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How I treat patients with HIV-related hematological malignancies using hematopoietic cell transplantation

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Hematopoietic cell transplantation (HCT) has now been shown to be safe and effective for selected HIV-infected patients with hematological malignancies. Autologous HCT is now the standard of care for patients with HIV-related lymphomas who otherwise meet standard transplant criteria. Limited data also support use of allogeneic HCT (alloHCT) in selected HIV-infected patients who meet standard transplant criteria. We recommend enrolling patients in clinical trials that offer access to CCR5Δ32 homozygous donors, if available. HIV-infected patients requiring HCT may also be considered for participation in trials evaluating the activity of gene-modified hematopoietic stem cells in conferring resistance to HIV infection. To be considered for HCT, patients must have HIV infection that is responsive to combination antiretroviral therapy (cART). Careful planning for the peri-HCT management of the cART can avoid risk of significant drug interactions and development of cART-resistant HIV. In general, we recommend against the use of boosted proteasome inhibitors and non-nucleotide reverse transcriptase inhibitors in the cART regimen, in favor of nucleoside reverse transcriptase inhibitors and integrase inhibitors (without cobicistat). After HCT, patients must be closely monitored for development of opportunistic infections (OI), such as cytomegalovirus. Prevention of OI should include prophylactic and pre-emptive antimicrobials. (*Blood*. 2017; 130(18):1976-1984)

Introduction

In the United States, more than 1.2 million individuals are infected with HIV.[1] After the widespread availability of combination antiretroviral therapy (cART) in 1996, patients with HIV infection have had a dramatically reduced risk of progression to AIDS or death.[2] Effective treatment with cART restores quantitative $CD4^+$ T-cell immunity and suppression of the HIV viral load below detectable levels, with a commensurate decrease in the risk of opportunistic infections (OI) and AIDS-related death.[2-10]

cART, however, is not a cure for HIV. The morbidity and mortality risks, including HIV-related cancers, remain significant for this patient population.[11] HIV-infected patients still have a risk of developing non-Hodgkin lymphoma (NHL) 24.2 times greater than does the general population. The risk of Hodgkin lymphoma (HL) is increased nearly 15-fold. Patients with HIV also remain at increased risk of acute leukemia,[12] myelodysplastic syndromes (MDS),[13] and cancers of the aeropharynx, lung, bladder, and gastrointestinal tract.[11]

The prognosis for patients with HIV-related lymphomas (HRL) currently parallels that of non-HIV-infected patients. HRL is now treated with regimens similar to those used as standard of care for the general population.[14-19] Hematopoietic cell transplantation (HCT) now plays an important role in the care of patients with HRL. Investigators continue to evaluate HCT-based therapies as a potential path toward cure of HIV infection itself.

Autologous hematopoietice cell transplantation (AHCT) for HIV-infected patients

The use of AHCT for patients with HRL is supported by the published experience of a number of groups, including the Hopital Pitie-Salpetriere group,[20-22] the City of Hope,[23,24] the AIDS Malignancy Consortium,[25] the Italian Cooperative Group on AIDS and Tumors,[26,27] the Spanish cooperative groups GELTAMO and GELSIDA,[28] and a retrospective review from the European Society for Blood and Marrow Transplantation Lymphoma Working Party registry.[28] The number of patients who received transplants in these publications ranges from 11 to 68. These largely retrospective trials demonstrate a treatment-related mortality (TRM) ranging from 0% to 7.5% and overall survival (OS) rates of 39% to 85% for patients with chemotherapy-sensitive, relapsed, and persistent HRL.

These findings were validated in the prospective Bone Marrow Transplant Clinical Trials Network (BMT CTN) 0803/AIDS Malignancy Consortium (AMC) 071 trial.[29] This study evaluated 40 HIV-infected patients with chemotherapy-sensitive, relapsed, or persistent HRL (including 16 patients with HL). Beyond meeting standard organ function criteria used in prior BMT CTN trials, patients needed to have HIV infection that was treatable with cART and have no concurrent OIs.[30] Patients were conditioned using BEAM (carmustine, etoposide, cytarabine, melphalan). cART was interrupted in all patients, beginning with initiation of BEAM and resumed after resolution of mucositis/enteritis. At a median follow-up of 24.8 months, 2-year OS was 87.3% and progression-free survival (PFS) was 79.8%. At 1-year post-AHCT the median $CD4^+$ T-cell count was 280.3 (range, 28.8-1148); 82.6% of patients had an undetectable viral load.

