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Hematopoietic Stem Cell Transplantation for AIDS related malignancies

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Abstract

Purpose of Review—AIDS related malignancies are an ongoing cause of mortality in individuals with HIV infection. In the HIV negative setting, high dose chemotherapy and stem cell transplantation (SCT) is an option for patients with hematologic malignancies. Prior to the advent of effective HIV therapy, SCT was not feasible for HIV positive patients. The purpose of this article is to explore the transplant options for HIV positive patients after widespread use of highly active antiretroviral therapy.

Recent Findings—The results of early autologous SCT studies were high relapse rates, but they did demonstrate that mobilization and engraftment of autologous stem cells was possible in AIDS patients. Recently, in less advanced AIDS lymphoma, ASCT resulted in low transplant related mortality (TRM) and durable remissions. In addition, case control studies of HIV positive versus HIV negative lymphoma patients undergoing ASCT have shown similar TRM and overall survival. The feasibility of allogeneic SCT in HIV infected individuals is less tested. There are challenges of drug interactions between HAART and immunosuppressive agents as well as the potential for higher infection rates.

Summary—The potential future applications of both autologous and allogeneic SCT are the cure of both the malignancy as well as the underlying HIV infection either by transplantation of naturally resistant or genetically modified stem cells.

Keywords

HIV; Stem; Cell; Transplantation

Introduction

The survival of patients with HIV infection dramatically improved after the introduction of highly active antiretroviral therapy.¹ Opportunistic infections that once typified the course of HIV infection and led to shortened survival are rare. However, certain AIDS defining and non-AIDS defining cancers continue to be a major source of mortality.² For example, the incidence of Hodgkin and non-Hodgkin lymphoma is increased in HIV infected patients compared to the general population. AIDS related lymphomas are typified by an advanced stage at presentation, and an aggressive clinical course.³

The treatment of AIDS related non-Hodgkin's lymphoma also changed after the introduction of highly active antiretroviral therapy. What was once the standard approach of low dose chemotherapy was supplanted by more aggressive therapy used in HIV negative patients such as R-CHOP. Furthermore, the remission rates seen when R-CHOP is combined with

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antiretroviral therapy approaches that of HIV negative patients.⁴ Hence, we are reaching an era where the standard treatment of HIV related lymphomas mirrors that of HIV negative patients.

It is therefore, not surprising that more aggressive therapies such as high dose chemotherapy and stem cell transplantation have been explored in the post HAART era. This review will highlight some of the recent studies of both autologous and allogeneic stem cell transplantation and discuss the future potential of hematopoietic stem cell transplantation in HIV positive patients.

Autologous Stem Cell Transplantation

Autologous stem cell transplantation in HIV positive patients was pioneered by the French in the pre HAART era.⁵ The initial patient, reported as a case study was a 40 year old male with HIV related NHL who was on Zidovudine and Zalcitabine for antiretroviral therapy. He was treated with BEAM (BCNU, Etoposide, Cytarabine, Melphalan) chemotherapy for relapsed lymphoma. The post transplant course was characterized by multiple opportunistic infections including cytomegalovirus viremia, mycobacterium pneumonia and cryptosporidiosis. Thus, this initial experience confirmed the concerns that the immune dysfunction conferred by the HIV infection would greatly increase risk of infection. Nonetheless, it also demonstrated the feasibility of mobilizing stem cells and successful engraftment in the bone marrow milieu of active virus.

In the post HAART era, French investigators initiated a larger trial.⁶ Their study included patients with refractory or relapsed lymphoma, seven out of the eight had undetectable viral loads at study entry. Conditioning regimens were either radiation based or chemotherapy alone. Four out of the eight were alive and in complete remission at the time of reporting, three died of lymphoma within the first six months post ASCT and one died of an opportunistic infection. The study, therefore, demonstrated that in the HAART era, the mortality due to infection was greatly reduced but that control of the underlying lymphoma remained the challenge.

