Durable remissions with autologous stem cell transplantation for high-risk HIV-associated lymphomas


The treatment of HIV-associated lymphoma has changed since the widespread use of highly active antiretroviral therapy. HIV-infected individuals can tolerate more intensive chemotherapy, as they have better hematologic reserves and fewer infections. This has led to higher response rates in patients with HIV-associated Hodgkin disease (HD) or non-Hodgkin lymphoma (NHL) treated with chemotherapy in conjunction with antiretroviral therapy. However, for patients with refractory or relapsed disease, salvage chemotherapy still offers little chance of long-term survival. In the non-HIV setting, patients with relapsed Hodgkin disease (HD) or non-Hodgkin lymphoma (NHL) have a better chance of long-term remission with high-dose chemotherapy with autologous stem cell rescue (ASCT) compared with conventional salvage chemotherapy. In a prior report we demonstrated that this approach is well tolerated in patients with underlying immunodeficiency from HIV infection. Furthermore, similar engraftment to the non-HIV setting and low infectious risks have been observed. Herein, we expand upon this early experience with the largest single institution series of 20 patients. With long-term follow-up we demonstrate that ASCT can lead to an 85% progression-free survival, which suggests that this approach may be potentially curative in select patients with relapsed HIV-associated HD or NHL. (Blood. 2005;105:874-878)

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Introduction

The incidence of Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL) in HIV-infected individuals is much greater than in the HIV-negative population.\(^1,2\) In earlier decades the treatment of lymphoma in the setting of immune deficiency was far less successful than in the HIV-negative patient.\(^3\) This was in part due to the poor hematologic reserves of HIV-infected patients but was also due to higher rates of infection and higher rates of relapse of the lymphoma. The advent of highly active antiretroviral therapy (HAART) altered the natural history of HIV infection by reducing the incidence of opportunistic infections and improving the underlying immune deficiency.\(^4\) In addition, combining HAART with chemotherapy or consolidating chemotherapy with HAART has increased remission rates in both HIV-associated Hodgkin and non-Hodgkin lymphoma.\(^5,6\) Recent studies also have confirmed that the International Prognostic Index (IPI) is applicable to patients treated with HAART and chemotherapy.\(^7\) For HIV-infected lymphoma patients with high-risk features as defined by the IPI, relapse rates are still high after conventional chemotherapy. Furthermore, for HIV-infected patients with either relapsed HD or NHL, the current salvage chemotherapy regimens offer little chance of long-term survival.

In the HIV-negative setting, studies have shown that high-dose therapy with autologous stem cell transplantation (ASCT) is the optimal therapy for relapsed HD and NHL.\(^8-10\) As the procedure-related mortality of ASCT has decreased, ongoing studies are exploring its use in high-risk first remission patients.\(^10\) Now that HIV-infected individuals have markedly improved immune and hematologic function, the use of both solid organ and asct is being explored in patients with underlying immunodeficiency and concomitant malignancy or organ dysfunction.\(^11-13\) Herein we report the City of Hope Comprehensive Cancer Center experience on the largest single institution series of patients with HIV-associated lymphomas undergoing ASCT. Our initial experience demonstrated the feasibility of this approach in terms of stem cell mobilization, engraftment, and low regimen-related toxicity.\(^16\) Now with long-term follow-up in a larger series of patients we demonstrate that ASCT can provide durable remissions in a subset of these high-risk patients.

Patients, materials, and methods

Patients

HIV-positive patients with NHL who failed to achieve complete remission (CR) after standard-dose front-line chemotherapy or had a chemosensitive relapse (partial relapse [PR] or CR) after an initial CR were eligible. HIV NHL patients with high-risk disease in first CR as defined by the IPI also were eligible. Patients with HD with a chemotherapy-sensitive relapse were eligible. All pathology was reviewed at the City of Hope by a hematopathologist. Inclusion criteria were the institutional standard criteria for ASCT--cardiac ejection fraction higher than 50% by either MUGA (gated resting...
cardiac-wall motion study) scan or echocardiogram, 24-hour urine creatinine clearance more than 60 cc/s per minute, diffusion capacity more than 50% predicted, liver function tests less than 2 x normal, less than 10% bone marrow involvement with lymphoma, and no central nervous system (CNS) involvement with lymphoma. Patients with prior positive cerebrospinal fluid (CSF) cytology were eligible if the CSF cleared with intrathecal therapy. Positive hepatitis serology was not an exclusion criterion but required further evaluation, including a liver biopsy. Initially, the first 5 patients were required to have an absolute CD4 count of more than 100 mcl at the time of lymphoma diagnosis or recurrence. However, this requirement was deleted for subsequent patients. All patients had to have an HIV viral load of less than 10 000 cp/mL by reverse transcriptase–polymerase chain reaction (RT-PCR) at enrollment. Patients had to be free of opportunistic infections for one year prior to enrollment, except for treatment for responsive thrush, mycobacterium, and herpes infections. All patients had to be receiving highly active antiretroviral therapy (HAART). The City of Hope’s Institutional Review Board approved the protocol, and informed consent was obtained from each patient in accordance with institutional guidelines.

