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The same but different: autologous hematopoietic stem cell transplantation for patients with lymphoma and HIV infection

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Abstract

In an earlier era, high-dose therapies were thought to be contraindicated in HIV-infected patients. Patients with HIV fared somewhat better with reduced-dose lymphoma therapies and salvage of relapsed patients was rarely possible. With more than a decade of effective anti-retroviral therapy, full-dose lymphoma therapies have become standard, and high-dose therapy with autologous hematopoietic stem cell rescue for those who fail frontline therapy or who are judged to have very high risk disease has been pursued with very encouraging results. Transplant-related mortality is less than 5%. With prophylaxis for pneumocystis and herpesvirus infections, deaths due to opportunistic infections are distinctly unusual. Most deaths have been associated with veno-occlusive disease or lymphoma progression. There is no need for quarantine of patients or special isolation procedures. Most patients with responsive lymphoma remain lymphoma free several years after high-dose therapy. $CD4^+$ cell count and HIV load seem not to be adversely affected in the long term. Much like diabetes, HIV infection should be regarded as a problem that requires special attention during high-dose therapy rather than a contraindication to high-dose therapy in patients with lymphoma who would otherwise be judged transplant candidates.

Keywords

transplantation; lymphoma; HIV

Introduction

Hematopoietic stem cell transplantation (HSCT) has had a very limited role in the management of patients with lymphoma and HIV infection until recently. In the late 1980s, recognition that the virus was harbored in hematopoietic cells led some to consider the possibility that ablation of the hematopoietic compartment in patients with lymphoma might destroy the reservoir of viral infection; these early efforts were unsuccessful.[1] For many years, high-dose therapy approaches were largely abandoned. However, more recent experience suggests that for some patients with HIV and lymphoma, the outcome of high-dose therapies are similar to the outcomes in the general population. This review is focused on the progress in HIV treatment, how it has impacted on the treatment of lymphoma in HIV patients and special considerations in the application of standard high-dose therapy regimens to patients with HIV and lymphoma.[2]

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AIDS, HIV, antiretroviral therapy, immune reconstitution and survival

The first antiretroviral (zidovudine) was approved in the United States in 1987.[3] Triple-combination therapy including protease inhibitors was initiated in 1995. With triple-drug therapy, immune function was often substantially restored, opportunistic infections often resolved, plasma viral RNA load often fell below the threshold of detection and projected survival of newly infected patients extended well beyond two decades.[4,5] However, hopes that 'undetectable' plasma viral load might translate into cure were not realized. Patients with 'undetectable' plasma RNA have 'archived' virus (including drug-resistant variants) that activates following withdrawal of antiretroviral agents leading to the reappearance of viral RNA in plasma.[6]

The incidence and types of lymphoma occurring in patients with HIV changed with combination antiretroviral therapy.[7] A meta-analysis estimated that AIDS and non-Hodgkin's lymphoma incidence fell 42% with effective antiretroviral therapy. The decline was greatest (58%) for central nervous system lymphoma and negligible for Burkitt's lymphoma. In contrast, Hodgkin's lymphoma seems not to have declined and some have suggested may have increased in patients treated with combination antiretroviral therapy.[8]

Treatment of lymphoma in HIV patients

The aggressive character of AIDS lymphomas as manifest in a propensity for extranodal disease, advanced stage and B symptoms led some investigators to explore a variety of intensive chemotherapy regimens.[9] Among these were 'third-generation' lymphoma regimens. Results were disappointing with many deaths attributable to opportunistic infection. A multi-institutional randomized trial was undertaken by the AIDS Clinical Trials Group.[10] Standard-dose chemotherapy was associated with more toxicity and no survival benefit. The adoption of 'half-dose' therapy as a standard in lymphoma therapy coincided with a consensus that there was little, if any, role for 'high-dose' therapy in HIV patients with lymphoma.

