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Hematopoietic Stem Cell Transplantation in HIV Infected Patients

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Additional information is available at the end of the chapter

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1. Introduction

In the highly active antiretroviral therapy (HAART) era, the survival of HIV infected patients has improved. Opportunistic infections and AIDS related syndromes in these individuals have declined (Palella et al, 1998). HIV infected individuals have an increased tendency to develop malignancy. These include a number of non-AIDS defining malignancies, as well as the AIDS defining malignancies which are Kaposi sarcoma, invasive cervical cancer and non-Hodgkin Lymphoma (NHL). Among the NHL group, the incidence of systemic NHL, CNS Lymphoma and primary effusion lymphoma are increased in this population. Malignancies continue to be an important cause of mortality in these individuals.

The incidence of NHL increases with progressive immunosuppression in HIV-infected patients. The majority of these cases are intermediate or high-grade and almost all are diffuse large B cell (immunoblastic variant) or Burkitt-like lymphomas. The incidence of Hodgkin lymphoma (HL) is also increased in the HIV positive population (Bigar R et al, 2006) though it is not an AIDS defining illness. Acute myeloid leukemia may also occur with higher frequency in the setting of HIV infection (Grulich A et al, 2007). NHL and HL occurring in HIV infected individuals are characterized by an aggressive clinical course with an advanced stage at presentation (Levine AM, 2000).

In the pre-HAART era, the standard treatment for AIDS associated NHL was low dose chemotherapy. It was thought that they would be unable to tolerate intensive chemotherapy because of the underlying immunodeficiency. Randomized trials of standard doses of combination chemotherapy versus reduced doses revealed inferior results in the standard dose arm due to increased hematologic toxicity and infections (Kaplan LD et al, 1997). In the post-HAART era, patients were treated more aggressively due to improved hematologic reserve in patients on HAART. Patients are now treated similar to non HIV NHL patients.

Their remission rates and median survival with aggressive combination chemotherapy and HAART is similar to their HIV negative counterparts (Boue, F et al, 2006).

Consequently, more aggressive therapies such as high dose chemotherapy and stem cell transplantation have been explored in the HAART era with encouraging results. This chapter will go through autologous and allogeneic stem cell transplantation in HIV infected individuals and also highlight some of the recent developments in the field.

2. Autologous Stem Cell Transplantation (ASCT)

Autologous stem cell transplantation means transplantation with a person's own hematopoietic stem cells which are harvested ahead of time and cryopreserved for later use. Pluripotent hematopoietic stem cells are those which are capable of self renewal and of differentiation. These are the cells targeted for collection. The main advantage of this procedure is to enable the patient to receive myeloablative dose intense chemotherapy for a malignancy that has demonstrated a dose response to chemotherapy. Stem cells collected from the peripheral blood after priming with G-CSF (Granulocyte Colony Stimulating Factor) are generally preferred to stem cells from the bone marrow due to shorter engraftment times, thereby reducing morbidity and mortality. Stem cell apheresis is an outpatient procedure where cells are collected through large volume apheresis over approximately 4-6 hours. These stem cells are either cryopreserved with DMSO directly or can be manipulated by methods such as CD34 positive selection and transduction prior to cryopreservation.

There are various preparative regimens used for stem cell transplantation in patients with hematologic malignancy. The ideal regimen should be able to eradicate the malignancy, have no mortality and manageable side effects or toxicity. Alas, no such treatments exist. There are several treatment regimens in use. Selection of high dose chemotherapy regimens is based upon the use of chemotherapeutic agents that have a dose response in the hematologic malignancy. In addition, drugs are chosen that have nonoverlapping toxicities save for the hematologic toxicity. For example in NHL, typical agents include Cyclophosphamide, Etoposide, Carmustine (BCNU) and melphalan. In Hodgkin lymphoma, frequently utilized preparative regimens include the CBV regimen with Cyclophosphamide, Carmustine (BCNU), and Etoposide (VP-16) and the BEAM regimen with Carmustine (BCNU), Etoposide (VP-16), Cytarabine (Ara-C) and Melphalan.

Patients typically receive the conditioning regimen followed by infusion of thawed autologous stem cells approximately 24- 48 hours post completion of chemotherapy. Thereafter ensues a period of profound neutropenia, also often mucositis and GI toxicity such as nausea and diarrhea. During this period of neutropenia, the risk of infection is significantly increased. Hence patients are housed in hepa filtered rooms, and placed on low bacteria diets in addition to other infectious precautions. Nonetheless, fever and infection can be common. Mucositis is a risk factor for infection as it increases the likelihood of intermittent bacteremia from the GI tract. The use of peripheral blood progenitor cells harvested from apheresis instead of bone marrow stem cells led to a shortening of engraftment of white blood cell times.

This thereby reduced the period of neutropenia and mucositis, which improved survival in patients.

This procedure has been the standard treatment for HIV negative patients with relapsed NHL since the landmark PARMA trial published by Philip et al in the New England Journal of Medicine (1995). In this trial, patients with relapsed chemosensitive aggressive NHL were treated with 2 cycles of DHAP (Dexamethasone, Cisplatin and Cytarabine) and if responsive, randomly assigned to receive either DHAP for 4 additional cycles or high dose chemotherapy with BEAC (BCNU/Carmustine, Etoposide, Cytarabine and Cyclophosphamide) followed by ASCT. The results of this study revealed an overall survival (OS) benefit of 53 versus 32 percent ($p=0.038$) in favor of the high dose chemotherapy arm. This approach has also been used in high risk patients who are in first remission (Haion, C et al, 1997). Non-randomized trials of this high risk group have demonstrated high rates of progression free survival (PFS). Similarly, trials of HIV negative patients with Hodgkin Lymphoma have shown that ASCT can provide long term PFS for patients with relapsed disease (Linch, 1993). All these studies were done in the HIV negative population.

