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High-dose therapy plus autologous hematopoietic stem cell transplantation for human immunodeficiency virus (HIV)-related lymphoma: results and impact on HIV disease

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A B S T R A C T

Background and Objectives. The aim of this study was to assess the feasibility of high-dose chemotherapy plus autologous hematopoietic stem cell transplantation (HDC/AHSCT) in AIDS-related lymphoma (ARL), and its long-term impact in patients with human immunodeficiency virus (HIV) treated with highly active antiretroviral therapy (HAART).

Design and Methods. Fourteen patients with relapsed or resistant ARL (8 with non-Hodgkin's lymphoma and 6 with Hodgkin's disease) were treated with HDC/AHSCT while on HAART. HIV-1 proviral DNA load was quantified in 11 grafts.

Results. Hematologic reconstitution was good. No toxic deaths occurred. Despite the large number of cells harboring HIV-1 proviral DNA (10^5 to 10^9) re-infused with the graft, HAART controlled HIV replication and led to CD4 cell reconstitution in 7 of the 8 patients who were still alive six months after AHSCT. Only two patients had opportunistic infections after AHSCT. There were no significant changes in viral load (VL) or CD4⁺ cell counts in most patients. One month after AHSCT, 10 patients were in complete remission (CR). Seven patients died from lymphoma between 1 and 10 months after AHSCT, and a further two patients died in CR (one from AIDS at 16 months, one from another tumor at 28 months). Five patients are alive: four are in CR, 14, 19, 32 and 49 months after AHSCT (median CD4⁺ cell count = 445/ μ L; undetectable VL in 3 patients), and one is being treated for relapsed lymphoma 36 months after AHSCT.

Interpretations and Conclusions. HDC/AHSCT is feasible in AIDS-related lymphoma, in terms of harvesting, engraftment, adverse events and HIV control. It should be proposed to patients with poor-prognosis chemosensitive lymphoma.

Key words: autologous hematopoietic stem cell transplantation, lymphoma, HIV, AIDS, chemotherapy.

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Human immunodeficiency virus (HIV) infection is associated with a high incidence of non-Hodgkin's lymphoma (NHL). The overall risk of lymphoma is about 150- to 250-fold higher among HIV-infected patients than among the general population.¹ Initial data on the incidence of lymphoma in the HAART era were conflicting.¹⁻⁸ According to recent papers, however, the incidence of systemic lymphoma has been halved and primary brain lymphoma has virtually disappeared.^{1,5,8} However, NHL remains one of the most lethal complications of the acquired immune deficiency syndrome (AIDS) in industrialized countries.⁹ Nevertheless, several recent reports underline that the outcome of lymphoma in this setting has improved due to HAART and chemotherapy. HAART has been shown to improve survival^{1,4,10-13} and may also increase the response rate to chemotherapy;^{10,13} it also

prevents AIDS triggered by lymphoma chemotherapy and has thus changed the gold standard of chemotherapy for HIV-related NHL. The debate on the optimal intensity of chemotherapy for patients with well-controlled HIV infection (low versus standard doses) is thus settled.¹⁴ It therefore seems reasonable to expect that high-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (AHSCT) would further improve the results. Indeed, HDC followed by AHSCT is considered the best treatment for HIV-seronegative patients with relapsed chemotherapy-sensitive NHL.¹⁵ It has also been widely tested as first-line treatment for patients with factors indicating a poor prognosis. The use of peripheral blood stem cells (PBSC) instead of bone marrow significantly shortens the time to engraftment after high-dose therapy, and has contributed to reducing trans-

Table 1. Patients' characteristics at the beginning of salvage therapy.

