

## Brief report

# Autologous stem cell transplantation for HIV-associated lymphoma

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**Is peripheral stem cell mobilization followed by autologous stem cell transplantation (ASCT) feasible in patients with human immunodeficiency virus (HIV)-associated lymphoma (HIV-L)?** Studies have demonstrated that, in the HIV-negative (HIV<sup>-</sup>) setting, ASCT may improve lymphoma-free survival in high-risk non-Hodgkin lymphoma (NHL) or relapsed Hodgkin disease (HD) and NHL. Given the poor prognosis of HIV-L with

conventional chemotherapy, this dose-intensive approach was explored. Nine patients with HIV-HD or NHL mobilized a median of  $10.6 \times 10^6$  CD34<sup>+</sup> cells/kg and engrafted after ASCT. CD4 counts recovered to pretransplantation levels and HIV viral loads were controlled in patients compliant with antiretroviral therapy. Seven of 9 patients remain in remission from their lymphoma at a median of 19 months after transplantation. Thus, pa-

tients with HIV-L on antiretroviral therapy can engraft following ASCT. Prolonged lymphoma remissions, without significant compromise of immune function, can be seen, suggesting that ASCT can be used in selected patients with HIV-L. (Blood. 2001;98:3857-3859)

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## Introduction

Highly active antiretroviral therapy (HAART) has changed the natural history of human immunodeficiency virus (HIV) infection by improving immune function in HIV-infected individuals.<sup>18</sup> However, multiple studies have shown no impact of HAART on the incidence of acquired immunodeficiency syndrome (AIDS)-related non-Hodgkin lymphoma (NHL) or Hodgkin disease (HD).<sup>1-6</sup>

Earlier therapeutic approaches to HIV-associated lymphoma (HIV-L) focused on reduction of chemotherapy dose intensity due to fears of further worsening the immune function in these patients.<sup>7</sup> In the era of HAART, more aggressive approaches are being explored.<sup>8-11</sup> In HIV-negative (HIV<sup>-</sup>) patients with relapsed aggressive NHL and HD, high-dose chemotherapy with autologous stem cell transplantation (ASCT) is the optimal therapy.<sup>12</sup> This modality has also been explored in patients with NHL in first remission who are considered to be at increased risk for relapse with conventional-dose chemotherapy.<sup>13,14</sup> We report here on our initial experience using ASCT in patients with HIV-L receiving HAART.

All patients were on HAART (Table 1) at the time of stem cell collection before transplantation and had undetectable HIV viral loads (VLs). Stem cells were mobilized with a combination of chemotherapy and 10 μg/kg granulocyte colony-stimulating factor (G-CSF) and collected as previously described.<sup>10</sup> A median of  $10.6 \times 10^6$  CD34<sup>+</sup> cells/kg was collected. Five patients had additional stem cells collected as part of a gene therapy trial, which was reported separately.<sup>16</sup>

High-dose chemotherapy with the CBV regimen (cyclophosphamide 100 mg/kg ideal body weight, 1,3-bis-(2-chloroethyl)1-nitrosourea (BCNU) 450 mg/m<sup>2</sup>, etoposide 60 mg/kg adjusted ideal body weight) was administered to all patients.<sup>13,17</sup> Autologous stem cells were reinfused on transplantation day 0. Five patients, who were also on the gene therapy trial, had genetically modified stem cells ( $0.5-2.0 \times 10^6$  CD34<sup>+</sup> cells/kg) reinfused after the infusion of unmanipulated stem cells.<sup>16</sup> Twenty-four hours after stem cell infusion, G-CSF (5 μg/kg) was started and continued until engraftment. Routine anti-infective prophylaxis was administered to all patients as previously described.<sup>10</sup> Most patients were able to continue HAART through the transplantation. Three patients missed one dose, one missed 3 doses, and only one patient missed all doses due to persistent nausea.

## Study design

Between March 1998 and May 2000, 9 HIV-L patients on HAART received myeloablative chemotherapy followed by ASCT at our institution. Informed consent was obtained from all patients in accordance with the City of Hope Medical Center institutional review board guidelines. The median age was 41.6 years (range, 11.4-54.3 years). Seven patients had NHL and 2 had HD (Table 1). The NHL patients who were in first remission had high-risk features as defined by the international prognostic index (IPI).<sup>15,19</sup>

## Results and discussion

Engraftment occurred in all 9 patients. White cell engraftment, defined as an absolute neutrophil count greater than 500/μL, occurred at a median of 11 days (range, 9-12). Platelet engraftment, defined as platelet transfusion independence and a platelet count greater than  $20 \times 10^9/\mu\text{L}$ , occurred at a median of 10 days (range, 7-15).