Outcomes for patients from the BMT CTN 0803/AMC 071 trial were compared with 151 non-HIV-infected matched patients from the Centers for International Bone Marrow Transplant Research (CIBMTR) database. There were no significant differences between these groups for OS, PFS, TRM, risk of lymphoma progression, or time to engraftment (Figure 1).[29] These data confirm findings from 2 prior case-control studies.[31,32] The effectiveness of hematopoietic progenitor cell (HPC) mobilization in HIV-infected patients also does not appear

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to differ from that of uninfected patients.[33] Risk factors for mobilization failures in HIV-infected patients include $CD4^+$ T-cell count of <237 per microliter, platelet count of $<160\,000$ per microliter, and mobilization with granulocyte colony-stimulating factor (filgrastim) alone.

There is no evidence that AHCT worsens or improves long-term virologic control of HIV. Most groups describe spikes in viral load and diminution of $CD4^+$ T-cell counts following AHCT. By 1-year posttransplant, most patients return to baseline control of their HIV infection and T-cell reconstitution.[22,24,26,29] AHCT cannot eradicate HIV infection. Patients with undetectable viral loads post-AHCT still have latent HIV in the form of plasma viremia and intracellular HIV-1 DNA, detectable in mononuclear cells.[34-36]

Case 1: AHCT

A 47-year-old man infected with HIV for 15 years developed progressive cervical lymphadenopathy. Excisional lymph node biopsy confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL). A computed tomography–positron emission tomography fusion study showed fluorodeoxyglucose-avid bilateral cervical, mediastinal, porta hepatitis, and retroperitoneal lymphadenopathy. There was no bone marrow or central nervous system (CNS) involvement. "B" symptoms were absent. Eastern Cooperative Oncology Group performance status was 1, and the lactate dehydrogenase was 362 (normal, <255). The man's International Prognostic Index score was 2 (low-intermediate risk). The patient had not had a prior AIDS-defining diagnosis. His cART regimen consisted of emtricitabine/tenofovir (Truvada) and raltegavir (Isentriss). At the time of DLBCL diagnosis, the HIV viral load was undetectable (<20 viral copies per milliliter), and the CD4 T-cell count was 348 per microliter.

The patient achieved a complete remission (CR) following 6 cycles of *R*-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), including prophylactic intrathecal therapy with methotrexate. After 18 months, he suffered a recurrence of NHL, with disease above and below the diaphragm but no extranodal involvement. The patient was referred for consideration of AHCT. After 2 cycles of RICE (rituximab, ifosfamide, carboplatin, etoposide), he achieved a second CR and was mobilized with filgrastrim.

The patient was conditioned for AHCT with the BEAM regimen. After transplant, he developed grade 3 oral mucositis and culture-negative febrile neutropenia, managed with standard supportive care and empiric antimicrobials. The patient engrafted to white blood cells on day +10 and platelets on day +15 post-AHCT. The patient's cART regimen was held from initiation of BEAM until resolution of mucositis (3 weeks total). Immediately post-AHCT, he had a rise in his HIV viral load to 1024 copies per milliliter and a fall in his $CD4^+$ T-cell count to 120 per microliter. By 1 year post-AHCT, the patient's HIV viral load was undetectable, and the $CD4^+$ T-cell count rose to 458 per microliter. The patient remains in CR now 1 year post-AHCT.

Key considerations in AHCT patient selection and treatment of HIV-infected patients

AHCT is the standard of care for patients with HRL with treatable HIV infections who otherwise meet standard transplant eligibility criteria.[29] This includes consideration of the underlying hematological malignancy and the prospects for cure using AHCT. Disease-based treatment considerations should reflect those used in the treatment of HIV-uninfected patients. In the majority of studies of HIV-infected patients, those with chemotherapy-sensitive, relapsed, or persistent NHL and HL have the best outcomes. The prognosis of patients with DLBCL or Burkitt lymphoma appears to be superior to those of patients with lymphomas that are commonly associated with more severe levels of immunocompromise, including primary CNS[37] or plasmablastic lymphomas.[38] HIV infection is associated with significant effects on many extraimmunological organs, including the heart,[39] lungs,[40] kidneys,[41] and CNS.[42] This patient population needs to be screened adequately to ensure that there is no compromise in performance status or organ function that would increase the morbidity and mortality risk of AHCT.