Case No.	Lymphoma histology	Age/sex	Status before salvage therapy	Interval between lymphoma diagnosis and AHSCT (months)
1	Hodgkin (nodular sclerosing)	53/M	Stage IV; CR after EBVP; 1st relapse at 5 mo	14
2	Hodgkin (mixed cellular)	27/M	Stage IV; CR1 after MOPP-ABV; CR2 after ESHAP and radiotherapy; 3 rd relapse 4 mo after CR2	50
3	Hodgkin (nodular sclerosing)	41/M	Stage IV; CR1 after Stanford V; 1 st relapse at 5 mo after CR1	14
4	Hodgkin (mixed cellular)	48/M	Stage IV; CR1 after Stanford V; 1 st relapse 14 mo after CR1	22
5	Hodgkin (mixed cellular)	35/M	Stage II; CR 1 after Stanford V; 1 st relapse and CR2 after Rx; 2 nd relapse 11 mo after Rx	30
6	Hodgkin (unclassified)	30/M	Stage IV; CR1 after EBVP; CR2 after MOPP; CR3 after Rx; CR4 after Rx; 4th relapse at 24 mo	58
7	Classic Burkitt	38/M	Stage IV; primary resistant lymphoma	8
8	Classic Burkitt	32/F	Stage IV; primary resistant lymphoma	4
9	Immunoblastic	37/M	Stage III; CR1 after CHOP; 1st relapse at 1 mo	12
10	Immunoblastic	35/F	Stage III; CR1 after ACVB; 1st relapse at 24 mo	32
11	Centroblastic	39/M	Stage III; CR1 after CHOP; 1st relapse at 28 mo	36
12	Centroblastic	28/M	Stage IV; CR1 after CHOP+rituximab; 1 st relapse at 12mo	21
13	Centroblastic	37/F	Stage I; CR1 after CHOP+rituximab; 1 st relapse at 12 mo	16
14	Primary effusion lymphoma	37/M	Stage IV; CR1 after CHOP; 1 st relapse at 2mo	13

BM: bone marrow; CR: complete remission; ESHAP;²⁰ Stanford V;³⁸ EBVP: epirubicin, bleomycin, vinblastine, prednisone; ACVB: doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisolone; AHSCT: autologous hematopoietic stem cell transplantation; Rx: radiotherapy.

plant-related morbidity and mortality.¹⁶ However, the potential impact of re-infusing peripheral blood mononuclear cells (PBMC), a reservoir of HIV provirus, has not yet been investigated. In addition, possible interactions between myeloablative therapy and total body irradiation – which compromise the ability of the immune system to reconstitute in adults – remain to be evaluated in HIV-infected patients treated with HAART. Thus virus control, CD4⁺ cell count, and lymphoma status all need to be investigated.

We have previously described 8 patients¹⁷ with relapsed or refractory lymphoma who underwent high dose chemotherapy followed by AHSCT. One of these patients is not included in this analysis, as he was treated before the advent of HAART. This previous study showed that the collection and grafting of peripheral blood stem cells was feasible in HIV-infected patients. Here, we report data on 14 patients, with a longer follow-up, offering a more accurate analysis of outcome after intensive therapy with AHSCT in HIV-infected lymphoma patients, and of the long-term impact of this treatment on HIV disease progression and lymphoma.

Design and Methods

Patients

We reviewed the files of 14 patients with refractory or relapsed HIV-associated lymphoma who received salvage therapy including AHSCT in our institution between September 1998 and January 2002. There were 11 men and 3 women, with a median age of 37 years (range 27 to 53 years). The interval between the diagnosis of HIV infection and lymphoma varied from 0 (in two patients, lymphoma revealed HIV infection) and 15 years (median 6 years). Only one patient⁹ had an AIDS-defining infection before lymphoma occurrence, and 4 had minor infections. The median CD4 cell count at lymphoma diagnosis was 300/mL (77 to 534/mL). Patients were considered for AHSCT regardless of their immune status (Table 1). The lymphomas were classified according to the updated Kiel¹⁸ and WHO¹⁹ classifications. Six patients had Hodgkin's disease, two had Burkitt's lymphoma, two had immunoblastic lymphoma, three had centroblastic lymphoma and one had primary effusion lymphoma. Four patients

with NHL had central nervous system (CNS) involvement and the 2 patients with bone marrow (BM) involvement also had CNS involvement. Three patients with Hodgkin's disease had BM involvement. At the beginning of AHSCT-based salvage therapy, 9 patients were in first relapse, 3 were in subsequent relapse, and 2 had primary resistant lymphoma.