Infectious complications during the period of neutropenia up to

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**Table 1. Patient characteristics**

UPN	DX	Disease status at transplantation	Age, y, at transplantation	Sex	Antiretroviral therapy	Prior chemotherapy/radiotherapy
202	NHL	2 <sup>nd</sup> CR	54	M	nelfinavir, lamivudine, stavudine	CHOP
203	HD*	2 <sup>nd</sup> CR	29	M	indinavir, lamivudine, stavudine	CHOP, Ifos/VP16, ESHAP, 4500Gy
204	NHL	1 <sup>st</sup> PR	52	M	nelfinavir, lamivudine, stavudine	CHOP, ESHAP, 3600Gy
208	NHL	1 <sup>st</sup> CR	41	M	nevirapin, nelfinavir, stavudine	CHOP, ESHAP
209	HD	1 <sup>st</sup> REL	46	M	indinavir, lamivudine	BOSE, ABVD, ESHAP
400	NHL	2 <sup>nd</sup> CR	11	M	nelfinavir, nevirapin, lamivudine	POG 8617, POG 9517, POG 9317
405	NHL	2 <sup>nd</sup> PR	44	M	efavirenz, lamivudine, stavudine	CHOP, ESHAP, Rituxan
406	NHL	1 <sup>st</sup> CR	38	M	indinavir, lamivudine, stavudine	CHOP
407	NHL	3 <sup>rd</sup> CR	37	F	ritonavir, saquinavir, nevirapin, stavudine	CHOP, Ifos/VP16, Rituxan, ESHAP

UPN indicates unique patient number; DX, diagnosis; NHL, non-Hodgkin lymphoma; CR, complete remission; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; Ifos, ifosfamide; VP-16, etoposide; ESHAP, etoposide, cytarabine, cisplatin, prednisone; REL, relapse; BOSE, bleomycin, oncovin, streptozocin, etoposide; ABVD, adriamycin, bleomycin, vincristine substituted for vinblastine, dacarbazine; POG 8617, cyclophosphamide, adriamycin, cytarabine; POG 9517, cyclophosphamide, adriamycin, methotrexate, cytarabine, ifosfamide, etoposide; and POG 9317, ifosfamide, etoposide, methotrexate, cytarabine.

\*Initially dx NHL then changed to HD (Hodgkin disease).

the day of engraftment were seen in 6 patients. These included coagulase-negative *Staphylococcus* or *Streptococcus pneumoniae* bacteremia in 4 patients. One patient developed a dental abscess. On transplantation day +11 one patient developed culture-negative sepsis, manifest as hypotension, gastrointestinal bleeding, and skin erythema. Infectious complications after engraftment included *Clostridium difficile* colitis in one patient at day +38. Two patients developed an interstitial pneumonia between day +40 and day +60. One of these patients also developed a lobar pneumonia in year 2 after transplantation as well as *Staphylococcus aureus* bacteremia and recurrent sinusitis. One patient developed a bacterial pneumonia, presumably after influenza, at +21 months for which he required temporary ventilatory support. All patients responded to antimicrobials.

Opportunistic infections were seen in 3 patients—an uncomplicated disseminated varicella zoster infection at 2 months after transplantation in one patient, cytomegalovirus viremia and fever at 37 days in another patient, and *Pneumocystis carinii* pneumonia (PCP) at 8 months and cytomegalovirus retinitis at 17 months after transplantation in one patient who stopped both PCP prophylaxis and antiretrovirals. All patients responded to treatment.