2.1. ASCT in HIV positive patients

ASCT in HIV positive patients was pioneered by the French in the pre-HAART era (Gabbare, J et al, 1996). The first patient was reported as a case study. He was a 40 year old male with HIV related NHL, receiving Zidovudine and Zalcitabine as antiretroviral treatment. He was treated with BEAM (BCNU, Etoposide, Cytarabine and Melphalan) chemotherapy for relapsed lymphoma followed by ASCT. His post-transplant course was complicated by several opportunistic infections including cytomegalovirus viremia, mycobacterium pneumonia and cryptosporidiosis. This report corroborated the fear that the immune impairment due to HIV augmented the infection risk. However, it also demonstrated that mobilizing stem cells and successful engraftment were feasible in this setting. In the post-HAART era, French investigators performed a study with fourteen patients with relapsed or refractory NHL. Eight patients died of which six deaths were from lymphoma. This study established that the mortality due to infection was substantially reduced, but that control of the underlying lymphoma remained the challenge (Gabbare et al, 2001). It set the stage for ASCT to be considered a feasible task in HIV patients, and revealed that infectious issues were manageable without apparent adverse consequences on the HIV infection.

Other centers have described similar findings. The larger City of Hope study had patients with less advanced lymphoma and disqualified chemotherapy refractory patients (Krishnan A, et al, 2005). The initial series consisted of 20 patients with HL or NHL. All patients were on HAART. The majority of patients underwent CBV (cyclophosphamide, BCNU, Etoposide) chemotherapy as conditioning. Engraftment times were comparable to HIV negative patients, median was 11 days. Despite efforts to continue HAART throughout the transplant period, only nine out of twenty were able to tolerate it. The remainder resumed it at a median of two months following ASCT. The poor tolerance of HAART was due to either nausea or mucositis. Transplant related mortality was low, as was the incidence of opportunistic infections. No patient died of an opportunistic infection. Although the CD4 count did nadir

at 6 months, post-transplant follow up demonstrated that the underlying HIV disease did not deteriorate as a result of the transplant and the CD4 counts recovered to pre-transplant levels by one year in all patients. PFS and OS were 85%. The improved result compared to the French experience may be from selecting patients with less advanced disease and chemotherapy sensitive disease.

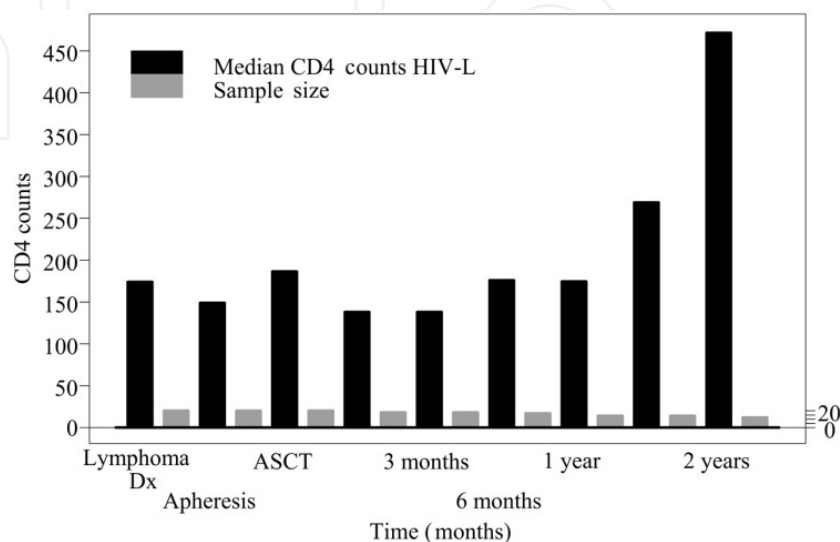


Figure 1. Median CD4 count trends during apheresis and after ASCT. Krishnan A et al. Blood 2005; 105:874-878 Blood: Journal of the American Society of Hematology by American Society of Hematology. Copyright 2009 Reproduced with permission of AMERICAN SOCIETY OF HEMATOLOGY (ASH) in the format Journal via Copyright Clearance Center.

The Italian cooperative group on AIDS and tumors (GIGAT) reported the long term results on 50 patients with HIV and relapsed or refractory lymphoma (Re A, et al, 2009). Similar to the City of Hope study, only patients with chemotherapy sensitive disease were selected to proceed with peripheral stem cell collection. Forty-six patients were already on HAART, two started at the time of study enrollment, and two at the time of stem cell mobilization. A minimum CD4 count of 100 cells/micro liter prior to initiating chemotherapy was a pre-requisite. There were no eligibility criteria for viral load and therefore the viral loads at study entry ranged considerably. Thirteen patients withdrew before stem cell collection. Among these, two withdrawals were from early toxic deaths, one patient refusal, and the remaining ten patients had chemotherapy refractory disease. Eventually, twenty seven patients underwent ASCT. Of these, seven temporarily suspended HAART, some for similar reasons to the City of Hope experience with mucositis, and others for hepatotoxicity. All patients received BEAM (Carmustine/BCNU, Etoposide, Cytarabine and Melphalan) as the conditioning regimen. Three year progression free survival for the patients who proceeded to transplant was also similar to the City of Hope experience at 76.3%. Multivariate analysis of prognostic factors for survival showed that bone marrow involvement, performance status less than 2, and CD4 count below 100 cells/micro liter were significant. No significant HIV-associated infections were noted. In those patients on effective HAART therapy, the infectious risk was similar to patients without HIV who underwent ASCT. The high patient

withdrawal rate before transplantation displays the obstacles in treating these aggressive lymphomas.