Salvage therapy

Salvage therapy consisted of two phases. The first was conventional second-line chemotherapy and graft collection, the drug regimen being chosen according to the type of lymphoma and first-line chemotherapy. As shown in Table 2, chemotherapy was a platinum-based chemotherapy regimen, ESHAP,²⁰ in 11 patients, ABVD²¹ in one patient (#2), and COPADM²² in two patients (#7 and 8). The second phase consisted of a conditioning regimen followed by AHSCT. The conditioning regimen was high-dose chemotherapy with or without total body irradiation (TBI), according to the features of the lymphoma. TBI was used in patients with extensive lymphoma, especially in cases of BM and CNS involvement. Pre-transplantation conditioning consisted of HDC alone in 6 patients (BEAM regimen²³ in 5 patients, busulfan plus cytosine arabinoside and melphalan in 1 patient) and HDC (cyclophosphamide in 5 patients, cyclophosphamide plus thiotepa in 2 patients and melphalan in 1 patient) combined with TBI in 8 patients (single-dose TBI in 5 and fractionated TBI in 3).

Hematopoietic stem cell (HSC) collection

PBSC were always collected after mobilizing chemotherapy and granulocyte colony-stimulating factor (G-CSF) administration (5 µg/kg); leukapheresis was performed when the peripheral blood CD34⁺ cell count reached more than 15/µL. G-CSF was stopped at the end of the collection phase. The goal was to obtain more than 3×10⁶ CD34⁺ cells/kg and 17×10⁴ CFU-GM/kg. A median of two leukapheresis sessions (range 1-5) was required. The grafts were cryopreserved using standard methods, with no special treatment of HSC, and were stored in special containers for samples from HIV-infected patients. HSC were thawed and infused on day 0, 48 hours after the last dose of conditioning chemotherapy.

Antiretroviral therapy and supportive care

All the patients had been receiving HAART, for a median of 24 months (4 to 63 months), at the time of transplantation; HAART was maintained throughout the HDC-AHSCT procedure (Table 2), except for short interruptions because of painful mucositis during aplasia. All the patients were also on trimethoprim-sulfamethoxazole prophylaxis. After AHSCT the patients were hospitalized in standard single rooms, without laminar flow. Gut decontamination was not used. Empirical antibiot-

ic therapy was only given to patients with febrile neutropenia, according to standard guidelines. G-CSF could be administered after AHSCT.

Assessment of toxicity and responses

Performance status and infections related to neutropenia were graded according to ECOG criteria. HIV viral load and CD4⁺ cell counts were determined before, during and after AHSCT. Plasma HIV-1 RNA was quantified using the Cobas Amplicor HIV-1 Monitor Assay v1.5 (Roche Diagnostic, Mannheim, Germany), which has a detection limit of 200 copies/mL (2.3 log₁₀ copies/mL). HIV-1 proviral DNA load was quantified retrospectively in PBMC collected from 11 patients on the day of graft harvest, by using a real-time polymerase chain reaction (PCR) assay simultaneously quantifying HIV-1 proviral DNA and albumin gene DNA, and detecting 5 copies of HIV-1 proviral DNA in 1×10⁶ PBMC.²⁴ This method was based on fluorescent TaqMan methodology and the ABI Prism 7700 Sequence Detection System (PE Applied Biosystems, Forster City, California, USA). The total amount of HIV-1 proviral DNA re-infused to each patient was calculated from the number of PBMC in the graft. The response to treatment was assessed after conventional second-line chemotherapy and after AHSCT, with full re-staging of all initially involved sites. Complete responses (CR) were defined as the disappearance of all evidence of disease. Partial responses (PR) were defined as a 50% to 75% reduction in tumor volume. Treatment failure was defined as lesser responses, disease progression or death from any cause.

Results

Effects of conventional second-line chemotherapy

ESHAP failed in five patients, who were switched to another regimen (MINE²⁵=4, ABVD=1). Conventional second-line chemotherapy induced responses in 5 of the 6 patients with Hodgkin's disease (4 CR, 1 PR) and failed in one. One of the two patients with Burkitt's lymphoma entered PR, while the other progressed. One of the two patients with immunoblastic lymphoma progressed, while the second entered PR. The three patients with centroblastic lymphoma were in CR before AHSCT, as was the patient with primary effusion lymphoma. Thus, overall, before AHSCT, 8 patients were in CR, 3 were in PR and 3 had progressive lymphoma.