With combination antiretroviral therapy and advances in supportive care, the treatment of lymphoma in HIV patients also met with increasing success (Table 1). Full-dose 'standard' chemotherapies proved to be tolerable.[11] Infusional regimens achieved especially promising results.[12–15] Rituximab likely also contributed to improved rates of CR although one trial suggested increased risk of bacterial infection.[16] A follow-up trial comparing a combination chemotherapy regimen with concurrent or sequential rituximab did not show increased infection rates in the concurrent rituximab arm.[17]

High-dose therapy in HIV patients

High-dose therapy with SCT was explored in several small studies.[18–22] Some reports were prospective (summarized in Table 2), others retrospective, some from single institutions, and some from cooperative groups. None included more than 50 patients and none involved a randomization. Populations undergoing therapy varied from trial to trial such that some reports included patients with high-risk first remissions, whereas others included only patients with relapsed or primary refractory disease. Most included both AIDS related and Hodgkin's lymphoma. Each of the reports suggested that there were patients with HIV and lymphoma who likely benefited from high-dose therapy.

In the published prospective reports (Table 2), 67 patients received PBSCT in aggregate. There were no infectious deaths and only two treatment-related deaths (both secondary to veno-occlusive disease). Other treatment failures or deaths were the result of progressive or relapsed lymphoma. Thus, as in the general population with aggressive non-Hodgkin's

lymphoma or Hodgkin's lymphoma, tumor relapse rather than treatment-related mortality was the major source of treatment failure. Of note, there was no long-term impact of high-dose therapy on $CD4^+$ cell count or HIV plasma copy number. Lymphoma-free survival ranged from 49.5% at median follow-up of 6 months in patients with primary refractory or relapsed disease in a cooperative group trial to 85% with a median follow-up of 32 months in patients with relapsed lymphoma or high-risk first remissions in a single-institution trial.

Special considerations

The evaluation and management of patients with HIV and lymphoma for high-dose therapy involves some special considerations:

Markers of HIV disease

The $CD4^+$ cell count is a rough indicator of immune function and is a predictor of infectious deaths in association with chemotherapy. HIV RNA has also emerged as an important predictor of survival in many settings. All of the prospective autologous peripheral blood stem cell transplantation studies excluded patients with uncontrolled HIV disease. Some investigators excluded patients with $CD4^+$ cell depletion,[18] others excluded patients with high HIV copy number,[20] patients who failed to clear detectable virus or achieve a falling HIV copy number,[21] and others patients with $CD4^+$ depletion or high HIV copy number.[22] There were no infectious deaths in any of these studies suggesting that passing any of these screens to exclude patients with uncontrolled HIV infection, yields a group of patients with risks of infectious mortality that are not very different from the general transplant patient population. Because autologous HSCT investigators have shied away from treating patients with lower $CD4^+$ counts and higher viral loads, there is little data to document the specific risks of mortality in patients with lower $CD4^+$ counts or higher viral copy number. At Johns Hopkins, except in the setting of a clinical trial, we generally exclude patients with $CD4^+$ counts $<75/mm^3$ or HIV copy number $>100\ 000/mm^3$. In the application of any criteria based on $CD4^+$ cell counts, it is important to understand the counts obtained after the initiation of chemotherapy are uninterpretable. $CD4^+$ counts fall with chemotherapy and then recover over many months. Transplant guidelines for exclusion refer to the $CD4^+$ count at the time of the original diagnosis of lymphoma or at the diagnosis of relapse. Occasionally, lymphoma is the first manifestation of HIV infection and leads to its diagnosis. Low $CD4^+$ counts in patients not yet treated with antiretroviral therapy may be expected to rise. However, if chemotherapy is initiated before antiretroviral therapy or at approximately the same time, the benefit of the antiretroviral therapy may not be reflected in the $CD4^+$ count. If the indications are for transplant and the $CD4^+$ cell count is low but was obtained before the patient had several months of antiretroviral therapy or after the initiation of chemotherapy, the HIV copy number rather than the $CD4^+$ count should guide decision-making.

Opportunistic infections

The manifestations of CMV infection are quite different in HIV patients and transplant recipients. CMV retinitis was common in HIV patients before effective antiretroviral therapy, but is a distinctly uncommon entity in transplant recipients. CMV pneumonitis is not uncommon in transplant patients but is rare in HIV patients. CMV viremia has been much more common disease and retinitis remains distinctly unusual. Standard monitoring for CMV DNA with early preemptive treatment with ganciclovir or valganciclovir is recommended. Shingles has been commonly reported in trials without valacyclovir prophylaxis. Pneumocystis jiroveci pneumonia has not been common, perhaps because all of the prospective studies have included prophylaxis.