It is essential to assess the treatability of the underlying HIV infection prior to AHCT. Patients with cART-unresponsive HIV infection should not be offered AHCT. Those with evidence of virological resistance to cART should be carefully assessed to ensure that they have a treatable infection prior to consideration of AHCT. Patients with previously untreated HIV infection should not be a priori excluded from consideration of AHCT but should be evaluated in close collaboration with an HIV specialist to screen for adequacy of virological control (or potential for treatment responsiveness) prior to AHCT. Except for the rare instance of high-level multidrug HIV resistance, HIV viral load thresholds or minimal CD4 counts should not be used as exclusions prior to AHCT.

It is important to plan carefully to avoid increasing the risk for development of HIV drug resistance in the peritransplant period. For agents such as the nonnucleoside reverse transcriptase inhibitor efavirenz, a single substitution at K103N in the HIV reverse transcriptase may confer high-level resistance to this agent as well as to nevirapine and delavirdine.[43] The start and stop and continued subtherapeutic levels of such antiretrovirals are associated with a greater risk of developing HIV resistance. Because AHCT relies on dose intensity of radio/chemotherapy for its effectiveness, to reduce the likelihood of significant gastrointestinal toxicity we recommend a planned interruption of cART during the period of therapy-related mucositis/enteritis. Although this strategy has not been prospectively validated, it does mitigate the risk of stops/starts and subtherapeutic cART therapy. This strategy was used in the prospective BMT CTN 0803 without evidence of emergence of HIV drug resistance.

cART regimens should also be screened by an HIV expert to consider substituting agents such as efavirenz and nevirapine during the peritransplant period.[44] If the patient has prior but inactive hepatitis B virus (HBV) infection (ie, HBV DNA negative), the cART regimen should contain appropriate anti-HBV agents, for example, tenofovir/emtricitabine coformulation.[45] While the patient is recovering post-AHCT following cART interruption, he or she should be monitored carefully for the emergence of OI. Because reactivation of cytomegalovirus (CMV) has been reported during this period, patients should undergo at least weekly screening using quantitative polymerase chain reaction (PCR) assessment of virus copy number from blood through at least day 100.[24] For patients with increasing CMV viral loads greater than 1000 copies per milliliter, we recommend preemptive treatment using ganciclovir, valganciclovir, or comparably effective anti-CMV chemotherapeutic drugs.

Most trials report peritransplant spikes in HIV infection and posttransplant decrements in $CD4^+$ T-cell counts. These are rarely associated with clinical sequelae. Most patients resume baseline virological control and reconstitution of T-cell immunity within 1 year post-AHCT. Although there are no national, consensus guidelines or recommendations related to posttransplant monitoring of HIV viral load, the goal following reinitiation of cART is that the patient should achieve an undetectable viral load within 3 months of resuming treatment. It is recommended that treating physicians perform viral load assessments every 2 to 4 weeks postresumption of