Graft collection

PBSC were collected after chemotherapy and G-CSF administration. The median CD34⁺ cell count in PBSC grafts was 5.8×10⁴/kg (range 2.8-20) and the median CFU-GM count was 50×10⁴/kg (range 26-89). No relationship was found between CD4 cell counts at lym-

Table 2. Antiretroviral therapy, conventional salvage therapy, AH SCT conditioning and outcome.

Case No	ARV regimen	Before AH SCT			Conditioning	After AH SCT	
		Duration of HAART (mo.)	Conventional salvage therapy	Lymphoma status		Early evaluation	Outcome
1	D4T+3TC+EFV	10	ESHAP (4 cycles)	CR (CR2)	BEAM	CR	Died of 2 nd tumor at 28 mo.
2	D4T+3TC+NFV	8	ABVD (4 cycles)	CR (CR3)	BEAM	CR	Alive and well at 49 mo.
3	D4T+3TC+IDV	29	ESHAP (3 cycles) which failed then MINE (2 cycles)	PR	CY/TBI	CR at 9 mo.	Died of relapse
4	D4T+3TC+NFV	31	ESHAP (2 cycles) which failed then MINE (2 cycles)	Prog	CY/TBI	PR	Died of disease progression at 3 mo.
5	D4T+3TC+ABC	28	ESHAP (3 cycles) which failed then ABVD (2 cycles)	CR (CR3)	BEAM	CR at 32 mo.	Alive and well
6	D4T+3TC+RTV+IDV	63	ESHAP (3 cycles)	CR (CR5)	BU/Ara-C/melphalan	CR	Alive and well at 19 mo
7	D4T+3TC+IDV	24	COPADM (2 cycles) which failed then ESHAP (2 cycles) which failed then CYVE (2 cycles)	Prog	CY/TTP/TBI	Prog	Died of disease progression at 1 mo.
8	D4T+3TC+NFV	4	COPADM (2 cycles) which failed then CYVE (2 cycles)	PR	CY/TTP/TBI	Prog	Died of disease progression at 1 mo.
9	D4T+SQV+NFV+EFV	14	ESHAP (3 cycles)	Prog	CY/TBI	Prog	Died of disease progression at 3 mo.
10	D4T+3TC+IDV	28	ESHAP (2 cycles) which failed then MINE (3 cycles)	PR	melphalan/TBI	CR	Lymphoma relapse at 36 mo. Patient alive at 41 mo., undergoing salvage therapy
11	3TC+ABC+EFV+RTV+SQV+APV	34	ESHAP (4 cycles)	CR	BEAM	CR	Died of AIDS at 16 mo.
12	3TC+EFV+RTV+LPV	22	ESHAP (3 cycles) which failed then MINE (3 cycles)	CR	CY/TBI	Prog	Lymphoma relapse at 6 mo. and death of disease progression at 10 mo.
13	D4T+3TC+NFV	54	ESHAP (4 cycles)	CR	BEAM	CR	Breast irradiation following BMT. Alive and well at 14 mo.
14	D4T+3TC+NFV	11	ESHAP (4 cycles)	CR	CY/TBI	CR	Died of relapse at 2 mo.

AH SCT: autologous hematopoietic stem cell transplantation; ARV: antiretroviral; D4T: stavudine; 3TC: lamivudine; ABC: abacavir; EFV: efavirenz; IDV: indinavir; SQV: saquinavir; NFV: nelfinavir; RTV: ritonavir; APV: amprenavir; LPV: lopinavir; CR: complete response; PR: partial response; ESHAP; 20 CYVE, 22 MINE; 25 BEAM; 23 COPADM: methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone; CY: cyclophosphamide; TBI: total body irradiation; BU: busulfan; TTP: thiotepa; Ara-C: cytarabine; OI: opportunistic infections

phoma relapse and the number of CD34⁺ cells harvested (*data not shown*). The median number of HIV-1 DNA copies per million PBMC in the graft was 4.0×10^3 (range 5 to 1.5×10^5), or 3.6 log₁₀, in the 11 cases studied. The

total amount of HIV-1 proviral DNA re-infused to each patient ranged from 1.0×10^5 to 8.5×10^9 copies (median 4.8×10^7 or 7.7 log₁₀ copies) (Table 3).

