Autologous Stem Cell Transplantation using MEAM Regimen for Relapsed AIDS-Related Lymphoma Patients Who Received Highly Active Anti-Retroviral Therapy: A Report of Three Cases

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Abstract

AIDS-related lymphoma (ARL) is a serious complication of HIV infection. We performed MEAM (MCNU + etoposide + cytarabine + L-PAM) regimen with autologous stem cell transplantation (ASCT) for three patients with refractory or relapsed ARL. All three patients had been treated with highly active anti-retroviral therapy (HAART) during the course of the treatment regimen and ASCT. The regimen was well tolerable, and no uncontrollable infection was noted. All patients are still alive and maintain complete remission at 24, 20 and 9 months after transplantation. ASCT using MEAM regimen as a conditioning regimen was feasible for our patients with refractory or relapsed ARL.

Key words: HIV, lymphoma, AIDS, MCNU, stem cell transplantation

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Introduction

The incidence of malignant lymphoma has increased 60 to 200 fold in individuals who are infected with HIV (1, 2). It is included in AIDS-defining diseases, in which the diagnosis determines that the patient with positive HIV is affected with AIDS. Since the introduction of highly active anti-retroviral therapy (HAART), the risk of opportunistic infection has been reduced and the prognosis of HIV infected patients has improved; nevertheless, AIDS related lymphoma (ARL) is still a major cause of death of HIV-infected patients.

Encouragingly, however, the recent reports of studies of first line chemotherapy for ARL, such as dose-adjusted EP-OCH (3), R-CHOP (4), and R-CDE (5), have shown 59 to 75% of long term survival. To date there are no satisfactory second line chemotherapy regimens for refractory or relapsed ARL. Several studies have reported success in the salvage therapy of refractory and relapsed ARL using high-

dose chemotherapy with stem cell support. We report three cases with relapsed or refractory ARL treated with MEAM (MCNU, etoposide, cytarabine, L-PAM) regimen as a high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation.

Case Report

Case 1

A 41-year-old woman presented with abdominal discomfort. A computed tomography and an endoscopic examination showed abdominal mass which invaded duodenum. An endoscopic biopsy revealed CD20 positive diffuse large B cell lymphoma stage IVA, and a serological screening test revealed HIV positivity and CD4 count was 19/ μ L. Then, 50% reduced dose CHOP and HAART (d4T + 3TC + NFV) was started concurrently. After the first course of CHOP, facial nerve hemiparalysis developed. A cerebrospinal fluid analysis and a MRI scan revealed central nervous system

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Table 1. MEAM Regimen

		day-6	-5	-4	-3	-2	-1	0
MCNU	300mg/m ²	○						
Etoposide	200mg/m ²		○	○	○			
Cytarabine	200mg/m ²		○	○	○			
L-PAM	140mg/m ²					○		
SCT ↓								

Table 2. Regimen- related Toxicity

Adverse events	Case1	Case2	Case3
Anorexia	Grade 3	2	1
Vomiting	0	0	0
Stomatitis	2	1	1
Diarrhea	3	2	1
FN	3	0	0

Grade; CTCAE3.0

FN: febrile neutropenia

(CNS) involvement of malignant lymphoma. Salvage chemotherapy using five courses of high-dose methotrexate (3.5 g/m²) and two courses of high-dose cytarabine (3 g/m² ×2) was started, and 5.2×10⁶/kg of CD34-positive cells were obtained at the hematological recovery from the first course of high-dose cytarabine using granulocyte-colony stimulating factor (G-CSF). Intra-theal administration of methotrexate (15 mg) and prednisolone (20 mg) was performed on the preceding day of each course of chemotherapy. After the second course of high-dose cytarabine, she noted her right breast mass, then a core needle biopsy of the breast tumor revealed relapse of non-Hodgkin's lymphoma. Therefore, we added RICE regimen (rituximab, ifosfamide, carboplatin, and etoposide) as a third line chemotherapy. Subsequently, auto-PBSCT using MEAM regimen (Table 1) as a conditioning regimen was undertaken, followed by infusion of 3.7×10⁶/kg of CD34 positive cells. At day 12 post transplantation, she achieved complete hematological recovery. The regimen-related toxicity was mild to moderate as described in Table 2. The quantification of HIV virus maintained good control (lower than 50 copies/μL) through the regimen. Since, she has remained complete remission.