The European Group for Blood and Marrow Transplantation conducted a retrospective, multicentre registry-based analysis of sixty eight patients from twenty institutions since 1999 (Balsalobre P et al, 2009). There were fifty patients with NHL and eighteen patients with HL. At the time of ASCT, sixteen patients were in first complete remission (CR1); forty four patients were in CR more than 1, partial remission, or chemotherapy-sensitive relapse; and eight patients had chemotherapy resistant disease. Most patients were treated with a chemotherapy based conditioning regimen (BEAM and variants). The median CD4 count at transplantation was 162 cells/micro litter, and eighty percent of patients had an HIV viral load under 200/mL. All patients engrafted at a median of eleven days, save one. The incidence of non relapse mortality (NRM) was 4.4% and 7.5% at 3 and 12 months, respectively. Three patients died from bacterial infection, two died of HIV related complications, and one patient died of an unknown cause while in CR. At a median follow-up of 32 months, progression free survival and overall survival were 56.5% and 61% at three years, respectively. On multivariate analysis, chemotherapy resistant disease and not attaining complete remission predicted poorer progression free survival and overall survival. This data indicates again similar to the HIV negative transplant setting, disease control with chemotherapy at the time of ASCT predicts a more favorable result.

Two case control studies also demonstrated that HIV status does not impact ASCT outcomes for lymphoma. The European Group for Blood and Marrow Transplantation undertook a retrospective study of 106 patients (Diez-Martin et al, 2009) which included 53 HIV-positive lymphoma patients who underwent transplant with controls matched for histology, non-age adjusted IPI (International Prognostic Index), and disease status at transplant. There were 66 percent NHL and 34 percent HL patients. Both groups were similar, other than the higher percentage of males, mixed cellularity Hodgkin lymphoma and patients receiving granulocyte colony stimulating factor before engraftment, and a smaller fraction receiving total body irradiation based conditioning within the HIV lymphoma cohort. With median follow-up of 30 months, progression free survival was 61 percent for the HIV-lymphoma group and 56 percent for the control lymphoma group. Overall survival was 61.5 percent for HIV-positive patients and 70 percent for controls ($p = \text{NS}$). There was a trend towards delay in platelet engraftment after transplant in the HIV group. It is uncertain whether this resulted from the more frequent granulocyte colony stimulating factor use in that cohort or to HAART therapy or to chronic HIV infection of the bone marrow. Incidence of relapse, overall survival and progression free survival were comparable in both groups. In the first year following ASCT, there was an elevated, but statistically insignificant non relapse mortality in the HIV lymphoma group, primarily from early bacterial infections. This data suggested that in the HAART era, HIV infection should not preclude lymphoma patients from undergoing ASCT. The authors recommended conscientious infection prophylaxis and vigilant immune recovery surveillance shortly following ASCT.

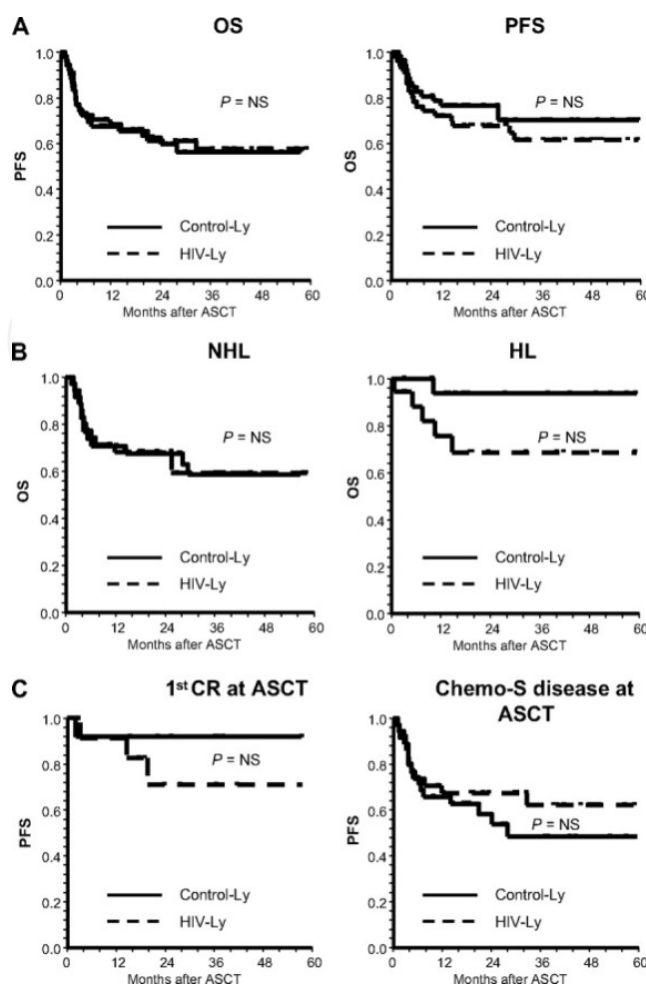


Figure 2. Survival according to HIV infection status: positive versus negative. Diez-Martin JL et al. Blood 2009; 113:6011-6014 Blood: Journal of the American Society of Hematology by American Society of Hematology. Copyright 2009 Reproduced with permission of AMERICAN SOCIETY OF HEMATOLOGY (ASH) in the format Journal via Copyright Clearance Center