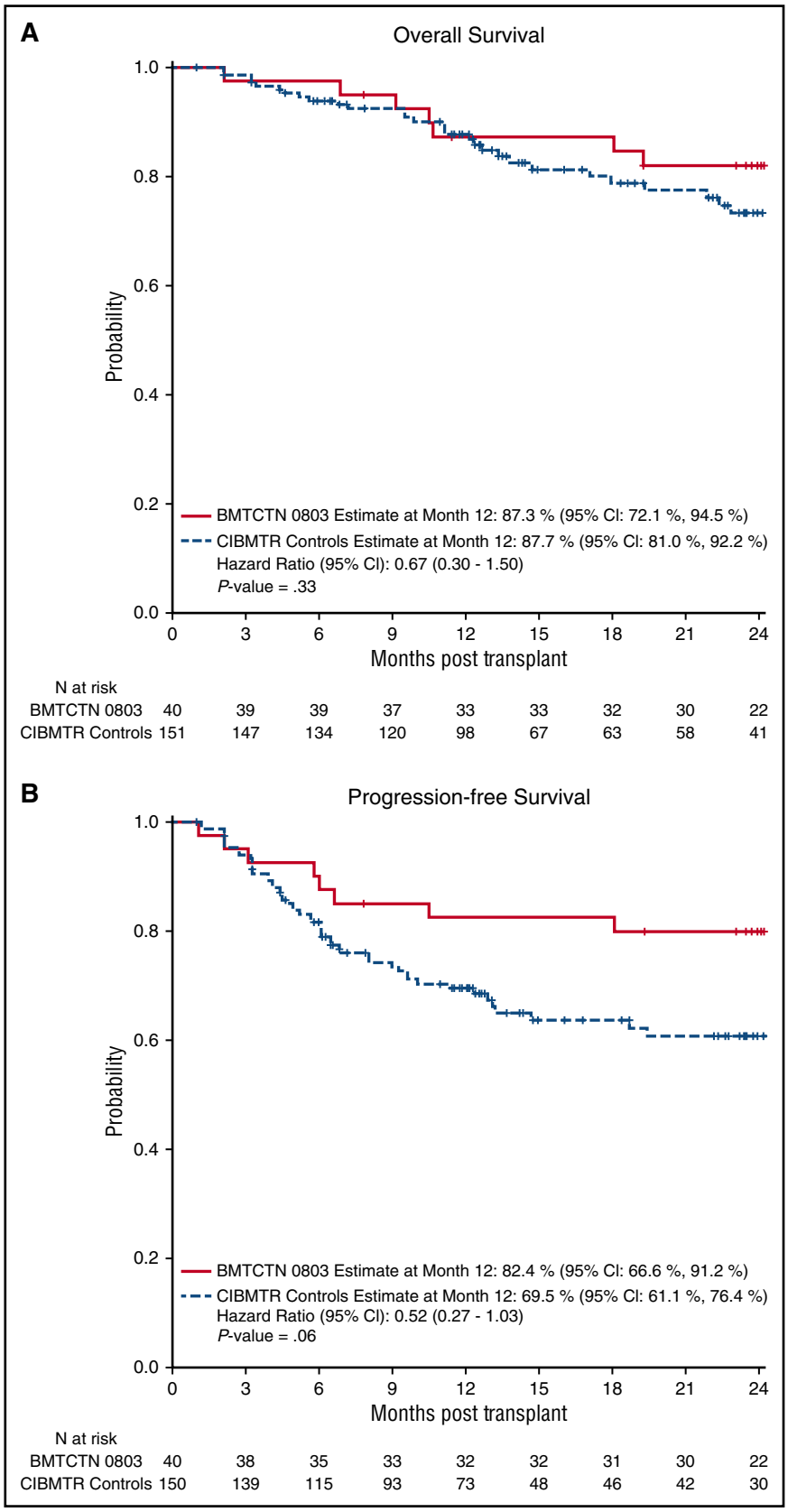

Figure 1. OS and PFS for HIV-infected and non-infected patients. Comparison of OS (A) and PFS (B) between HIV-infected patients treated under BMT CTN 0803/AMC 071 in comparison with 151 matched controls from the CIBMTR data registry. CI, confidence interval. Reprinted from Alvarnas et al.[29]

cART until that status is achieved. $CD4^+$ T-cell counts and HIV viral loads should thereafter be reassessed every 3 months. Patients should receive appropriate prophylaxis for *Pneumocytis jiroveci*, herpes viruses, and *Mycobacterium avium* complex until they achieve adequate recovery of $CD4^+$ T-cell counts, as recommended for general management of AIDS patients.[45]

Allogeneic HCT (alloHCT) for HIV-infected patients

Reports of allogeneic cell infusions or alloHCT for HIV-infected patients date to 1985.[46-50] Prior to effective anti-HIV treatment, alloHCT outcomes were extremely poor. A CIBMTR registry study found that although 4 of 9 survived alloHCT post-cART (1996-2003), only 2 of 14 patients undergoing transplant before 1996 (pre-cART) survived.[51] Data supporting the use of alloHCT for HIV-infected patients are more limited than are those supporting AHCT. The bulk of current data are based on single-institution, retrospective studies with small patient numbers.[52-58] In a recent retrospective publication, 5 patients with hematological malignancies underwent alloHCT from either sibling (2) or unrelated donors (3) at a single institution between 2010 and 2016.[59] All patients engrafted within 17 days with no TRM. Four patients experienced CMV reactivation, 3 relapsed from their original malignancies (6- to 13-months post-alloHCT), with 2 patients surviving for 42 and 55 months. Other investigators have published successful alloHCT transplant data, including evidence of effective virological control while on cART post-alloHCT.[56,57]