Table 3. Results of harvesting and hematological reconstitution after AHST.

Patient No.	Harvesting					Graft			Reconstitution (days)			
	1	2	3	4	5	HIV-1 proviral DNA		8	9	10	11	12
1	80	2	7	89	2.3×10 ¹⁰	5.3×10 ³	1.25×10 ⁸	0	9	11	9	14
2	189	3	4.5	51	5.6×10 ¹⁰	7.5×10 ³	4.2×10 ⁸	8	10	11	10	14
3	185	2	5	43	NA	NA	NA	8	11	12	12	16
4	87	1	7.3	26	1.2×10 ¹⁰	3.9×10 ³	4.7×10 ⁷	0	12	13	13	21
5	133	5	2.8	39	5.7×10 ¹⁰	1.5×10 ⁵	8.5×10 ⁹	7	12	24	15	24
6	250	3	7	39	1.8×10 ¹⁰	2.0×10 ²	3.7×10 ⁶	0	10	11	10	NR
7	674	1	20	71	1.8×10 ¹⁰	6.3×10 ²	1.1×10 ⁷	11	12	13	21	NR
8	207	2	6.5	32	2.1×10 ¹⁰	5.0	1.0×10 ⁵	11	13	15	18	NR
9	45	2	5	50	NA	NA	NA	7	12	13	NR	NR
10	454	1	5.2	52	1.8×10 ¹⁰	2.0×10 ³	3.6×10 ⁷	0	14	14	10	19
11	140	1	4.5	60	2.1×10 ¹⁰	4.8×10 ⁴	1.0×10 ⁹	4	12	12	21	NR
12	200	1	5.3	40	1.4×10 ¹⁰	1.7×10 ³	2.4×10 ⁷	5	10	11	10	14
13	186	2	5.2	39	NA	NA	NA	6	5	7	5	13
14	23	1	8.6	67	2.7×10 ¹⁰	4.2×10 ³	1.1×10 ³	0	13	13	11	13

1: CD4⁺ cell count at salvage therapy outset; 2: N. of leukapheresis sessions; 3: CD34 (×10⁶/kg); 4: CFU-GM (×10⁴/kg); 5: N. of PBMC reinfused; 6: N. of copies 10⁶ PBMC; 7: N. of copies reinfused; 8: G-CSF; 9: Granulocyte counts >0.5×10⁹/L; 10: Granulocyte counts >1.0×10⁹/L; 11: Platelet counts >20×10⁹/L; 12: Platelet counts >50×10⁹/L. CFU-GM: granulocyte-macrophage colony-forming units; NA: not applicable; NR: not reached; G-CSF: granulocyte colony-stimulating factor; PBMC: peripheral blood mononuclear cells

AHST conditioning and hematologic reconstitution after AHST (Table 2)

After transplantation, the median time required for granulocyte counts to reach 0.5×10⁹/L was 12 days (7 to 14 days). Nine patients received G-CSF after AHST for a median of 7 days (4 to 11 days); the median time to reach 0.5×10⁷ granulocytes per liter was the same in patients with and without G-CSF (12 days). Platelet reconstitution could not be assessed in one patient (#9) because the lymphoma progressed shortly after AHST. In the remaining patients the platelet count reached 20×10⁹/L after a median of 11 days (5 to 21 days).