City of Hope undertook a retrospective matched case-control study (Krishnan, et al, 2010) to study long-term outcome in HIV positive NHL patients (cases) and HIV negative NHL patients (controls). Twenty nine patients with HIV positive NHL were matched with HIV negative NHL controls with respect to sex, time to ASCT, year of transplant, histology, age, disease status, number of prior regimens, and conditioning regimen. A higher ratio of HIV positive NHL patients had high grade disease versus the HIV negative NHL controls. There were mostly male patients in both groups. The median CD4 count at study entry was 153.5, and the viral load was 6500. All patients in the HIV cohort were on HAART at the time of transplant; however thirteen patients had to interrupt treatment. The median follow-up for HIV-positive NHL patients was 62.4 months, and 48.4 months for the HIV-negative NHL controls. The median time to neutrophil engraftment was comparable for both groups. Non relapse mortality was also comparable for the two groups. Infectious complications did differ between the two groups, with more opportunistic infections occurring in the HIV-positive cohort, however this did not affect survival. There were more opportunistic viral

infections in the HIV-positive group, with three cases of cytomegalovirus viremia, one case of adenovirus viremia, and one case of varicella infection. Disease free survival and overall survival were not significantly different between the two groups. The two year disease free survival for the HIV-positive NHL group was 76 percent and 56 percent for the HIV-negative group. The overall survival for both groups was also similar at 75 percent notwithstanding a higher proportion of poor risk HIV positive NHL patients.

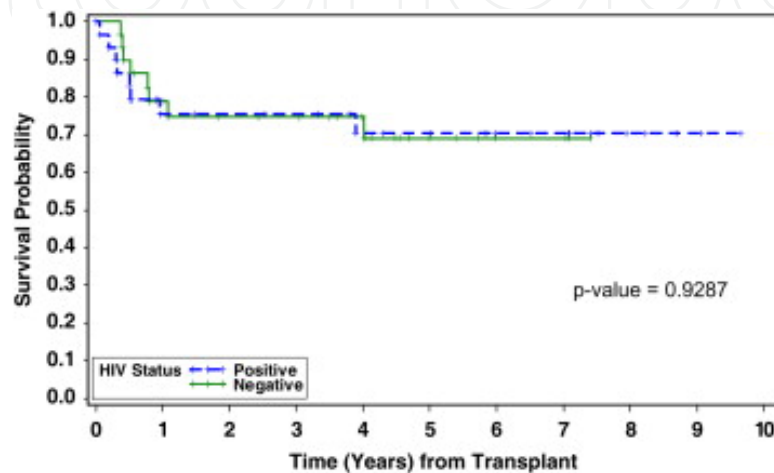


Figure 3. Probability of overall survival by HIV status. Krishnan A, Palmer J, Zaia J, et al. Vol. 16, (September 2010), pp. 1302-08. "Reprinted From: HIV Status Does Not Affect the Outcome of Autologous Stem Cell Transplantation (ASCT) for Non-Hodgkin Lymphoma (NHL) *Biology of Blood and Marrow Transplantation* 16:1302-1308 (2010), with permission from Elsevier"

Causes of death in the HIV-positive cohort were mostly from relapsed lymphoma, and not infection. Disease status at the time of transplant was the only clear predictor of outcome. This single-institution series corroborates the European data.

This data from the European Group for Blood and Marrow Transplantation (Balsalobre et al, 2009) and the City of Hope experience (Krishnan, et al, 2010) revealed better progression free survival rates in the HIV-positive lymphoma patients compared to their HIV-negative counterparts. This improved early outcome is interesting. Perhaps incorporating HAART in the regimen improves the result. Maybe transplant with high dose chemotherapy resets the clock on the immunologic effects of HIV, either by depleting the HIV reservoir or by its alterations on the T cell reconstitution. Inherent genetic variability may also play a part. Homozygosity for the 32-bp CCR5 allele CCR-Δ 32 has been shown to confer resistance to HIV infection (Liu R et al, 1996). This same deletion may also offer defense against lymphoma development in HIV patients (Dean M et al, 1999). A trial in the United States of ASCT for HIV lymphoma via the Bone Marrow Transplant Clinical Trials Network will prospectively analyze the genotypes and the CCR5 mutation to find its association with disease free survival. Correlative studies will also assess the pre and post-transplant HIV viral reservoir.

2.2. Immune recovery post transplant

An Italian study (Simonelli et al, 2010) prospectively evaluated 33 lymphoma patients of whom 24 were HIV positive and nine were HIV-negative. All patients had relapsed or refractory disease and both groups were given similar high dose chemotherapy and ASCT protocols. The study compared the immunological baseline features in the two groups. The study showed that front line chemotherapy resulted in immunodepression in the general population, which qualitatively differs from that observed in HIV-infected patients. HIV-positive patients had higher CD8+ T cell counts and inverted ratios of CD4+ cells to CD8+ cells than HIV-negative patients. There were no significant differences in the CD4+ cell compartment and thymic reservoir, between the groups. The authors attributed this finding to good control of HIV-RNA levels from ongoing HAART therapy. The initial differences in the dynamics of immune recovery between the populations also diminished with longer follow-up. Specifically, the CD8+ subpopulation, together with CD56+ NK cells quickly recovered in both groups of patients, leading, to a reversal of the ratio of CD4+ cells to CD8+ cells in the HIV-negative patients for up to two years following transplantation. In the HIV-infected population, high dose chemotherapy produced a different immune incompetence compared with conventional chemotherapy, which primarily impacted the CD4+ T cell subset without significantly affecting the CD4/CD8 ratio. In the first three months post ASCT, significantly more infectious episodes occurred in the HIV-positive group. The authors demonstrated that HIV-positive patients with early post-transplant infections had significantly lower CD4+ T cell counts during the third month post ASCT, compared with HIV-negative patients without infections. There was no difference in the frequency of infection or the dynamics of CD4+ T cell reconstitution beyond three months post ASCT. Overall, the study showed that high dose chemotherapy and ASCT in HIV-infected lymphoma patients does not worsen initial immune impairment or enhance viral replication or peripheral HIV reservoir in the long term. The temporary elevation in the incidence of early infectious events in the HIV-positive group may be related to an arrest in the CD4+ T cell count increment during the first three months post ASCT. There were no significant changes in the HIV DNA levels during the follow-up period, with values at 24 months significantly lower than those at baseline.