**Results**

Between March 1998 and August 2003, 20 patients with HIV-associated lymphomas were enrolled. Median age at ASCT was 44 years (range, 11-68 years). Most had relapsed disease or failed to achieve a CR with front-line therapy: 7 in first relapse, 2 in second relapse, 5 in first PR. Four patients with a high-risk IPI score were in first CR and one in second and third CR, respectively. The histologic subtypes and chemotherapy regimens are listed in Table 1. Patients received a median of 2 chemotherapy regimens prior to ASCT (range, 1-4 regimens).

The median CD4 count at lymphoma diagnosis was 174 cells/mcl (range, 30-500 cells/mcl), and median viral load at lymphoma diagnosis was 26 120 cp/mL (range, 500-1 300 000 cp/mL). At study entry 17 patients had undetectable viral loads, and the remaining 3 had a viral load ranging between 700 and 6500 cp/mL. The median CD4 count at study entry was 175 cells/mcl (range, 25-1064 cells/mcl). Fifteen patients were on a protease inhibitor–based regimen and the remainder on a non-nucleoside reverse transcriptase inhibitor–based regimen. One patient had concomitant hepatitis B infection. His liver biopsy prior to ASCT showed no evidence of cirrhosis.

A median of 10.6 × 10^8 CD34+ cells/kg were collected after a median of 4 days of apheresis. One patient required prolonged

<table>
<thead>
<tr>
<th>UPN</th>
<th>DLC</th>
<th>Histology</th>
<th>Disease status at ASCT</th>
<th>Prior chemo</th>
<th>OI after ASCT</th>
<th>Status</th>
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<tbody>
<tr>
<td>202</td>
<td>DLC</td>
<td>First rel</td>
<td>CHOP</td>
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<td>CR 67 months</td>
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<td>CR 61 months</td>
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<td>First PR</td>
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<td>208</td>
<td>DLC</td>
<td>First CR</td>
<td>CHOP, ESHAP</td>
<td>Zoster</td>
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<td>209</td>
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<td>BOSE, ABVD, ESHAP</td>
<td>HEP C</td>
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<td>400</td>
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<td>CHOP, ifos/VP16, RTX, ESHAP</td>
<td>Pneumocystis, CMV retinitis</td>
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<tr>
<td>410</td>
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<td>First PR</td>
<td>MBACOD, ESHAP + RTX</td>
<td>CMV viremia</td>
<td>CR 49 months</td>
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<tr>
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<tr>
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<td>BL</td>
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<td>None</td>
<td>CR 20 months</td>
<td></td>
</tr>
<tr>
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<td>DLC</td>
<td>First rel</td>
<td>EPOCH, CHOP</td>
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<td>CR 20 months</td>
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<td>First rel</td>
<td>CHOP + RTX, ICE</td>
<td>None</td>
<td>CR 6 months</td>
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</table>

ALC indicates anaplastic large cell; HD, Hodgkin disease; BL, Burkitt lymphoma; DLC, diffuse large cell; ABVD, adriamycin, bleomycin, vincristine/vinblastine, dascarbazine; Ara-C/MTX, cytarabine, methotrexate; BOSE, bleomycin, oncovin, streptozocin, etoposide; CAV, cyclophosphamide, vincristine, adriamycin, CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; CODOX-M, cyclophosphamide, vincristine, adriamycin, methotrexate; ESHAP, etoposide, cytarabine, platinol, solumedrol; RTX, rituxan; MBACOD, methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, cytarabine, dexamethasone; POG 9317, ifosfamide, etoposide, methotrexate, cytarabine; POG 9517, ifosfamide, etoposide, methotrexate, cytarabine; POG 8617, cyclophosphamide, adriamycin, cytarabine; OI, opportunistic infection.
apheresis (10 days). No significant toxicity in terms of rise in HIV viral load or opportunistic infections was seen during apheresis.