Antibiotic prophylaxis

We use trimethoprim-sulfamethoxazole (TMP-SMX)-SS (single strength) daily during the preparative therapy, stop TMP-SMX from the day of stem cell infusion (day 0) until engraftment and then resume TMP-SMX prophylaxis until 6 months post transplant. Patients who are allergic to or intolerant of TMP-SMX receive alternative prophylaxis with dapsone or atovaquone. Fluconazole 200 mg daily is begun during mobilization and continued 2 months post transplantation. We also prophylax with ciprofloxacin during neutropenia. Valacyclovir 1 g, b.i.d. is begun during mobilization and continuing for 6 months after transplant.

Tumor

Aggressive B-cell lymphoma and Hodgkin's lymphoma in the non-HIV setting are generally regarded as potentially curable malignancies with high-dose therapy and stem cell rescue. Most studies in HIV patients have included both groups of patients. Most patients who undergo autologous HSCT in first remission remain in remission at 2 years. In patients with controlled HIV infection, with lymphoma in remission or responding to chemotherapy after first relapse, a 60% or better long-term lymphoma-free survival can be anticipated. This contrasts with a 10% long-term lymphoma-free survival that might be anticipated in this group of patients without autologous HSCT.

Antiretroviral chemotherapy

When, and if, antiretroviral therapy should be combined with cytotoxic chemotherapy or other high-dose therapy has generated a great deal of discussion (Table 3). 'Best' practices continue to evolve but insofar as zidouvidine is myelosuppressive in its own right, it is generally not used in combination with high-dose therapy. Similarly, ritonavir, a viral protease inhibitor, which is a potent CYP3A inhibitor, has often been avoided in high-dose therapy regimens because of concerns with possible interactions. Many other antiretrovirals also may perturb hepatic metabolism and it is prudent to review the details of the antiretroviral and preparative regimens with the potential for such interactions in mind. The metabolism of drugs commonly used in HSCT[23] and of antiretrovirals have been reviewed.[24]

Although it is tempting to suggest withholding or interrupting the antiretroviral regimen for high-dose therapy, it is increasingly recognized that the abrupt discontinuation of antiretroviral therapy also poses some dangers.[25]

Consider the pharmacology of the non-nucleoside reverse transcriptase inhibitors (NNRTIs). These agents have emerged as especially important in antiretroviral therapy because they are very effective in inhibiting viral replication and are better tolerated than many other classes of agents. In addition many have long half-lives that facilitate once daily dosing.[26] However, used as monotherapy, NNRTIs rapidly and reproducibly yield resistant virus. NNRTI resistance mutations are particularly problematic insofar as single nucleotide changes can render virus resistant to NNRTIs—not only the particular agent the patient was treated with but other NNRTIs as well. When used in a triple-drug antiretroviral regimen, NNRTIs may be cleared much more slowly than the other agents in the regimen. As a result, discontinuation of drugs simultaneously will effectively result in NNRTI monotherapy. The issue is now well recognized and strategies for stopping antiretrovirals have been elaborated —but the transplant team must work closely with their infectious disease colleagues to ensure that interruptions of therapy do not needlessly lead to the development of resistance. Similarly, initiating antiretroviral therapy at the time of high-dose therapy (with risks of nausea, vomiting and interruption of oral intake) leads to the idea that if antiretroviral therapy has not yet been initiated at the time of consideration of transplant, delaying the

initiation of such therapy until completion of the preparative regimen would seem perfectly appropriate.

Infectious disease consultants

The availability of infectious disease consultants with expertise in HIV management issues is a prerequisite for the management of HIV patients with cytotoxic chemotherapy or any other serious illness. However, experience to date with high-dose therapy in the high-dose autologous SCT setting suggests that infectious complications related to such therapy are not very different in severity or type from those complications seen in patients without HIV infection or from those seen in HIV patients undergoing standard dose chemotherapy for lymphoma. Thus, the infectious complications are generally familiar to transplant physicians (febrile neutropenia, bacteremia, candida, CMV infection, zoster). It is the management of the anti-retroviral medicines and the issues associated with interruption of antiretrovirals that most requires infectious disease expertise.