It is well-recognized that HIV persists at low levels in peripheral blood mononuclear cells, mostly in infected resting CD4+ T cells which constitute a stable reservoir for HIV, even when viral replication is well controlled with antiretroviral therapy. Analysis of HIV-1 DNA (HIV DNA) (Koelsch, KK et al, 2008) in peripheral blood mononuclear cells is therefore an accessible virological marker for estimating HIV infection. Bortolin's study of 22 patients with HIV associated relapsed or refractory lymphomas treated with salvage high dose chemotherapy followed by ASCT looked at the kinetics of the predictive value of HIV DNA. HIV DNA was measured by real-time PCR in the peripheral blood mononuclear cells. At baseline, HIV DNA was found to be associated with HIV-1 RNA (HIV RNA), but not with CD4 counts. HIV RNA load was under control throughout follow-up, while HIV DNA levels were nearly always detectable. The overall survival analysis demonstrated that patients with higher HIV DNA levels at baseline had a higher and nearly significant risk of death

when compared with patients with lower levels (HR, 8.33, 95% CI 0.99 - 70.06, $p=0.05$). At the time of publication, of the 22 patients, 14 (63.6%) were still alive, of which 13 were in remission and one relapsed; 8 (36.5%) died, of which 6 deaths were from relapsed lymphoma and 2 were from opportunistic infections. Of note, baseline HIV DNA levels were significantly different between alive and deceased patients. Results from this study established HIV DNA as an valuable additional tool to optimize and tailor therapy, and also predict treatment outcome in these patients.

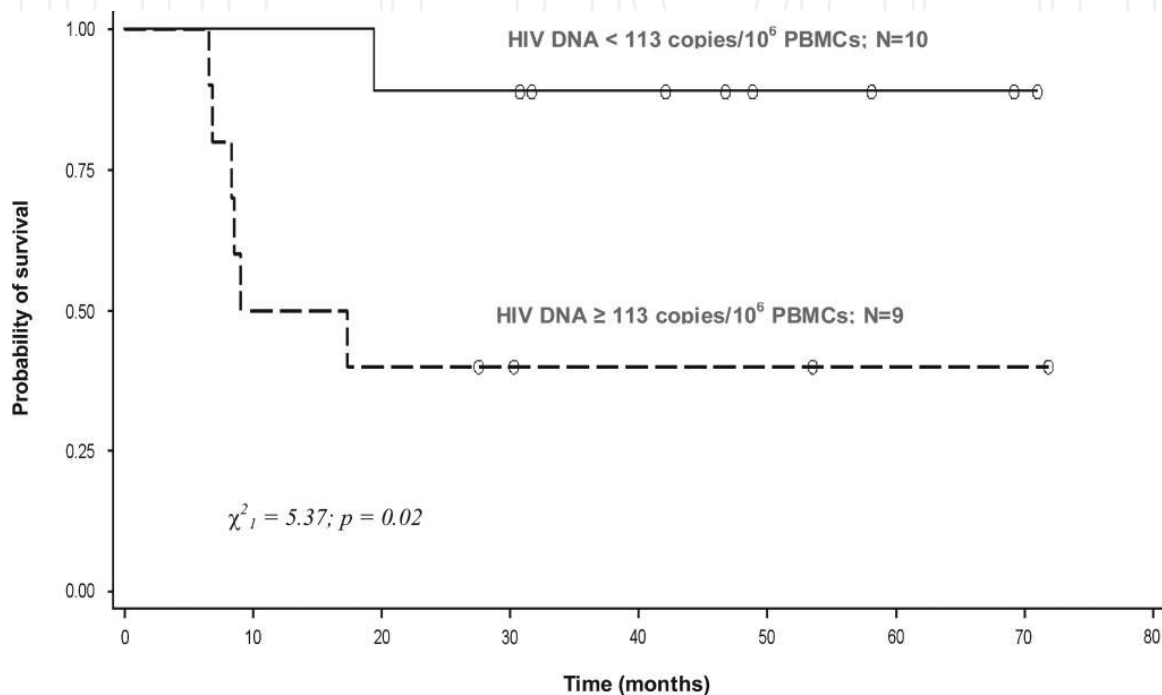


Figure 4. Kaplan–Meier curve showing survival according to baseline HIV DNA levels ($n = 19$) Bortolin MT, Zanussi S, Talamini R, et al. *AIDS Research and Human Retroviruses*. Vol. 26, No. 2, (2010), pp. 245-251. " The publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers."

3. Allogeneic transplantation

Allogeneic transplantation refers to hematopoietic stem cells which come from an HLA matched donor. Allogeneic transplants typically have a higher morbidity and mortality than autologous transplants mostly due to infection or graft versus host disease. The 'graft' refers to the transplanted hematopoietic stem cells transplanted from the donor (sibling or matched unrelated donor) and the 'host' refers to the patient. In graft versus host disease, the donor's immune cells attack the recipient's organs. Virtually any organ can be affected, but frequently affected organs include the skin, liver and gut. Graft versus host disease (GVHD) is a major impediment to the success of bone marrow transplantation. Treatment and prevention of GVHD includes immunosuppressive medications and sometimes steroids. The incidence of chronic graft versus host disease (that occurring after 100 days post transplant)

is up to 80% in recipients of allogeneic peripheral blood stem cells. On the other hand, allogeneic transplant has the advantage of lower rates of relapse due to the 'clean graft' as well as the immunologic effects of the donor graft, the so called graft versus tumor effect. These immunologic effects could be potentially even more beneficial in the treatment of HIV infection if the attendant risks of the procedure in the HIV infected patient could be overcome.