The largest prospective trial to date is the BMT CTN 0903/AMC 080 trial. In this multi-institutional trial, 17 patients underwent either reduced-intensity (9) or fully ablative (8) alloHCT. Patients underwent alloHCT for treatment of acute myeloid leukemia (AML) (9), acute lymphoblastic leukemia (2), MDS (2), or HRL (4). When feasible, cART was not interrupted during the peritransplant period. The primary study endpoint was 100-day nonrelapse mortality (NRM). Study inclusion criteria included cART-treatable HIV infection and standard alloHCT inclusion criteria adapted from prior BMT CTN trials. Day 100 NRM was 0%. Grade II-IV graft-versus-host disease (GVHD) developed in 41% of patients, who were treated with institutional standard treatments. Cause of death for study patients included disease relapse (5), GVHD (1), liver failure (1), and adult respiratory distress syndrome (1). At 24 months median follow-up, the estimated 1-year OS was 57% (95% confidence interval, 31% to 77%). The authors concluded that alloHCT should be considered standard for HIV-infected patients with treatable HIV infection who meet standard transplant criteria.[60]

HIV investigators are emboldened to explore alloHCT as a means of altering the natural history of HIV infection by the solitary example of the "Berlin patient." This patient underwent alloHCT from an unrelated donor homozygous for the CCR5Δ32 mutation of the CCR5 receptor, with apparent eradication of his HIV-infection posttransplant. The "Berlin patient" initially received alloHCT for relapsed AML but suffered a second relapse. After reinduction, he received a second infusion of HPCs from the same donor following 2 Gy of total-body irradiation. He subsequently achieved complete donor chimerism and remains in hematological remission. Extensive evaluation of multiple body tissues has not demonstrated HIV viral RNA or DNA.[61,62] The patient remains off cART and free of evidence of HIV infection over 8 years posttransplant.

The Δ32 mutation (CCR5Δ32) is a 32-basepair inactivating deletion within the CCR5 receptor gene.[63] Homozygotes for the mutation have inherited inhibition of R5 trophic HIV viral entry into $CD4^+$ T-cells. The CCR5Δ32 allele is found in up 10% of the northern European population,[64] with ~3% homozygosity, but is less prevalent among people of African and Asian origin. The success of the "Berlin patient" awaits validation. Six AIDS patients with hematologic malignancy have received allogeneic HCT from CCR5Δ32 homozygous donors.[65] Graft sources included human leukocyte antigen (HLA)-matched related and unrelated umbilical cord blood, with or without added haploidentical donor cells. All patients died of relapsed disease or treatment-related complications.[66]

There is some evidence for a potential allogeneic anti-HIV effect. Two HIV-infected patients who underwent nonmyeloablative alloHCT using wild-type CCR5 donors developed donor-derived $CD8^+$ T cells with reactivity against HIV epitopes.[67] Even in the absence of a detectable viral load, donor-derived anti-HIV T-cell responses can be generated, as was confirmed by a recent report about 3 additional alloHCT patients.[68] These data suggest the possibility of a graft-versus-HIV effect.

Case 2: alloHCT

A 25-year-old patient with an 8-year history of HIV infection, who had undergone AHCT for HL 18 months previously, presented with 2 months of refractory pancytopenia. The patient's white blood cell count was 1200 per microliter, hemoglobin 7.5 gm/dL, and platelet count 12 000 per microliter. Bone marrow aspirate and biopsy demonstrated refractory anemia with multilineage dysplastic changes consistent with MDS. Cytogenetics showed monosomy 7 in 16 of 20 metaphases. He remained in CR from HL at the time of his MDS presentation. His cART regimen at this time consisted of efavirenz/emtricitabine/tenofovir. His cART regimen was changed to emtricitabine/tenofovir combined with raltegravir. Viral load pretransplant was undetectable, and his $CD4^+$ T-cell count ranged from 500 to 700 per microliter.

AlloHCT was recommended. An appropriately matched, HLA-compatible donor was identified. Although donors were screened on a clinical trial for Δ32 homozygosity, no such donor was identified. The patient was conditioned with fludarabine/melphalan using tacrolimus/sirolimus as a GVHD prophylaxis. cART was continued uninterrupted. The patient engrafted to neutrophils and platelets on days +16 and +20, respectively. A day-100 bone marrow sample demonstrated normal trilineage engraftment, karyotype, and complete donor chimerism. At 3 months post-AHCT, the patient's HIV viral load was undetectable. At 1 year posttransplant, the HIV viral load remained undetectable with a $CD4^+$ T-cell count of 726 per microliter. He remains in CR from both HL and MDS at 7 years and 5 years posttransplant, respectively.