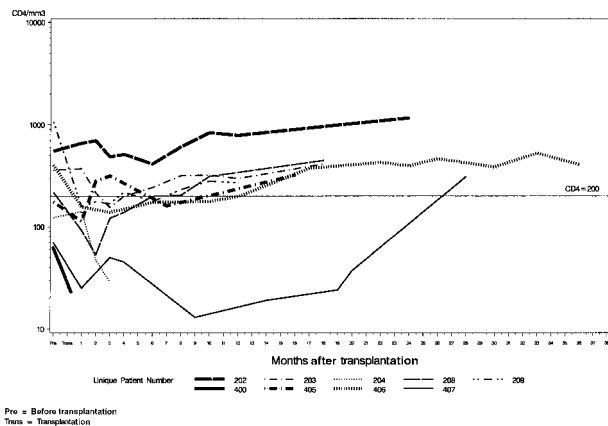
Conditioning regimen-related complications included grade 2 mucositis in 6 patients and grade 2 hyperbilirubinemia in one patient. One of these patients also had BCNU pneumonitis, presenting as interstitial infiltrates at day +55; this responded well to oral prednisone. All toxicity was graded according to common toxicity grading criteria version 2.0.

The CD4 counts gradually decreased after transplantation in all

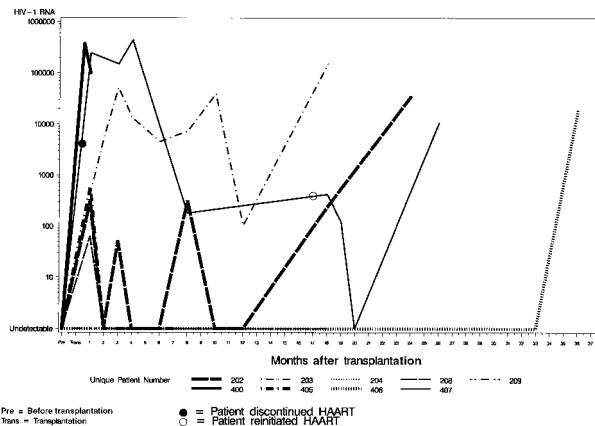
9 patients and reached a nadir of 138/ $\mu$ L (range, 25-411) at a median of 2 months in 7 evaluable patients (Figure 1). Two nonevaluable patients died at approximately 4 months after transplantation with relapsed lymphoma. Six of these 7 evaluable patients recovered CD4 counts to pretransplantation levels by a median of 14 months (range, 2-28). One patient (UPN 209) had the highest CD4 counts before transplantation (> 1000/ $\mu$ L), which may account for the failure to return to this baseline.

Six patients had a rise in their HIV VL in the first month following the transplantation, whereas 3 patients maintained an undetectable VL (Figure 2). In 5 of the 7 patients evaluable at 12 months, the VL was at undetectable levels (b-DNA assay or RNA polymerase chain reaction Roche Amplicor assay). One patient (UPN202), had a significant rise at 18 months and one (UPN406) at 36 months due to noncompliance with HAART. Two patients (UPN203, UPN407) had a persistently high VL after transplantation. UPN203 required multiple changes in his regimen. He was compliant with HAART, hence his high VL may reflect the inability of HAART to eradicate the latent HIV reservoir. Patient UPN407 stopped all antiretroviral therapy for a prolonged period after transplantation for psychosocial reasons, which explains the continued high VL.

We report here on the largest single institution series of patients with HIV-L on HAART treated with ASCT. All patients received the same high-dose chemotherapy conditioning and achieved long-term engraftment with stem cell rescue in a time course similar to HIV<sup>-</sup> patients. Pre-engraftment infectious complications



**Figure 1. CD4 count after SCT.**



**Figure 2. HIV viral load after SCT.**

were similar to the HIV<sup>-</sup> setting with bacterial infections predominating.<sup>12</sup> Conditioning regimen-related complications were also similar to the HIV<sup>-</sup> setting in that there was no increase in mucositis or hepatotoxicity associated with combining HAART and high-dose chemotherapy. After transplantation, the several opportunistic infections that occurred responded well to treatment. In the majority of patients we have seen recovery of immune function as manifest by low VL and rising CD4 counts. This is similar to changes in immune parameters in HIV-L patients treated with CHOP and concomitant antiretroviral therapy.<sup>20</sup> Future studies will address the pharmacokinetic effects of myeloablative therapy in combination with HAART and the reconstitution of immune function after ASCT. The effects of this approach on lymphoma-free survival remain to be seen. The surviving patients have been followed for a median of 19.0 months (range, 12-36 months). Two

patients relapsed with disease in the bone marrow at 40 days and 95 days, respectively, and died. All other patients remain in remission.