Allogeneic stem cell transplantation (alloSCT) is more difficult than ASCT in HIV infected individuals due to the need for chronic immunosuppression in an already immunosuppressed individual. Solid organ transplantation set the stage for allogeneic stem cell transplantation in that solid organ transplant patients also need chronic immunosuppression. There have been several published reports of solid-organ transplantation in HIV positive patients who are receiving HAART, which demonstrated that, in most cases, HIV infection does not affect the outcome of transplantation. Drug interactions were handled by requisite dose adjustments. The underlying HIV infection was controlled provided patients remained on antiretroviral therapy. (Ragni MV et al, 1999; Prachalias AA et al, 2001; Kuo PC, 2001; Gow PJ & Mutimer D, 2001 as cited in Halpern et al, 2002). Some solid organ transplant centers regard HIV patients akin to other high risk patients, for example, diabetics, or the elderly (Persad G et al, 2008).

The literature on allogeneic transplantation in HIV positive patients is considerably more limited than ASCT. Experience with ASCT in HIV-positive patients has shown that HIV infection did not impede engraftment provided myelosuppressive medications like azidothymidine were avoided. Therefore, in the allogeneic field, comparable engraftment times were expected. Allogeneic transplantation data indicates the rate of immune reconstitution after transplant is related to the type of conditioning regimen, HLA compatibility of the donor and host, and the occurrence of GVHD. In an allogeneic transplant with an HIV negative recipient, T lymphocyte recovery occurs by thirty days following transplant, although initially with primarily CD8+ T cells (Keever, CA et al, 1989). CD4+ cell recovery often takes up to six months.

Early reports of allogeneic transplant were in the pre-HAART period. Holland et al (1989) at Johns Hopkins published a case of a forty one year old male with HIV lymphoma who received a conditioning regimen consisting of total body irradiation and Cyclophosphamide followed by allogeneic bone marrow transplantation. Prior to the transplant, he was given high dose azidothymidine and following the transplant, he was given a lower dose. There was no significant regimen-related toxicity, and he engrafted at day seventeen, but thereafter died of lymphoma at day forty seven. At autopsy, no evidence of HIV, either by culture, or PCR was found in tissue specimens. Although the result was poor, this early report demonstrated the achievability of the procedure and raised the intriguing question, could allogeneic transplant be a route to treat HIV infection.

Woolfrey et al (2008) published a series of two HIV-positive patients who received nonmyeloablative transplants at the Fred Hutchinson Research Center. They received conditioning with Fludarabine and 200 cGy total body irradiation. They got HLA-matched peripheral blood stem cells, one from a sibling and the other from an unrelated donor. Post-transplantation cyclosporine and mycophenolatemofetil were given for graft versus host disease pro-

phylaxis. HAART was continued with adjustments to prevent drug interactions. The HIV RNA remained undetectable and no HIV associated infections were noted. The first patient died of GVHD. The second patient remained alive at the time of publication, more than 180 days following transplant. It is notable that both patients' donor cells expressed wild-type CCR5 co receptor, and not the CCRΔ32 allele which is linked with resistance to HIV infection. Reconstitution of CD4+ and CD8+ subsets was in accordance with other nonmyeloablative transplants. New HIV-1 specific CD8+ T cell responses were produced after transplant. The gradual loss of detectable proviral DNA in the patient who achieved full donor chimerism suggests that the reservoir of latently infected lymphocytes died out after transplantation. This study alluded to the dual benefits of allogeneic transplantation.

Larger studies are needed to determine if the benefits of allogeneic transplant can be preserved in the myeloablative setting with its accompanying elevated morbidity and mortality. The largest series was a retrospective study of thirty patients with various hematologic malignancies transplanted between 1987 and 2003 from the European Group for Blood and Marrow Transplantation (Gupta V, et al, 2007). Treatment related mortality at 100 days was 46 percent. There was a striking difference in survival in patients transplanted after 1996 after availability of HAART. Prior to 1996, only two out of twenty two patients survived, but after 1996, four out of eight patients survived. This study revealed that reduction of transplant related mortality and control of HIV infection together are imperative in carrying out successful allogeneic transplants in this population.

4. Allogeneic transplantation for HIV infection

Allogeneic hematopoietic stem cell transplantation has the exciting prospect of controlling the HIV infection. HIV-1 enters host cells by binding to a CD4 receptor and then interacting with either CCR5 or the CXCR4 chemokine receptor (CXCR4). Homozygosity for a 32-bp deletion (delta 32) in the CCR5 allele confers natural resistance to infection with CCR5 tropic HIV strains (R5 HIV) because of the lack of CCR5 cell-surface expression. (Dean M et al, 1996 as cited in Allers et al, 2011)

A case report from Germany by Hutter et al (2009) published in the *New England Journal of Medicine* described a 40 year old patient with a ten year history of HIV who underwent allogeneic stem cell transplantation (SCT) in February 2007 for relapsed acute myelogenous leukemia from an HLA-matched unrelated donor who was homozygous for the CCR5 delta 32 allele. HAART was given until the day prior to transplantation. The patient relapsed at day 332 and was treated with a second transplant from the same donor after reinduction therapy with cytarabine and gemtuzumab along with single dose total body irradiation. There was no viral rebound twenty months after transplantation and discontinuation of antiretroviral therapy. Tissue sites, such as the intestines, serve as reservoirs, and were looked at to detect the HIV virus despite the absence of viremia. In this patient, the rectal biopsy performed at 159 days after transplant did reveal that CCR5-producing macrophages were still present in the intestinal mucosa, which demonstrated they had not yet been replaced by the new im-

immune system. Although these long-lasting cells from the host can be viral reservoirs even after transplantation, HIV-1 DNA was not found in his rectal mucosa. Immunologic studies showed a loss of anti-HIV virus specific interferon gamma producing T cells. This indicated that HIV antigenic stimulation was not present post transplant. His viral load continued to be undetectable despite the presence of non-CCR5 tropic X4 virus variants. After nearly two years of follow-up, the patient's CD4 cell count normalized with all cells exhibiting the homozygous CCR5-deleted gene. This observation is notable because homozygosity for CCR5 delta 32 deletion is related to high but not complete resistance to HIV-1.