Key considerations in alloHCT patient selection and treatment of HIV-infected patients

Although clinical evidence for alloHCT in HIV-infected patients is more limited than is that for AHCT, for selected patients with hematological malignancies who otherwise meet standard transplant criteria, alloHCT is a reasonable option. In a manner similar to the HIV-specific considerations described for AHCT, patients need to have evidence of treatable HIV infection and adequate end-organ function. Those patients not meeting these HIV-specific criteria should not be offered alloHCT. The presence of an active, concurrent OI should be considered a contraindication to transplant.

Given the increased prevalence of HRL in HIV-infected patients, there is a growing likelihood that this group of patients may include those who have undergone prior AHCT. These patients need to be evaluated carefully to ensure that they have adequate organ function and that their underlying hematological malignancy has demonstrated adequate treatment response prior to alloHCT.

Peritransplant management of cART is more complex for alloHCT than for AHCT because of the number of potentially relevant drug-drug interactions between cART and the conditioning chemotherapeutic agents, immunosuppressive drugs, antimicrobials, and supportive care agents commonly used. We have summarized potential drug

interactions between transplant agents and cART drugs and made recommendations in Table 1. Myelotoxic agents such as zidovudine should not be included in the cART regimen owing to the risk of delayed engraftment. Ritonavir-boosted protease inhibitors should be avoided. Integrase inhibitors have a drug interaction and toxicity profile that makes them a useful alternative unless formulated with cobicistat.[69]

Because many of these patients may be candidates for reduced intensity or nonmyeloablative preparative regimens in which gastrointestinal toxicities may be minimal, some may be able to continue cART without interruption, because of the reduced risk of impaired drug absorption or start/stop interruptions in cART. In the absence of clear evidence, many investigators have applied this approach to their study populations. Our preference is to continue cART uninterrupted when feasible for patients undergoing reduced-intensity or nonmyeloablative alloHCT.

None of the published data justify significant deviation from standard practice for prophylaxis and management of GVHD in this population. Patients should be treated with standard preparative regimens and GVHD prophylactic therapy, some of which are listed in Table 1. There is no evidence from any of the published reports that HIV-infected patients are at any greater risk of end-organ complications of alloHCT than are noninfected patients.

Because alloHCT involves significant levels of therapy-related immunosuppression due to neutropenia, immunosuppressive prophylaxis, and immunosuppressive therapy of GVHD, HIV-infected patients need to be monitored for the emergence of OI. Should they demonstrate evidence of pulmonary toxicity (eg, obliterative bronchiolitis) or hepatotoxicity (eg, sinusoidal obstructive syndrome), OI should always be considered in the differential diagnosis and integrated into confirmatory diagnostic planning.

On the basis of the BMT CTN 0903 trial, surveillance for CMV reactivation for the first 100 days posttransplant is extremely important. Our practice screens biweekly with blood PCR assays. If viral load is >1000 copies per milliliter, patients commence preemptive treatment with gancyclovir, valgancyclovir, or another appropriate agent with continued monitoring of viral load. As with patients undergoing AHCT, alloHCT patients should remain on appropriate OI prophylaxis for *Pneumocytis jiroveci*, herpes viruses, fungus, and *Mycobacterium avium* complex on the basis of CD4 counts.[45]

HIV viral load and $CD4^+$ T-cell reconstitution should be followed as described for patients undergoing AHCT. When feasible, alloHCT using a homozygous CCR5Δ32 donor should be performed on a clinical trial so that the effectiveness of the "Berlin patient" paradigm can be validated. Post-alloHCT planned interruption of effective cART should not be performed outside of the context of an appropriately designed clinical trial. In pre-alloHCT counseling, the unlikelihood of a virological cure of HIV infection should be carefully discussed with patients.