Impact of AHST on HIV replication and immune status

The median HIV-1 plasma viral loads before and one and six months after AHST showed no significant variation (2.3 log₁₀ copies/mL) (Figure 1). Patient #11 had a documented multidrug-resistant virus and persistently high viral load. Two patients (#8 and 9) had a marked increase in viral load shortly after transplantation, related to HAART interruption during post-AHST aplasia because of severe TBI-induced mucositis. In two patients, viral load became undetectable late after grafting, probably because of better adherence (#5) or more appropriate antiretroviral drugs (#2). The CD4⁺ cell count increased rapidly after AHST (Figure 1). The median CD4⁺ cell count one month after AHST was slightly but not significantly higher than before transplantation (209/μL, range 22 to 530, ver-

sus 113/μL, range 5 to 272; *p*=0.08). This trend towards higher CD4⁺ cell counts early after grafting was observed regardless of G-CSF administration during aplasia. Indeed in the 5 patients who did not receive G-CSF during aplasia, the median CD4⁺ cell count was 113/mL before grafting (range 5 to 272) and 169/μL (range 23 to 460) one month later, while in the 9 patients who received G-CSF, the respective values were 132/μL (range 34 to 251) and 247/μL (range 22 to 530). Six and 12 months post-transplantation, the median CD4⁺ cell count was respectively 236/μL in 8 assessable patients and 276/μL in 6 assessable patients. Therefore, in those patients who remained on HAART, HDC-AHST appeared to have little impact on HIV plasma viral load or on CD4⁺ cell reconstitution.

Infections

The median total hospital stay was 23.5 days (range 19 to 37), including a median of 14.5 days after transplantation (range 10 to 28 days). The median number of days with fever >38°C was 6 (range 2 to 24 days). Patient #6 had grade 3 febrile neutropenia with pneumonia, while the other 13 patients had grade 2 neutropenia-related infections requiring parenteral antimicrobial chemotherapy. No AHST-related deaths of infectious origin occurred. Similarly, no AIDS-related events occurred during follow-up in 12 of the 14 patients. Two patients (#2 and #11) had an asymptomatic CMV reactivation (viremia) one month after transplantation, and were treated with ganciclovir. Patient #11 developed pancytopenia after ganciclovir

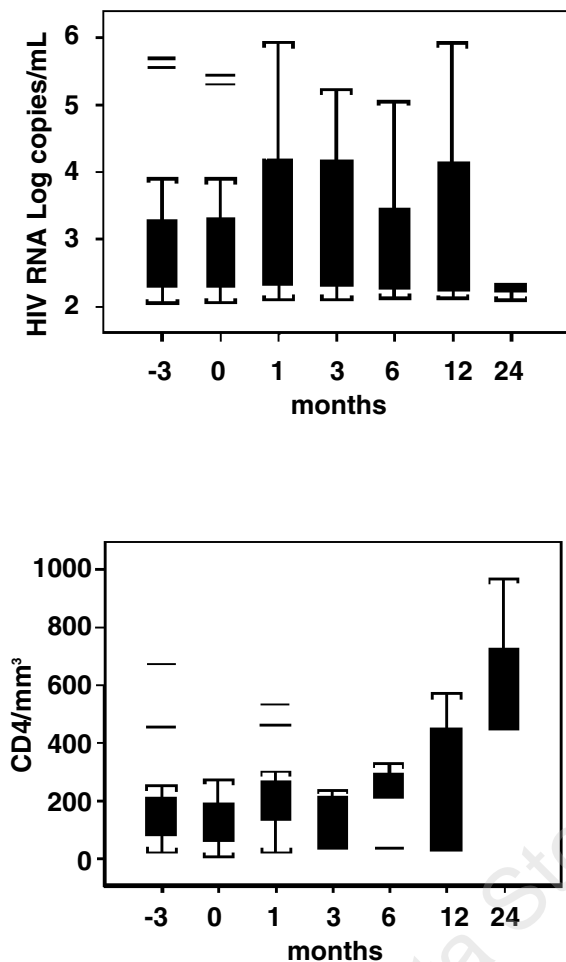


Figure 1. CD4 cell count and viral load before and after AHSCT.

treatment, 60 days after AHSCT, necessitating platelet and red-cell transfusions; the bone marrow was hypercellular with dyshematopoietic features, without lymphomatous involvement, and the karyotype was normal. The pancytopenia persisted one year after AHSCT and necessitated intermittent red-cell transfusions. This patient died of AIDS (invasive aspergillosis and *Pneumococcus* septicemia) 16 months after AHSCT.

