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Blood and marrow transplant for lymphoma patients with HIV/AIDS

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Abstract

Purpose of review—Important strides in the management of patients with HIV/AIDS-related lymphomas have been made in recent years. This review will discuss the role of bone marrow or peripheral stem-cell transplantation as a modality for patients with HIV and lymphoma.

Recent findings—In the era of highly active antiretroviral therapy, patients with HIV-associated lymphoma are generally being treated with standard or only slightly modified chemotherapy regimens. Autologous bone marrow and stem-cell transplant approaches in lymphoma patients have been successful. Case reports suggest that allogeneic transplantation for patients with HIV and hematologic malignancies merits further investigation.

Summary—High-dose hematopoietic stem-cell therapies with curative intent should be considered as standard therapeutic options in patients who otherwise are appropriate for such therapies.

Keywords

autologous bone marrow/stem-cell transplantation; HIV/AIDS; non-Hodgkin's lymphoma

Epidemiology

Early data from cancer and AIDS registries revealed that the relative risk of non-Hodgkin's lymphoma was much higher for individuals with HIV compared with those without HIV. Aggressive B-cell non-Hodgkin's lymphoma is formally recognized as an AIDS-defining illness. With highly active antiretroviral therapy (HAART), the overall incidence of lymphoma is decreasing, with the most marked decrease occurring in primary brain lymphoma. Time from HIV infection to a diagnosis of lymphoma is increasing, as is the CD4⁺ cell count at the time of diagnosis. The risk for Hodgkin's lymphoma is also increased in HIV-infected persons. Interestingly, the incidence of Hodgkin's lymphoma has temporally increased despite or perhaps because of the availability of HAART [1,2]. Hodgkin's lymphoma typically develops in HIV patients with relatively high CD4 counts maintained over several years.

Historical background

In the late 1980s, lymphoma regimens in AIDS patients were associated with a high treatment-related mortality rate [3]. In profoundly immunosuppressed patients, the antitumor effects of cytotoxic chemotherapy had to be balanced against the associated myelosuppressive and immunosuppressive side effects. With the advent of HAART, improved opportunistic infection prophylaxis, hematopoietic growth factors and perhaps some change in the character of the tumors emerging in HIV-infected patients, the landscape has changed.

Upfront chemotherapy regimens

Infusional chemotherapy regimens have attracted a great deal of interest in AIDS-related non-Hodgkin's lymphoma. Cyclophosphamide, doxorubicin and etoposide (CDE) as a 96-h continuous infusion combined with rituximab has yielded complete response rates of 70% with an estimated 2-year overall survival of 64% [4^{**}]. A National Cancer Institute study demonstrated 92% disease-free survival (DFS) at 53 months with infusional etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) [5]. These survival outcomes reflect a dramatic improvement compared with trials before the era of HAART. Although a randomized trial from the AIDS Malignancy Consortium suggested that rituximab might increase the risk of life-threatening infections [6^{**}], such infections were not increased with the infusional CDE and rituximab regimen [4^{**}]. Noninfusional regimens, such as cyclophosphamide, adriamycin, vincristine and prednisone (CHOP), have also been studied. In particular, a German multicenter trial, aimed at evaluating whether HAART could safely be administered simultaneously with CHOP, found that not only was dose intensity achievable, but the survival for patients with standard-risk disease (defined as CD4 of at least 50/mm³, absence of opportunistic infections, and a maximum World Health Organization performance status of 2) was comparable to patients without HIV [7].

Most patients with HIV infection and Hodgkin's lymphoma present with advanced-stage disease, and as such, combination chemotherapy is nearly always the mainstay of therapy. In a retrospective review, treatment with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) in combination with HAART was associated with complete response rates near 90%, with 5-year event-free survival (EFS) rates of 71% [8]. Good results have also been reported with Stanford V [9].

Salvage regimens

Few salvage chemotherapy regimens have been formally evaluated. Etoposide, methylprednisolone, high-dose cytarabine and cisplatin (ESHAP) is probably the best studied [10]. Data regarding salvage therapy for relapsed HIV-associated Hodgkin's lymphoma are lacking.

Autologous hematopoietic stem-cell transplantation

High-dose therapy with autologous stem-cell (or bone marrow) transplant (AuSCT) has been explored in a series of small studies that have included Hodgkin's and non-Hodgkin's

lymphoma (Table 1) [11,12^{**},13^{*}, 14,15]. As in other settings [16], the best outcomes were in studies whose enrollment was limited to patients with chemosensitive disease, while trials including patients with primary refractory disease reported a lower DFS rate (29% at 25 months) [14]. The highest DFS rate was reported in a single institution trial that included high-risk patients transplanted in first complete response [12^{**}].