Gene-modified hematopoietic cell transplantation (gmHCT) for HIV-infected patients

Despite the example of the "Berlin patient," HIV remains an incurable source of significant morbidity and mortality for infected patients.[11,70-72] The challenges of eliminating HIV are several-fold and include the need to eradicate the viral reservoir while protecting the patient from future infection/reinfection by providing them with immunological resistance to HIV. The issue of eradicating the HIV viral reservoir is challenging because latent virus may exist in a number of other tissues, including the lymph nodes, gut, and CNS. The latter may act as a sanctuary site.[73] There is evidence of persistent CNS inflammation and viral replication, even in the face of effective systemic therapy.[74]

The promise and limitations of gmHCT in HIV-infected patients are illustrated by 2 landmark studies. The first, a randomized, double-blind, phase II study, evaluated 74 HIV-infected patients who received either placebo HCT or gmHCT transduced with a gammaretrovirus encoding a *tat-rev* specific anti-HIV ribozyme.[75] HPCs were mobilized with filgrastim alone. Because of safety considerations, participants did not receive conditioning prior to HPC infusion. Patients were monitored for 100 weeks postinfusion. Although there were no adverse events reported during the trial, there was no statistically significant difference in HIV viral load between the control and treatment arms at the primary study point (weeks 47-48 posttreatment). $CD4^+$ T-cell counts, however, were higher in the treatment group than in the placebo group.

The second landmark study involved transduction of $CD34^+$ peripheral blood stem/progenitor cells with a lentivirus encoding three anti-HIV RNA-based moieties, a CCR5 ribozyme, a transactivation response decoy, and a *tat/rev* short hairpin RNA (shRNA).[76] In this City of Hope trial (NCT00569985), 4 patients received salvage treatment of HRL using standard, ablative AHCT preparative regimens. All patients received both gene-modified and unmodified HPC grafts.[77] All 4 patients engrafted on day +11 following transplant. There were no unusual toxicities related to the gene-modified HPC products. Stable, low-level expression of gene-modified blood mononuclear cells was detected in 3 of 4 patients up to 24 months post-AHCT.

A critical need in developing scalable gene-modified cellular therapy of HIV/AIDS is establishing safe and effective conditioning regimens. One of the theories behind the success of the "Berlin patient" was that his receipt of 2 Gy total-body irradiation prior to his second transplant may have helped reduce his viral reservoir. Two ongoing trials (NCT01734850 and NCT02500849) use a dose escalation of busulfan in healthy HIV-infected patients, with infusion of autologous HSPCs genetically modified with either a bivalent anti-HIV lentivirus encoding the C-46 mutant peptide and siRNA to CCR5, or a zinc finger nuclease disruption of CCR5.

Case 3: gmHCT

A 25-year-old HIV-infected man with chemotherapy-sensitive, persistent NHL was referred for consideration of gene-modified AHCT. One year prior to referral the patient presented with stage IVA DLBCL, without evidence of CNS or marrow involvement. After diagnosis, the patient began cART (efavirenz/emtricitabine/tenofovir). The patient had persisting NHL following 6 cycles of *R*-EPOCH, including prophylactic intrathecal methotrexate. He subsequently received 2 cycles of RICE and achieved a CR.

Upon referral the patient was offered participation in a clinical trial utilizing gene-modified AHCT, and he consented. Prior to initiating mobilization for stem cell collection, cART therapy was suspended so as not to compromise the lentiviral transduction of the gene-modified stem cell product. The patient's cART therapy remained on hold through the preparative regimen and period of mucositis/enteritis to avoid induction of HIV resistance. He subsequently underwent BEAM preparation, followed by infusion of both gene-modified and unmanipulated HPC. The gene-modified $CD34^+$ HPC product underwent lentiviral transduction to express 3 RNA-based anti-HIV moieties: *tat/rev* shRNA, a transactivation response decoy, and a CCR5 ribozyme. Prior to AHCT, the HIV viral load was <400 copies per milliliter, and his $CD4^+$ T-cell count was 577 per microliter. The patient

Table 1. Potential drug interactions between antiretroviral agents and transplant agents