Case 2

A 31-year-old man, who was transmitted HIV virus by blood product, had been treated with HAART (TDF + 3TC + ATVr) for ten years. He was admitted to the hospital because of bilateral axillary lymph node swelling. A CT scan and a lymph node biopsy revealed CD20-positive diffuse large B cell lymphoma clinical stage IIA. He received three courses of CHOP and involved-field irradiation. Three months after the completion of irradiation, a FDG-PET scan demonstrated re-growth of the tumor at bilateral axillary, and Rituximab(R)-EPOCH was administered, but no im-

provement was obtained. Therefore, R-ESHAP was started as a third regimen. He received four courses of R-ESHAP and peripheral blood stem cells (48.9×10⁶/kg of CD34-positive cells) were harvested using G-CSF at the hematological recovery from the third course. Then he received MEAM regimen followed by transplantation of 3.9×10⁶/kg of CD34-positive cells. The day of engraftment was day 10 and regimen-related toxicity was mild. He could take HAART drugs without any discontinuation and the HIV virus was maintained in good control (lower than 50 copies/μL). He is alive and well without relapse.

Case 3

A 41-year-old man was admitted to our hospital for autologous stem cell transplantation for relapsed ARL. At another hospital, a mediastinal bulky tumor was noted and CT guided needle biopsy revealed that it was CD20 positive diffuse large B cell lymphoma stage IIA. Serological screening tests revealed that it was HIV positive. Initially, he was treated with ten courses of 70% dose of CHOP regimen with HAART (d4T, 3TC, NFV) and he achieved complete remission. Five months after completion of chemotherapy, he was found to have recurrence of a mediastinal tumor. He was administered three courses of R-EHSAP as salvage chemotherapy. During the recovery from the second course of R-ESHAP, 2.3×10⁶/kg of CD34-positive cells were obtained using G-CSF, and total 30 Gy of irradiation was added to the residual tumor of the mediastinum. Subsequently, he was treated with MEAM regimen followed by ASCT. He achieved engraftment on day 10 post transplantation and no significant regimen-related toxicity was observed. The HIV virus load was maintained at less than 50 copies/μL during salvage chemo-radiation-therapy and transplantation. He is also alive without relapse.

Discussion

High-dose chemotherapy followed by autologous stem cell transplantation for high risk first remission, refractory to first-line chemotherapy or relapsed ARL has been reported by several institutes. The first study on ASCT for ARL was reported by Gabarre et al in 2000 (6). Krishnan et al reported long-term remission in 20 patients of high risk ARL (7).

In terms of conditioning regimen, CBV (cyclophosphamide, BCNU, etoposide) (6), BEAM (BCNU, etoposide,

Figure 1. Transition of CD4 positive cell count before and after MEAM with autologous stem cell transplantation (ASCT).

cytarabine, melphalan) (8), total body irradiation-based regimen (6), and BU-CY (busulfan, cyclophosphamide) (9) have been reported.

In this case series, we used MEAM regimen which was based on BEAM; BCNU was replaced with MCNU. MCNU containing high-dose chemotherapy followed by autologous stem cell transplantation, such as MCVAC (MCNU, cytarabine, etoposide, cyclophosphamide) (10) and MEAM (11), have been reported. MCNU is a water-soluble nitrosourea, and is considered to have good permeability to the central nervous system (12). In the first case, the patient had invasion of lymphoma to CNS, this is why we chose MEAM regimen. Indeed this case was controlled with intrathecal chemotherapy first, it would also be possible that MCNU-containing regimen, high-dose cytarabine, and high-dose methotrexate worked altogether for CNS lesion control.