Follow-up and survival

One month after AHSCT, 10 patients were in CR and 4 patients had resistant disease. Five of the six patients with Hodgkin's disease, neither of the two patients with Burkitt's lymphoma, and one of the two patients with immunoblastic lymphoma were in CR. The three patients with large-cell lymphoma were in CR, as was

the patient with primary effusion lymphoma (#14). The four patients with resistant disease (#4, 7, 8, 9) died of lymphoma progression, 1, 1, 3 and 3 months after AHSCT. Among the 10 patients who were in CR after grafting, four had lymphoma relapses. Patient #14 relapsed at 2 months and died shortly afterwards. Patient #12 relapsed at 6 months and died at 10 months. Patient #10, who relapsed 36 months after AHSCT, is currently receiving salvage therapy. Patient #3 relapsed at 6 months and died at 9 months; this patient's conditioning regimen was HDC plus TBI. The relapse was characterized by severe pancytopenia associated with autoimmune hemolytic anemia. Blood transfusions were ineffective and medical treatment was unsuccessful. Emergency splenectomy was performed during the 7th month post-AHSCT; histologic examination disclosed Hodgkin's disease in the spleen, liver and bone marrow. The hemolytic syndrome improved slightly after splenectomy but B symptoms worsened. Salvage chemotherapy was ineffective and the patient died of progressive Hodgkin's disease 9 months after AHSCT.

Two patients died in CR of events unrelated to lymphoma: patient #1, who was negative for markers of hepatitis B and C infection, died 25 months after AHSCT of undifferentiated liver cancer; patient #11, who had uncontrolled HIV disease, died of AIDS 16 months after AHSCT. Five patients are currently alive. Four patients are in CR, 14, 19, 32 and 49 months after AHSCT (Figure 2); the other patient (#10) is being treated for relapsed lymphoma.

Discussion

We confirm here the feasibility of AHSCT in HAART-treated HIV-infected patients with relapsed or refractory lymphoma, and show that HIV infection is controlled in patients in remission who remain on HAART.

To our knowledge there are no published data on salvage therapy for HIV-related Hodgkin's disease, and the few reports of salvage therapy for relapsed or refractory HIV-related NHL²⁶⁻²⁹ were mainly published in the pre-HAART era. They suggested that few patients could be cured after failure of first-line therapy, with CR rates of between 11%²⁷ and 26%²⁸ and a median survival time of around 3 months. In Spina's series,²⁶ only 2 of 40 patients with resistant or recurrent lymphoma entered long-term CR; however, the CR rate was 31% and the median survival time 7.1 months in patients treated with ESHAP;²⁹ most of whom were also on HAART. Chemotherapy is therefore mainly palliative in this setting.

In addition, few data are available on HSC trans-

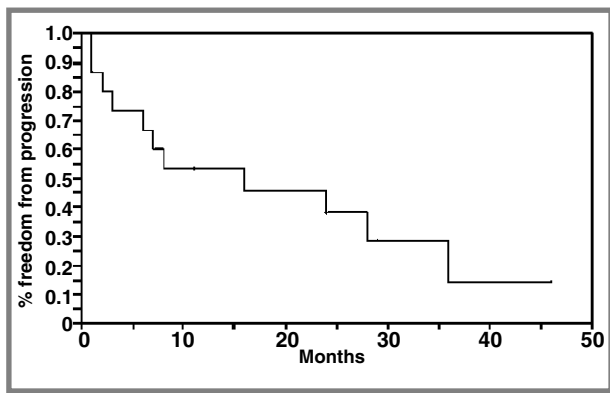


Figure 2. Progression-free survival (n=14 patients).

plantation in HIV-infected patients with hematologic malignancies, and most concern allogeneic or syngeneic grafting³⁰ intended to cure both the tumor and AIDS. There are only a few reports of AHSCT for lymphoma.^{17,31-34} We show here that HIV infection does not impair HSC graft collection, even in patients with advanced HIV disease. HSC mobilization with chemotherapy and G-CSF was effective in all our patients whatever their CD4 counts or viral loads, confirming previous reports by ourselves¹⁷ and others.³²⁻³⁵ Schooley *et al.*³⁶ reported successful PBSC harvesting, even though patients with baseline CD4⁺ cell counts below 500/ μ L had a low CD34 cell count peak during mobilization compared with patients with CD4⁺ cell counts exceeding 500/mL. Campbell *et al.*³⁷ observed a transient increase in HIV replication in some patients during PBSC mobilization and harvesting, suggesting that treatment with G-CSF and leukapheresis could activate HIV-1 replication. We did not monitor viral load during graft collection.