Transplant agents	Protease inhibitors (PIs)	Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Nucleoside reverse transcriptase inhibitors (NRTIs)	Integrase inhibitors
Conditioning Regimens				
Fludarabine/Melphalan Reduced Intensity	May be used without modification	May be used without modification	May be used without modification	May be used without modification
Busulfan/Fludarabine Reduced Intensity or Myeloablative	Discontinue ritonavir or cobicistat >48 hrs prior to start of busulfan. Consider substitution of non-PI ART agent	May be used without modification	May be used without modification for non-boosted regimens	May be used without modification for non-boosted regimens
			Not recommended for cobicistat-containing regimens.	Not recommended for cobicistat-containing regimens.
Total Body Irradiation (TBI) cyclophosphamide Myeloablative	Discontinue ritonavir or cobicistat >48 hrs prior to start of cyclophosphamide. Consider substitution of non-PI ART agent	Not recommended. May increase levels of cyclophosphamide metabolites through induction of CYP3A4 and CYP2B6	May be used without modification for non-boosted regimens	May be used without modification for non-boosted regimens
			Not recommended for cobicistat-containing regimens.	Not recommended for cobicistat-containing regimens.
Immunosuppressants				
Cyclophosphamide	Discontinue ritonavir or cobicistat >48 hrs prior to start of cyclophosphamide. Consider substitution of non-PI ART agent	Not recommended May increase levels of cyclophosphamide metabolites through induction of CYP3A4 and CYP2B6	May be used without modification for non-boosted regimens	May be used without modification for non-boosted regimens
			Not recommended for cobicistat-containing regimens.	Not recommended for cobicistat-containing regimens.
Tacrolimus	Significant increase in tacrolimus levels through inhibition of CYP3A4. Consider substitution of non-PI ART agent	Likely to decrease levels of tacrolimus through induction of CYP3A4. Monitor levels and adjust dosing based upon tacrolimus levels	May be used without modification for non-boosted regimens	May be used without modification for non-boosted regimens
			Not recommended for cobicistat-containing regimens.	Not recommended for cobicistat-containing regimens.
Sirolimus	Significant increase in sirolimus levels through inhibition of CYP3A4. Consider substitution of non-PI ART agent	Likely to decrease levels of sirolimus through induction of CYP3A4. Monitor levels and adjust dosing based upon sirolimus levels	May be used without modification for non-boosted regimens	May be used without modification for non-boosted regimens
			Not recommended for cobicistat-containing regimens.	Not recommended for cobicistat-containing regimens.
Methotrexate (MTX) Pham and Flexner 2011	Unlikely interaction, MTX CY3A4 independent	Unlikely interaction, MTX CY3A4 independent	No evidence of significant interaction	No evidence of significant interaction
Mycophenolate Mofetil Foy et al. 2014	May be used without modification	May be used without modification	Not recommended. May increase antiviral effects	May be used without modification
Antifungals				
Fluconazole	Fluconazole dose should be limited to 200 mg daily for patients receiving ritonavir or cobicistat. Otherwise not limited	May be used without modification	May be used without modification for non-boosted regimens	May be used without modification for non-boosted regimens
			Not recommended for cobicistat-containing regimens.	Not recommended for cobicistat-containing regimens.
Triazoles	Consider substitution of non-PI ART agent	Not recommended. Two-way interaction based on CYP3A4	May be used without modification	May be used without modification
Echinocandins	May be used without modification	May be used without modification	May be used without modification	May be used without modification
Amphotericin B related	May be used without modification	May be used without modification	May be used without modification	May be used without modification

Red cells indicate prohibited drug combination. Yellow cells indicate combinations not recommended owing to drug interactions. Green cells indicate acceptable combinations. Recommendations in this table are based in part on Pham and Flexner[78] and Foy et al.[79]

ART, antiretroviral therapy.

engrafted to neutrophils by day 11 post-AHCT. After recovery from mucositis, the patient resumed his prior cART regimen and promptly achieved suppression of his HIV viral load to undetectable levels. He demonstrated evidence of detectable gene-modified blood cells for 12 months post-AHCT. He remains in CR 2 years post-AHCT.

Key considerations in patient selection and treatment of HIV-infected patients using gene-modified therapeutics

As of this time, treatment of HIV-infected patients with gene-modified therapeutics is only available during a clinical trial. Because of the significant scientific questions regarding the promise of this treatment approach, participation in well-designed clinical trials evaluating the impact of gmHCT for the HIV-infected patient population should be strongly supported.

Conclusion

Despite availability of effective antiretroviral treatment, the morbidity of HIV infection remains significant. Patients with HIV-related blood cancers may benefit from use of hematopoietic cell transplantation. For patients with treatable HIV infection and HRL who otherwise meet standard autologous transplant criteria, AHCT is the standard of care. The data supporting use of alloHCT for HCT-infected patients, though limited, are encouraging. Patients with treatable HIV infection, who meet standard alloHCT criteria, should be offered transplant as participants in a clinical trial that offers the prospect of alloHCT using CCR5Δ32 homozygous donors. For those patients who are potential candidates for gmHCT trials, such trials should be considered carefully when comparing patient treatment options. Gene-modified transplantation may provide an avenue for affecting the underlying HIV infection in the continued search for a cure.

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