Major regimen-related toxicity of BEAM was gastrointestinal damage, such as mucosal damage of oropharynx, diarrhea, abdominal pain and gastrointestinal bleeding. Mills et al reported that 73% of patients required intravenous opiate analgesia and total parenteral nutrition was necessary in 76% of patients who were treated with BEAM regimen (13). In the present cases, grade 2 stomatitis and grade 3 diarrhea were noted in case 1, in the other patients, gastrointestinal symptoms were mild. In all cases, neither liver toxicity nor renal damage was noted (Table 2).

In order to prevent reactivation of HIV, HAART was continued during the process of conditioning regimen and ASCT, as tolerated. In the present cases, HAART was well tolerated and no discontinuation was observed. Krishnan et al reported that one patient of 20 treated with stem cell transplantation experienced delayed engraftment after treatment with ZDV (7). We avoided ZDV containing HAART regimen, because of its bone marrow toxicity. And we used

d4T/3TC/NFV or TDF/3TC/ATVr during ASCT. HIV viral load was well suppressed and no HAART associated adverse reaction was noted in all cases.

As described in Fig. 1, CD4 positive cell count was suppressed before the ASCT in all cases, and it increased after ASCT accompanied with hematological recovery. It has been maintained above 100/ μ L and no opportunistic infection as a delayed complication of stem cell transplantation has been noted. Previous reports noted that CD4 count showed decline at various extents after a stem cell transplantation, and substantial recovery in a few months (7, 14, 15).

We administered levofloxacin as a prophylactic antibiotic against gram negative bacteria, and sulfamethoxazole/trimethoprim for prevention of *Pneumocystis jirovecii* pneumonia (discontinued on day 1 in all cases, and was restarted when engraftment was confirmed), fluconazole or itraconazole for fungal infection, and azithromycin for *Mycobacterium avium-intracellulare* complex to all patients. One of three patients developed grade 3 febrile neutropenia, however, neither *Pneumocystis jirovecii* pneumonia, MAC infection, nor other serious infection was noted.

Peripheral stem cell mobilization was successfully done in all cases, $2.3\text{--}48.9 \times 10^6/\text{kg}$ of CD34 cells were collected. Infused CD34-positive cells ranged from 2.3 to $3.9 \times 10^6/\text{kg}$, and hematological recovery was prompt in all cases without secondary graft-failure (Table 3).

The anti-tumor efficacy of the BEAM regimen was well demonstrated. EBMT-lymphoma party performed BEAM regimen or TBI-based regimen followed by stem cell transplantation for 68 patients with ARL, and reported 56% of progression-free survival and 61% of overall survival at 3 years (8). The published study about the MEAM regimen followed by ASCT was small, and the efficacy of the MEAM regimen was not fully known (11). All three cases

Table 3. Summary of Three Cases

	Case1	Case2	Case3
Age	41	31	41
Sex	Female	Male	Male
Prior chemotherapy	CHOP HD-MTX RICE	CHOP-RT R-EPOCH R-ESHAP	CHOP R-ESHAP
Disease status at ASCT	CR	CR	CR
Collected CD34 cells($\times 10^6/\text{kg}$)	5.2	48.9	2.3
Infused CD34 cells($\times 10^6/\text{kg}$)	3.7	3.9	2.3
Engraftment(ANC $>500/\mu\text{L}$)	day12	day10	day10
Relapse free survival (months)	24+	21+	9+

are still alive without relapse. ASCT using MEAM regimen as a conditioning regimen for relapsed or refractory ARL appears to be well tolerable, efficient and equivalent to

ASCT with BEAM regimen. Further prospective large studies would be valuable to clarify the more precise efficacy and safety of this treatment.

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