The largest review of AuSCT in HIV lymphoma patients was recently reported at the 2006 ASH meetings by the European Bone Marrow Transplant Lymphoma Working Party [17]. Forty-four patients, including 34 with non-Hodgkin's lymphoma and 10 with Hodgkin's lymphoma, were transplanted. Disease status at the time of AuSCT included 22 patients in complete response (13 in first complete response); 18 in partial response/chemosensitive relapse, and four in primary induction failure/chemo-resistant relapse. The median times for neutrophil and platelet recovery were 11 and 14 days, respectively. The DFS and overall survival rates were 55% and 60% at a median of 36 months.

Special considerations

These results indicate that AuSCT in HIV patients with lymphoma is often associated with a satisfactory outcome. There are, however, some special considerations.

CD4⁺ cell counts and HIV—Most centers have required HAART therapy and CD4⁺ cell counts greater than 50/mm³. Many have required undetectable or at least stable viral load. There has been no consistent impact on HIV RNA copy number associated with these therapies. With transplant, CD4⁺ cell counts transiently decrease and then recover to baseline when HAART is maintained. In the first multicenter study evaluating AuSCT in HIV-associated lymphoma patients in the USA, Spitzer *et al.* [15] found that a modified busulfan and cyclophosphamide preparative regimen is well tolerated and has favorable outcomes in HIV patients. The study also found no consistent temporal trend with either viral load or CD4⁺ cell counts and a high degree of interpatient variability (Table 2).

Opportunistic infections and management of neutropenia—Patients with active opportunistic infections have been routinely excluded from consideration for transplant. Screening for infections has become fairly standardized in the transplant setting. Cytomegalovirus (CMV) reactivation is quite common in both the transplant setting and in patients with HIV in general. Interestingly, the manifestations of CMV are quite different in HIV and blood and marrow transplant (BMT) patients. CMV retinitis was common in HIV patients before HAART, but is a rather uncommon entity in transplant patients. In contrast, CMV pneumonitis is not uncommon in transplant patients but is rare in HIV patients. In the five studies of AuSCT in HIV patients summarized above, nine patients developed asymptomatic CMV viremia and one developed CMV retinitis. All responded to therapy. These results suggest that CMV-associated disease is not commonly associated with AuSCT but does occur. CMV retinitis was distinctly unusual but did occur. Many would advocate routine ophthalmologic screening of patients being considered for such therapy.

The infectious complications encountered prior to count recovery are fairly similar to those seen in HIV-negative patients and mostly consist of Gram-positive and negative bacteremia, and less frequently fungal pneumonia. Prophylaxis with antibacterial, antifungal and

antiherpesviral agents with quinolones, azoles and acyclovir or similar drugs has been standard. In addition, *Pneumocystis jirovecii* prophylaxis is routine during the conditioning regimen and following hematologic count recovery. Shingles or disseminated varicella infections occur frequently in this patient population and investigators at the City of Hope extend antiherpesviral prophylaxis to 1 year following transplant.

Granulocyte colony-stimulating factor (G-CSF) was routinely administered following AuSCT and continued until hematopoietic engraftment in all [11,12^{**},13^{*},15] but one of the above studies, which had no specific guidelines but did allow for G-CSF [14]. Nine of these 14 patients received G-CSF for a median of 7 days. The median time for granulocyte reconstitution of 12 days did not differ between those treated or untreated with G-CSF.

Stem-cell mobilization/engraftment

Collection of the targeted numbers of CD34⁺ cells presents no special obstacles in HIV patients so long as zidovudine is not included in the HAART regimen. A limited investigation showed no correlation between CD4 cell counts and CD34 cells harvested [13^{*}]. HIV, pneumocystis prophylaxis with trimethoprim sulfamethoxazole or HAART may impact on time to count recovery and some groups have reported delays in HIV patients in comparison with historical controls [13^{*}].

Potential drug interactions

The safety of HAART in combination with cytotoxic chemotherapy has been best studied in upfront chemotherapy regimens. Although some interactions have been reported, adverse reactions have been modest with the exception of regimens that include zidovudine. Additional studies have suggested increased toxicity with some of the protease inhibitors, known potent inhibitors of the cytochrome P450 system [18]. While all of the studies planned for patients to continue on HAART during the transplant, many patients were discontinued secondary to gastrointestinal toxicity with either severe nausea or mucositis, although no adverse events directly attributable to the HAART per se were described. The optimal integration of antiretroviral therapy during the transplant remains uncertain; however, extrapolating from the data on upfront chemotherapy regimens suggests that long-term lymphoma-free survival can be achieved with either concomitant or delayed HAART.

Allogeneic hematopoietic stem-cell transplantation

In contrast to AuSCT, allogeneic transplantation for lymphoma has not been systematically explored. Several case reports describe the use of allogeneic stem-cell transplant for patients with HIV and various hematologic malignancies [19–23]. A single case describes successful unrelated cord blood transplantation for an HIV-positive patient with acute lymphoblastic leukemia [24]. The Center for International Blood and Marrow Transplant Research (IBMTR) [25] reported on 27 HIV-positive patients who underwent allogeneic transplant, including 19 identical sibling, five syngeneic, and three unrelated donor transplants between 1986 and 2003. The diseases transplanted included lymphoma, leukemia, myelodysplastic syndrome, aplastic anemia, and nonmalignant conditions including HIV. Most of the cases

in the literature are from the 1990s, prior to the availability of HAART, and must be interpreted with caution.