The advent of effective antiviral therapy now allows us to administer dose-intensive and potentially curative chemotherapy to HIV-infected individuals with lymphoma. Infectious complications can be managed through a combination of prophylaxis and close monitoring after transplantation. Hence, HIV status should no longer by itself preclude ASCT for treatment of lymphoma.

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## References

- Bower M, Matthews G, Powles T, Mandalia S, Nelson B, Gazzard B. Changes in AIDS related lymphoma (ARL) in the era of highly active antiretroviral therapy (HAART) [abstract]. *Proc Am Soc Clin Oncol*. 2000;19:17a.
- Jacobson L, Yamashita T, Detels R, et al. Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma among HIV-1 infected individuals. *J Acquir Immune Defic Syndr*. 1999;21:S34-S41.
- Levine A, Seneviratne L, Espina BM, et al. Evolving characteristics of AIDS-related lymphoma. *Blood*. 2000;96:4084-4090.
- Matthews GV, Bower M, Mandalia S, Powles T, Nelson MR, Gazzard BG. Changes in acquired immunodeficiency syndrome-related since the introduction of highly active antiretroviral therapy. *Blood*. 2000;96:2730-2734.
- Cote TR, Biggar RJ, Rosenberg PS, et al. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. *Int J Cancer*. 1997;73:645-650.
- Re A, Casari S, Stellini R, Cadeo G. Increased incidence in HIV-associated Hodgkin's disease in the era of highly active antiretroviral therapy (HAART) [abstract]. *Blood*. 2000;96:830a.
- Kaplan LD, Straus DJ, Testa M, et al. Low-dose compared with standard dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. *N Engl J Med*. 1997;336:1641-1648.
- Little R, Pearson D, Steinberg S, Elwood P, Yarchoan R, Wilson W. Dose adjusted EPOCH chemotherapy in previously untreated HIV-associated non-Hodgkin's lymphoma [abstract]. *Proc Am Soc Clin Oncol*. 1999;18:10a.
- Errante D, Gabarre J, Fasan M, et al. Feasibility of the integration of Stanford V chemotherapy (CT) regimen with highly active antiretroviral therapy (HAART) and G-CSF in patients (pts) with Hodgkin's disease and HIV infection (HD-HIV) [abstract]. *Proc Am Soc Clin Oncol*. 1999;18:11a.
- Molina A, Krishnan A, Nademanee A, et al. High dose therapy and autologous stem cell transplantation for human immunodeficiency virus-associated non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy. *Cancer*. 2000;89:680-689.
- Gabarre J, Azar N, Autran B, Katlama C, Leblond V. High dose therapy and autologous haematopoietic stem cell transplantation for HIV-1 associated lymphoma. *Lancet*. 2000;335:1071-1072.
- Philip T, Guglielmi C, Hagenbeek A, Somers R, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333:1540-1545.
- Nademanee A, Molina A, O'Donnell M, et al. Results of high-dose therapy and autologous bone marrow/stem cell transplantation in poor-risk intermediate and high-grade lymphoma: international index high and high intermediate risk group. *Blood*. 1997;90:3844-3852.
- Haouan C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol—a Groupe d'Etude des Lymphomes de l'Adulte Study. *J Clin Oncol*. 2000;18:3025-3030.
- Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993;329:987-994.
- Zaia J, Krishnan A, Rossi JJ, et al. Treatment of AIDS lymphoma with high dose chemotherapy and genetically modified stem cells: a model for evaluation of gene therapy [abstract]. Bethesda, MD: International AIDS Malignancy Conference; May 16-18, 2000.
- Nademanee A, O'Donnell MR, Snyder DS, et al. High dose chemotherapy with or without total body-irradiation followed by autologous bone marrow and/or peripheral blood stem cell transplantation for patients with relapsed and refractory Hodgkin's disease: results in 85 patients with analysis of prognostic factors. *Blood*. 1995;85:1381-1390.
- Flexner C. HIV protease inhibitors. *N Engl J Med*. 1998;338:1281-1292.
- Navarro JT, Ribera JM, Oriol A, et al. International prognostic index is the best prognostic factor for survival in patients with AIDS-related non-Hodgkin's lymphoma treated with CHOP: a multivariate study of 46 patients. *Haematologica*. 1998;83:508-513.
- Weiss R, Mitros P, Arasteb K, Schurmann D, Huhn D. HIV related lymphoma: changes in immune parameters and viral load during chemotherapy [abstract]. *Blood*. 2000;96:134a.



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