Need for quarantine

There is no indication to isolate HIV patients from other transplant or cancer patients in any way.[2] The question sometimes arises as to whether special quarantine measures are required for HIV patients or for their blood products. Regarding stem cell collection and processing standard operating procedures for products with any positive infectious disease screening markers (anti-HIV1/2, anti-HCV, HBsAg, anti-HBcore, anti-HTLVI/II, HIV NAT, HCV NAT) stem cell bags should be marked with appropriate biohazard and warning labels, physically separated from others by placing the cryobag in an overwrap bag which is then sealed, and storing in the vapor phase of nitrogen to reduce the risk of cross-contamination.

Medical care payer coverage

As in patients without HIV, the specifics of coverage vary with the third-party payer involved. Although we have encountered the need to educate certain payers, we have fairly consistently been successful in persuading payers that autologous HSCT is appropriate in HIV patients with relapsed responsive lymphoma.

Prospects for the future

It seems likely that allogeneic and perhaps gene therapy strategies will be involved in the management of malignancies in HIV patients and the management of HIV itself. At present, however, for patients with AIDS-related or Hodgkin’s lymphoma beyond first remission, high-dose therapy with autologous stem cell rescue should be considered as a standard option. For the patient with HIV infection, much like the patient with diabetes, treatment of lymphoma with high-dose therapy requires attention to detail and some extra monitoring, but is not fundamentally different from the treatment of patients without HIV. The Blood and Marrow Transplant Clinical Trials Network and the AIDS Malignancy Consortium are planning an intergroup multicenter phase 2 trial to better define the outcomes of high-dose therapy in HIV patients.

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Table 1

Chemotherapy for the treatment of AIDS-related non-Hodgkin's lymphoma

Regimen	Comment	Reference	Year
mBACOD (reduced vs full dose)	Favors reduced dose	10	1997
CHOP (1/2 dose vs full dose) with combination antiretroviral therapy	Full dose well tolerated	11	2001
CDE	This trial bridging the introduction of highly active combination antiretroviral therapy demonstrated the efficacy of this regimen and the contribution of antiretroviral therapy to improved outcomes	12	2004
CHOP-R vs CHOP with combination antiretroviral therapy, CDE-R	Concerns raised regarding possible infectious complications in rituximab-treated patients	13,16	2005

Table 2

Prospective autologous HSCT studies

Investigators	Patients receiving stem cells	Lymphoma types	Minimum $CD4^+$, maximum HIV/mm^3	Conditioning regimen(s)	Transplant-related mortality (number of patients)	Progression-free/event-free survival	Overall survival
Re *et al.*[18]	16	NHL, HL	100 $CD4^+$, no HIV exclusion	BEAM	0	6/10 in CCR at 8months	6/10 at 8 months
Krishnan *et al.*[20]	20	NHL (includes high-risk first remission), HL	Formal exclusion for $CD4^+$ dropped after 5 patients, HIV <10 000	BEC, fTBI+etoposide/ CY	1	85% at 32 months	85% at 32 months
Serrano *et al.*[21]	11	NHL (includes high-risk first remission), HL	No formal exclusion, lowest $CD4^+$ in a patient was 74, viral load was undetectable or falling	BEAM, BEAC	0	65% at 30 months	65% at 30 months
Spitzer *et al.*[22]	20	NHL, HL	50 $CD4^+$, viral load <110 000 copies/ mm^3	BUCY	1	49.5% at 6 months	74.4% at 6 months

Abbreviations: BEAC=carmustine, etoposide, cytarabine, CY; BEAM=carmustine, etoposide, cytarabine, melphalan; BEC=carmustine, etoposide, CY; fTBI+VP-16/CY=fractionated TBI, etoposide, CY; HL=Hodgkin's lymphoma; NHL=non-Hodgkin's lymphoma.

Table 3

Antiretroviral agents and high-dose cytotoxic chemotherapy

Key considerations regarding antiretroviral chemotherapy and high-dose therapy:	
1	Zidovudine is myelosuppressive and has been generally excluded during time of stem cell collection, myeloablative therapy and period of count recovery.
2	Ritonavir is a potent CYP3A4 inhibitor and possible drug interactions with agents in the preparative regimen (e.g., etoposide) should be considered.
3	Stopping or changing antiretroviral regimens that include agents with very different half-lives, especially NNRTIs, may lead to the development of resistance to these agents. Given that nausea and an inability to take oral antiretroviral medications may lead to an interruption of therapy during mobilization phase or myeloablation, it is prudent to consider a regimen with antiretrovirals that have similar half-lives. The transplant team must partner with an infectious disease specialist to review anticipated changes in the regimen.