Hematopoietic stem cell-based gene therapy

Experience demonstrating the feasibility of AuSCT in HIV-positive patients led to consideration of the possibility that stem-cell based gene therapy might allow for the establishment of a population of cells resistant to HIV. In one of the initial studies conducted a decade ago, five patients with HIV-associated lymphomas were treated with AuSCT and received selected CD34⁺ cells transduced with an oncoretroviral vector encoding ribozymes targeted to tat and rev [26]. The gene marking was safe but not durable. Alternative vectors, viral envelopes and new strategies for selecting and expanding transduced cells have been or are being explored [27*]. Clinical impact has yet to be achieved but investigations continue.

Conclusion

AuSCT in patients with HIV has proven to be effective in patients with non-Hodgkin's lymphoma and Hodgkin's lymphoma. Failures are mainly of the sort associated with AuSCT in general, i.e. tumor relapse, preparative regimen toxicity and infection during neutropenia. There is no consistent impact on HIV disease per se as manifest in HIV RNA copy number or CD4 count. Although pneumocystis, CMV and other opportunistic infections occasionally arise, they are relatively infrequent and respond to standard therapies. Pneumocystis prophylaxis begins before stem-cell harvest and continues for at least 12 months after count recovery. There may also be a role for prolonged antiherpesviral therapies to prevent complications of zoster or disseminated varicella. HAART regimens may be administered concomitantly with transplant preparative regimens, although zidovudine should be avoided. Hematopoietic growth factors present no special issues. In summary, with the advent of HAART therapy, HIV should not be regarded as a contraindication to high-dose or stem-cell therapies. Much like diabetes, there are some special considerations and some special risks but the principles of AuSCT in other settings extrapolate well to HIV patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 241).

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Table 1
Summary of results from reported trials evaluating autologous stem-cell transplantation in patients with HIV-related lymphoma

Author, year of publication	Nature of study	No. patients enrolled,	No. received AuSCT/histology	Dz status at AuSCT	Regimen	HAART	CR rate, %	Median DFS	TRM
Re <i>et al.</i> 2003 [11]	Multicenter prospective	16	4 HL 6 NHL	1 PR 2 1st relapse 3 2nd relapse 4 refractory	BEAM	Yes	89%*	67% at 8 mos. *	0%
Gabarre <i>et al.</i> 2004 [14]	Retrospective review	14	6 HL 8 NHL	9 1st relapse 1 2nd relapse 1 3rd relapse 1 4th relapse 2 refractory	Various regimens of chemotherapy±TBI	Yes	71%	29% at 25 mos.	0%
Krishnan <i>et al.</i> 2005 [12••]	Single institution prospective	20	2 HL 18 NHL	4 CR1 1 CR2 1 CR3 3 PR 9 1st relapse 2 2nd relapse	BEC (n=17) fTBI + VP16/Cy (n=3)	Yes	90%	85% at 32 mos.	5%
Serrano <i>et al.</i> 2005 [13•]	Multicenter prospective	14	3 HL 11 NHL	6 CR1 4 CR2 4 PR	BEAM (n=10) BEAC (n=1)	Yes	73%	65% at 30 mos.	0%
Spitzer <i>et al.</i> (in press) [15]	Multicenter prospective	27	5 HL 15 NHL	6 CR 2 PR 12 CS	Dose-adjusted Bu/Cy	Yes	53%	50% at 6 mos.	5%

AuSCT, autologous stem-cell transplantation; BEAC, carmustine, etoposide, cytarabine, cyclophosphamide; BEAM, carmustine, etoposide, cytarabine, melphalan; BEC, carmustine, etoposide, cyclophosphamide; BusuBu/Cy, busulfan, cyclophosphamide; CR, complete response; CS, chemosensitive disease (improvement of at least 25% in bidimensional tumor measurements or an improvement in evaluable disease sustained over 4 weeks); DFS, disease-free survival; Dz, disease; fTBI + VP-16/Cy, fractionated total body irradiation, etoposide, cyclophosphamide; HL, Hodgkin's lymphoma; mos, months; NHL, non-Hodgkin's lymphoma; PR, partial response; TRM, transplant related mortality.

* Response is based on eight patients, so it is too early to assess response in one patient.

Table 2Median CD4⁺ cell count and HIV viral load at baseline and timepoints following transplant

	Baseline	2 weeks	1 month	2 months	3 months	6 months	9 months
CD4 ⁺ cell count/mm ³	203	153	158	85	123	163	203
HIV viral load copies/ml	317	257	233	784	415	341	106

Table adapted from Spitzer *et al.* (in press) [15].