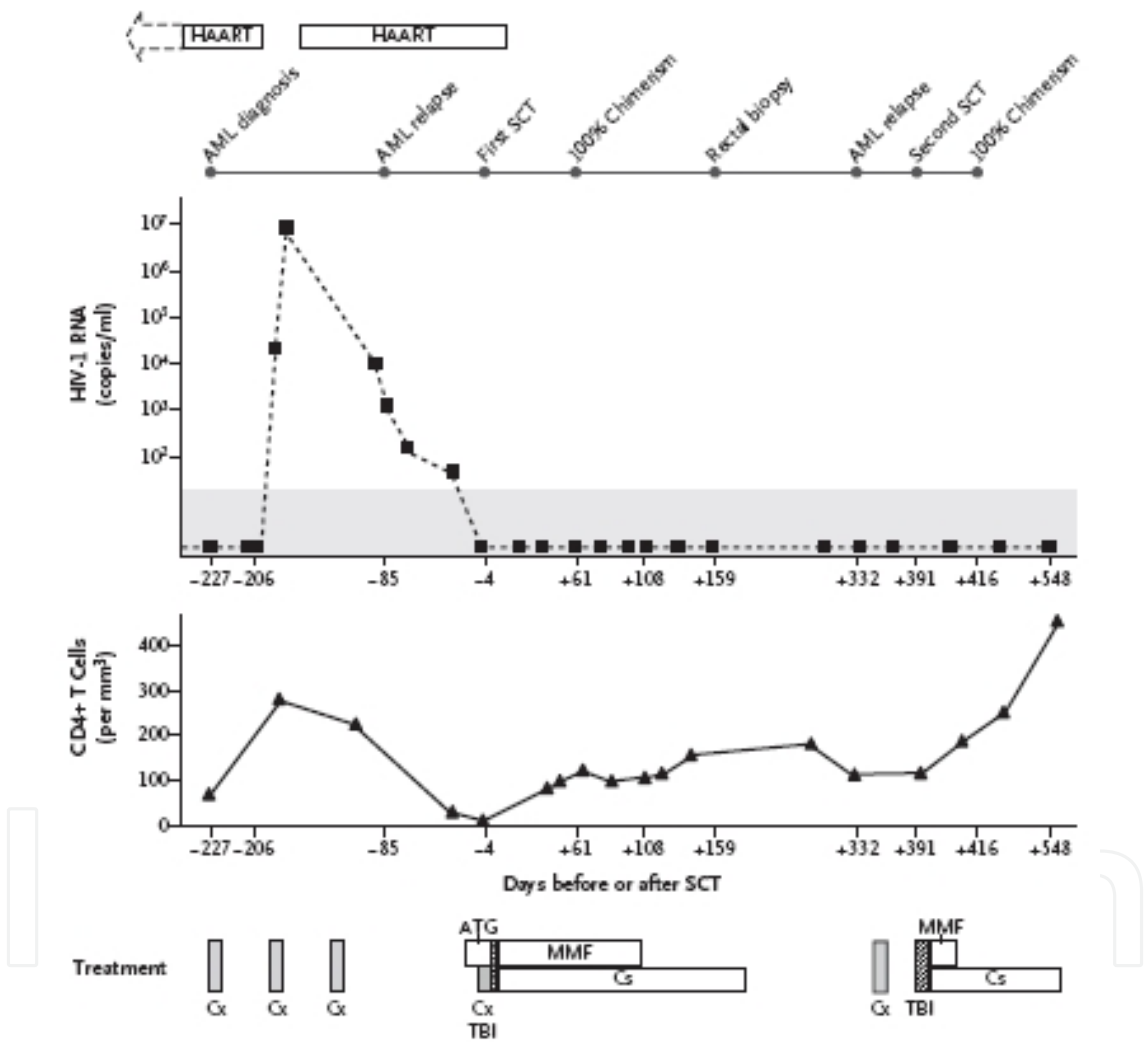


Figure 5. Clinical Course and HIV-1 Viremia. Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *The New England Journal of Medicine*, Vol. 360, No. 7, (February 2009) pp. 692-8. Permission granted. Copyright MMS

Allers et al (2011) published an article involving the same patient with extended follow-up, which reveals that he had remained off HAART and had no evidence of HIV disease for 45 months after the transplant. During his treatment course, he underwent multiple colonoscopies with biopsies to rule out GVHD, in addition to a liver biopsy and brain biopsy for

evaluation of leukoencephalopathy. This study also looked at 10 HIV negative stem cell transplant controls and 15 HIV negative healthy controls, 5 of whom underwent colonoscopy as a cancer preventive examination. It was found that CD4⁺ T cell reconstitution increased continuously and, after two years reached levels within the normal range of age matched healthy patients. There was 100 percent donor chimerism, which was shown by absent CCR5 expression. Among the CD4⁺ T cells, there were more activated effector memory cells and less naïve cells when compared with healthy controls. CD4⁺ T cell reconstitution also occurred in the gut mucosa of the reported patient, similar to the stem cell transplant control patients, with cells exclusively derived from the donor hematopoietic system. There was more than a twofold increase in mucosal CD4⁺ T cells in the transplant patients compared to healthy controls, which demonstrates that conditioning and transplant elicits the enrichment of HIV target cells in the gut mucosal immune system.