Seventeen patients received the chemotherapy-based conditioning regimen, and 3 received the radiation-based regimen. Antiretroviral therapy was given to all patients from the start of conditioning onward, but only 9 patients were able to tolerate it throughout. The remainder were intolerant due to gastrointestinal toxicity such as nausea in the majority or mucositis in the FTI patients. The same HAART regimen was restarted in all but 2 patients after a median of 21 days. One patient did not resume his antiretroviral therapy, as he developed multiorgan failure. Another patient was changed from the 2 nucleoside reverse transcriptase inhibitors (NRTI) zidovudine and lamivudine and one non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine to abacavir, lamivudine, and efavirenz. Most patients were able to resume HAART by 2 months after ASCT with the exception of one, who had persistent nausea and noncompliance that was in part ascribed to depression. Genotyping was not performed prior to the resumption of HAART. All patients engrafted at a median of 11 days for neutrophil engraftment (range, 9-23 days). The markedly delayed engraftment of 23 days was in part ascribed to depression. Genotyping was not performed prior to the resumption of HAART. All patients engrafted at a median of 11 days for neutrophil engraftment (range, 9-23 days). The markedly delayed engraftment of 23 days was in part ascribed to depression.

Other treatment-related toxicities included liver function abnormalities in most patients: grade 1 to 2 in 16, and grade 3 to 4 in 3. Of these patients, the oldest in the series, age 68, ultimately developed cardiomyopathy and renal failure and died at day +22 after ASCT. The other recovered uneventfully, and the third had late hepatotoxicity over 10 months after ASCT that responded to a change in his antiretroviral regimen. Two patients developed an engraftment syndrome manifested as high temperatures, hypotension, skin rash, and fluid retention. Both responded to corticosteroids. Interstitial pneumonitis that was ascribed to the carmustine used in one patient and was successfully treated with corticosteroids. Pericarditis presumed to be secondary to cyclophosphamide was seen in one patient and was treated with nonsteroidals and a 5-day course of low-dose prednisone. This same patient also developed transient atrial fibrillation that was treated with medical therapy. Another patient with a history of supraventricular (SVT) arrhythmias prior to the transplant developed recurrent SVT and had to be cardioverted. The patient who had delayed engraftment after ASCT developed subdural hematomas during a period of thrombocytopenia after a lumbar puncture. They ultimately required surgical drainage. The patient also developed hemorrhagic cystitis that responded to bladder irrigation.

Early infectious complications prior to engraftment included gram-positive bacteremias in 4 patients and fever and neutropenia in 8 patients. One patient had vancomycin-resistant enterococcus isolated from a bronchoalveolar lavage. Postengraftment, opportunistic infections were more common. Two patients who were not compliant with prophylaxis developed pneumocystis pneumonia. One of these patients also developed pulmonary aspergillus after steroid treatment for his pneumocystis. One patient never had documented pneumocystis but was treated empirically for this after a chest x-ray demonstrated interstitial infiltrates. Two patients developed disseminated herpes zoster. Cytomegalovirus (CMV) retinitis developed in one patient, and 2 had asymptomatic viremia. All patients responded to therapy. At one year after ASCT, one patient acquired hepatitis C, which was found upon evaluation of liver function abnormalities.

The underlying HIV infection did not worsen as a result of the transplant. While CD4 counts nadired at approximately 6 months after transplant, they recovered to pretransplant levels by one year in all patients (Figure 1). The median CD4 count at one year was 187 cells/mcl and 472 cells/mcl at 2 years. The HIV viral load tended to fluctuate, in part due to prolonged noncompliance with HAART in one patient. Most (76%) had undetectable viral loads at one year (range, 0-500 000 cp/mL); 2 of the 4 with detectable viral loads at one year were undetectable at study enrollment. However, one of these patients did not resume HAART until one year after ASCT. Of the 17 long-term survivors, 10 required changes in their antiretroviral regimen during the observation period, due to viral failure.

Median length of follow-up is 31.8 months (range, 5.5-70). Of the 20 patients, 17 are alive and in remission. One patient with a follow-up of 5.5 months had a positive positron emission tomography (PET) scan at his 100-day restaging, but no CAT scan correlation. Two patients died of relapsed lymphoma early after transplant (2 months, 4 months, respectively). One patient died of regimen-related toxicity at day +22. The progression-free survival (PFS) is 85% (95% CI 69-100), and overall survival is 85% for the entire group (Figure 2). For the patients who received transplants beyond first CR, the overall survival (OS) is 81% (95% CI 62-100) (Figure 3) and PFS is 81% (69-100).

Discussion

ASCT has become an accepted standard of care for patients with relapsed aggressive NHL and certain patients with relapsed HD. The mortality of this procedure has declined to the point that we are now performing transplants in older patients as well as in patients with other comorbid illnesses. However, this has not become a standard of care with HIV lymphoma, despite significant advances in the treatment of HIV infection. Patients are living longer and suffering from fewer opportunistic infections.

