be treated with standard cytotoxic regimens (4). Because Patient 1 had HIV-associated dementia, we started induction therapy with single-agent ATRA out of consideration of his compliance. We selected LPA 99 for consolidation therapy because using ATRA and anthracycline is more straightforward for cases with poor compliance, and the dose from the intermediate-risk group was adopted for the low-risk group. For Patient 2, based on our experience with Patient 1, we selected LPA 2005 with a dose reduction to truncation. In previous reports, chemotherapy and concurrent ART were tolerated well (13, 16), and standard treatment for APL should be performed if patients have an adequate performance status (5, 15). HIV agents have also improved, as mentioned

above, and standard therapy for APL might be well tolerated when administered concurrently with ART. Of note, care must be taken with regard to infection in the neutropenic periods induced by APL chemotherapy and in selecting the optimal approach to the management of the patient's HIV disease, including opportunistic complications of AIDS.

The authors state that they have no Conflict of Interest (COI).

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