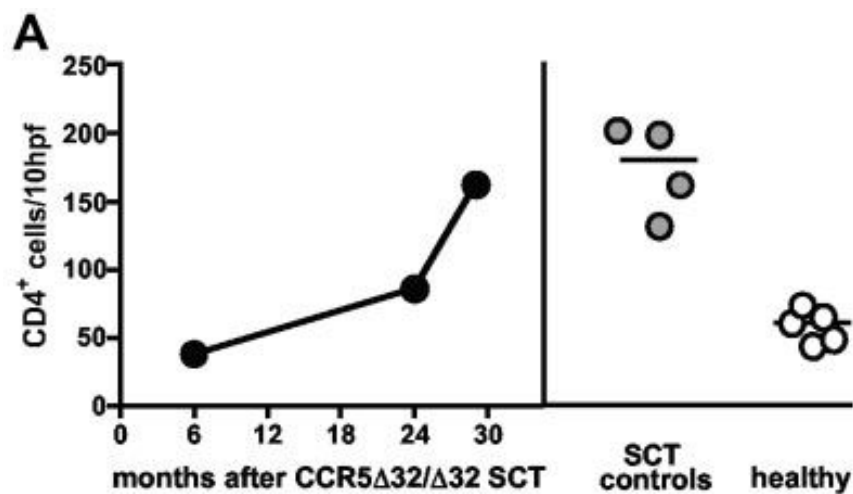


Figure 6. The mucosal immune system has been efficiently repopulated with donor-derived CD4⁺ T cells. (A) Immunohistochemical quantification of CD4⁺ T cells in colon tissue of the CCR5Δ32/Δ32 SCT patient, SCT control patients (27 ± 9 months after transplantation), and healthy control patients. The horizontal lines denote the median values of each group. Allers K, Hütter G, Hofmann J, et al. *Blood*. Vol. 117, No. 10, (March 2011), pp. 2790-2799. *Blood: journal of the American Society of Hematology* by American Society of Hematology. Copyright 2009 Reproduced with permission of AMERICAN SOCIETY OF HEMATOLOGY (ASH) in the format Journal via Copyright Clearance Center

HIV RNA and DNA were not detected in the peripheral blood or biopsy specimens obtained from various tissues. These biopsies revealed that tissue macrophages were ultimately replaced by donor-derived macrophages without CCR5 expression (Parker and Sereti, 2011). The T cells of the reported patient do not express normal levels of CXCR4 and appear vulnerable to X4-tropic HIV. HIV specific antibodies declined over time, with only envelope antibodies being detectable at the time of publication.

The study suggests that CCR5Δ32/Δ32 SCT has probably led to a cure of HIV infection in this patient. However it remains difficult to conclusively demonstrate eradication of HIV and its latent reservoirs, and the chance of resurgence of lingering X4 strains which survived the chemotherapy and radiation, leading to X4 HIV rebound still exists. Host-originating

CD4⁺ T cells appear to be totally removed from the immune system; however tissue macrophages are practically resistant to conditioning and less susceptible to the cytopathic effects of HIV infection, making them resilient viral reservoirs (Swingler S et al, 2007). One of the most promising findings of this report was the demonstration that later in the course of immune reconstitution, host-originating macrophages became undetectable in the GI mucosa by both phenotypic and genotypic analysis. These findings suggest that the replacement of host tissue cells with donor derived cells has reduced the size of the viral reservoir during the course of the immune reconstitution, which consequently had reduced the risk of HIV rebound over time.

5. Gene therapy and the future

Gooley et al (2010) reported impressive decreases in allogeneic transplantation-related mortality. Nevertheless, the risk of allogeneic SCT is inappropriately high to recommend it in the absence of an underlying malignancy that requires it as therapy. It cannot be proposed as a treatment strategy for the bulk of HIV-infected patients who can live long healthy lives with the use of HAART. Homozygosity for the delta 32 mutation is only found in a minority of the population, so it is not feasible to find such HLA-matched donors for the majority of patients. Preferably, one would aspire to integrate the benefits of transplantation of cells with the CCR5 mutation without the hazards of allogeneic SCT. One potential way to achieve this would be to transplant autologous stem cells that were genetically modified to be CCR5 negative. We have performed two trials at the City of Hope using this approach. The most recent employed a lentivirus-based system to transduce stem cells with a combination of three forms of anti-HIV RNA. This incorporated RNA1 in the form of a short-hairpin RNA targeted to an exon in HIV-1 tat/rev, a decoy for the HIV tat reactive element and a ribozyme that targets the host cell CCR5 chemokine receptor. Krishnan et al (2008) reported four patients with AIDS-related lymphoma transplanted with autologous lentiviral-transduced modified stem cells and unmanipulated stem cells following high-dose chemotherapy. All patients engrafted and exhibited low levels of genetically modified cells. Future trials will address how to augment engraftment of the genetically modified stem cells. Further plans are for planned interruption of HAART which would further demonstrate the functionality of these genetically modified cells. It is likely that an amalgamation of approaches with an aim to limit CD4 T cell targets and target viral reservoirs may be necessary to achieve a cure.

6. Conclusion

In the HAART era, the barrier of HIV infection as an obstacle to transplant has been broken. The role of ASCT has been well established in the HIV negative population for the treatment of relapsed or high-risk lymphoma. Numerous studies have now shown that ASCT can be safely performed in HIV-positive patients, and that it may lead to durable remissions in pa-

tients with HIV-related lymphomas. Similar to well controlled diabetes, well controlled HIV infection does not significantly increase the risk of infections following ASCT if a program of adequate surveillance and prophylaxis is used. Allogeneic stem cell transplantation remains a more difficult task, is still in its infancy, and lacks larger studies. The Hutter and Allers experience of allogeneic SCT with a CCR5 negative donor has given a name and face to the cure of HIV. The task of finding more feasible options for the enormous global population living with HIV remains.

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