Notably, in the current era, despite the use of HAART, lymphoma remains a major cause of morbidity and mortality in patients suffering from fewer opportunistic infections.
HIV-infected individuals.17,18 While the use of concomitant chemotherapy and HAART has increased remission rates and improved survival, options for patients with refractory or relapsed lymphoma are limited.19,20 Results even in the HAART era with salvage therapy have been poor. For example, in a group of 13 patients with refractory or relapsed HIV-NHL, 7 of whom were on protease inhibitor–based therapy, all treated with ESHAP (etoposide, cisplatinum, cytarabine, solumedrol), median survival was only 7.1 months.19 An even shorter median survival in the pre-HAART era was reported from an Italian group who treated 21 patients with HIV-NHL either refractory to primary chemotherapy or in first relapse. Of the 19 evaluable patients, 5 achieved a CR (26%), and median survival in the CR patients was 13 months, but for the entire cohort median survival was only 2.1 months.20 Thus, for these high-risk patients, better treatment options are clearly needed.

Prior to the advent of HAART, HIV infection was considered a contraindication to both solid organ and stem cell transplantation. Certainly this was borne out by the early allogeneic transplant experience in HIV-infected patients, which was characterized by high rates of opportunistic infections.21,22 However, as our understanding of how to administer antimicrobial prophylaxis in conjunction with antiretroviral therapy has improved, centers have revisited the issues of transplantation in patients with HIV lymphoma.

One of the early series of ASCT was from France. Gabarrre et al used both radiation and chemotherapy-based conditioning regimens for a group of patients with HIV HD and NHL.24 They included multiply relapsed patients as well as primary refractory patients. Infectious complications were similar to our series, with opportunistic infections including CMV viremia noted. Of the 14, 6 (43%) were alive at the time of reporting, with the longest follow-up being 31 months. Another series, a multi-institutional trial from Italy, was performed using a standard chemotherapy-based conditioning regimen of BEAM (carmustine, cytarabine, etoposide, melphalan).13 They too included refractory as well as relapsed patients. The patients received debulking chemotherapy prior to ASCT, although details of disease status at the time of ASCT were not provided. Sixteen patients were enrolled in the trial and analyzed on an intent-to-treat basis. Fifteen patients underwent stem cell collection. Three patients failed to mobilize adequate stem cells for ASCT. Of the remaining 12, 2 had disease progression before ASCT, one did not proceed to ASCT, and one did and subsequently died of progressive disease 4 months after ASCT. Ten other patients went on to ASCT, of which 9 were evaluable at the time of reporting. Median follow-up is short (8 months), but 8 patients achieved a CR or PR after ASCT. Median disease-free survival and overall survival of the cohort undergoing ASCT was 11 months and 18 months, respectively. Projected 2-year overall survival for the entire group is 39%.

The most recent series reported from Spain included many first CR patients.21 However, their definition of first CR also included patients who required more than one line of chemotherapy to achieve a CR, as well as Burkitt-type lymphoma patients who were initially undertreated and then achieved CR with other therapy. All patients but one were in CR at the time of ASCT. The majority received BEAM as the conditioning regimen; median follow-up was 21 months (range, 1-28). Disease-free survival was 73%. Infectious complications were similar to all other series and included one case of herpes zoster and one case of pulmonary aspergillosis.

The varied results reported in these series may in part reflect patient selection. For example, the inclusion of chemotherapy refractory patients in the French series, as well as patients with multiple relapses, may have been a factor in the lower disease-free survival in this study. Similarly, the Italian series analyzed all patients with HIV lymphoma who were considered for transplant. Not surprisingly, they demonstrated a markedly better survival in the patients who went on to ASCT, moreover, the median survival of this subgroup is similar to the other series. Our experience is unique in that it is a single institution experience and provides the longest follow-up. Patient selection may have played a bias in our good results in that most patients had to demonstrate chemotherapy-sensitive disease, but we too included multiply relapsed patients as well as those patients not in CR after first-line chemotherapy. Moreover, our transplant selection criteria in regards to the underlying lymphoma are no different than that in our HIV-negative lymphoma patients. In fact, we consider the HIV infection to be akin to a chronic illness that can be managed with appropriate prophylaxis and surveillance. However, we do require that eligible patients must have well-controlled HIV infection as manifested by low HIV viral loads to optimize the chance of stem cell mobilization and minimize infectious risks. The other series do not include this criteria, although the Italian series did require a CD4 count of more than 100/mcl and an effective HAART regimen. Hence, one can postulate that in part, the superior disease-free survival in our series is mediated by well-controlled HIV infection. Certainly in the nontransplant setting, studies have demonstrated that the use of HAART is an independent prognostic factor for event-free survival in HIV NHL.25,26 The experience of all the centers suggests that ASCT should be considered earlier after demonstration of chemotherapy sensitivity for those in first relapse or with primary refractory disease, as the procedure can be performed with low procedural-related mortality. Further research is needed for those with high-risk first CR. Our long-term follow-up confirms that ASCT can provide durable remissions and can be a potentially curative option for those with otherwise dismal prognosis with conventional therapy.

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References