We confirm that HIV infection does not impair engraftment, in keeping with our previous results and those of Krishnan *et al.*³³ Adverse events during the early post-AHSCT period were comparable to those observed in HIV-seronegative patients undergoing AHSCT. Thus, neither HIV infection nor HAART had a negative impact on AHSCT conditioning or engraftment. One of our patients with uncontrolled HIV disease developed post-AHSCT pancytopenia concomitant with ganciclovir treatment for CMV reactivation, but it is difficult to determine whether ganciclovir or failed engraftment was the cause.

Despite the control of viral replication by HAART, it is well known that HIV persists at low levels in PBMC. The AHSCT procedure thus involves engraftment of HIV-infected cells. We show here that large numbers of HIV-1 proviral DNA copies (10^5 to 10^9 copies) were

re-infused with the graft. The median HIV-1 DNA copy number per million PBMC was 3.6 \log_{10} in our patients, a value close to that observed (3.1 \log_{10}) in a similar population of patients responding to HAART for at least 6 months²⁴ (viral load below 1000 copies/mL and CD4⁺ cell count below 200/ μ L).

Nevertheless, continuous HAART was successful in controlling HIV replication after transplantation and thereby prevented CD4 cell depletion. Indeed, no major changes in viral load or CD4⁺ cell counts were observed after AHSCT in patients receiving HAART. Regarding the impact of AHSCT on HIV disease status, only one of the 14 patients developed a severe opportunistic infection and died from AIDS.

Therefore, HDC followed by AHSCT is, at least in the short term, an effective salvage treatment for patients with HIV-related lymphoma. However, despite a high rate of complete responses to this intensive therapy (10/14 patients), no plateau phase was observed and events (mainly lymphoma relapses) occurred continuously. On this important point, our results conflict with those of Krishnan *et al.*,³⁴ who observed an early plateau in the progression-free survival curve. It is important to underline that this discrepancy could be explained by differences between the patient populations. Indeed, Krishnan enrolled patients with less aggressive features, some of whom were in first CR. In contrast, most of our patients were in second or subsequent relapse, and some had primary resistant lymphoma.

HDC/AHSCT is only effective on chemosensitive lymphoma in HIV-seronegative patients,¹⁵ being unable to eradicate lymphomas resistant to conventional second-line chemotherapy. This also seems to be the case in HIV-infected patients.

Nearly half our patients had Hodgkin's disease, although this form represents less than 20% of all HIV-related lymphomas in our institution. This recruitment bias may be explained by the fact that Hodgkin's lymphoma responds better to salvage than does NHL, and by the less aggressive nature of Hodgkin's disease.

In conclusion, hematopoietic stem cell transplantation is feasible in HIV-infected patients with lymphoma (Hodgkin's disease and NHL), in terms of graft collection, engraftment, and adverse events.

In addition, despite the large number of infected autologous cells re-infused, AHSCT is compatible with long-term control of HIV replication and with CD4 reconstitution on HAART. HDC followed by AHSCT thus appears to be an effective treatment for HIV-infected patients with lymphoma, especially those with chemosensitive forms, but long-term results in patients with advanced lymphoma are disappointing. We consider that this treatment should be offered earlier than in the current study, to patients with poor-

prognosis but chemosensitive lymphoma, especially those in relapse or partial remission, regardless of their HIV serostatus.

AGM: contributed to writing the article and performed virological tests, together with VC; NA also participated in the writing phase and

was in charge of graft collection, while FN was responsible for graft cryopreservation. SC, YL, RT, JPV and MS were the doctors principally responsible for the patients. FC was the pathologist. VL performed the statistical analysis. BA: participated in the writing phase and performed immunological tests; VL: participated in the writing phase and oversaw the study. The authors reported no potential conflicts of interest.

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