The City of Hope experience included patients with less advanced lymphoma and excluded chemotherapy refractory patients.⁷ The initial series was comprised of twenty patients with either Hodgkin or NHL. All patients were on highly active antiretroviral therapy (HAART) and were required to have HIV viral loads <10,000 by RT PCR. The majority of patients received a chemotherapy based conditioning of CBV (cyclophosphamide, BCNU, etoposide). Engraftment times were similar to HIV negative patients, except for one patient who had delayed engraftment until day 23. This patient engrafted only after the discontinuation of the zidovudine that was part of his antiretroviral therapy. While all attempts possible were made to continue antiretroviral therapy throughout the transplant period, in reality only nine of the twenty were able to tolerate it. The others had either nausea or mucositis that prevented good tolerance of oral medication. Progression free survival was superior to the French series likely due to the inclusion of only chemosensitive patients. At the time of initial reporting the progression free survival (PFS) was 85% and overall survival 81%. The cohort has expanded to twenty eight patients and with a median of 41 months followup, the PFS remains high at 78%. In addition, transplant related mortality was low and no patient succumbed to an OI.

The Italian cooperative group on AIDS and tumors (GICAT) recently reported the long term results on fifty patients with HIV and relapsed/refractory lymphoma.⁸ Forty six patients were already on HAART, two started at the time of study enrollment and two at the time of stem cell mobilization. Interestingly, in contrast to the City of Hope eligibility, no viral load criteria were included, though CD4 counts >100 cells/ul before first line chemotherapy were

required. Hence, the viral loads at study entry ranged from 204–750,000 copies/ml. Of note, thirteen patients withdrew before stem cell collection. Two because of toxic death, thirteen due to progressive disease, one due to patient refusal. Ultimately, twenty seven patients underwent stem cell transplantation. Of these, seven temporarily suspended HAART some for similar reasons to the City of Hope experience; mucositis, others for hepatotoxicity. Three year PFS for the patients who proceeded to transplant was also similar at 76.3%. Multivariate analysis for prognostic factors for survival showed that marrow involvement, performance status <2, CD4 count <100 cells/ul were significant. An EBMT retrospective multicenter trial of sixty eight patients from twenty institutions has been recently published. At the time of transplant sixteen patients were in first complete remission (CR), 44 had more advanced disease including eight patients with chemorefractory disease. Relapse or progression occurred in 29.5% of patients. Analysis of prognostic factors demonstrated that histology other than diffuse large cell lymphoma, the use of more than two pre ASCT treatment lines, and not being in CR at the time of transplant were significantly associated with a higher risk of post ASCT relapse.⁹

Another multicenter trial, this time from the United States AIDS malignancy consortium had somewhat inferior results to the Italian and City of Hope experience.¹⁰ Initially twenty seven patients were enrolled and ultimately twenty went to transplant. The viral load allowed for study entry was much higher than the City of Hope trial at 110,000 copies/ml. However, this did not seem to have much impact in regards to early transplant related complications. However, long term outcome was inferior to the European and the City of Hope results, with event free survival 49.5% and overall survival 74.4%. It is unclear whether this is due to patient selection in regards to lymphoma status or due to poorer control of the underlying HIV infection or due to the lower intensity of the Busulfan based conditioning regimen that was used.

Case control studies have been performed to further delineate the effects of HIV status on outcome for HIV related lymphomas. A retrospective study from the EBMT compared fifty three HIV positive lymphoma patients who underwent transplant with controls matched for histology, non age adjusted IPI, and disease status at transplant.¹¹ In addition, three optional criteria of age at transplant, year and country of transplant were considered. Median follow up was 30 months. Overall survival was 61.5% (CI 47–76) for HIV positive patients and 70% for controls (p=NS). There was a trend towards delay in platelet engraftment post transplant in the HIV cohort. It is unclear whether this related to the higher use of GCSF in that group or to antiretroviral therapy or to chronic HIV infection. A nonstatistically significant difference in nonrelapse mortality was seen in the HIV cohort, primarily due to the higher rate of bacterial infections. Interestingly, although there was not a difference in relapse rates between groups, there was a favorable tendency for lower rates in the HIV lymphoma group. This same trend was seen in the City of Hope case control series. In that series twenty nine HIV positive patients were compared with HIV negative NHL patients. Two year disease free survival was 76% for HIV positive patients versus 56% for controls (p=NS). (unpublished data)

Future prospective studies will address the potential reasons for this improved outcome in the HIV positive patient. Some of the possibilities include the benefits of HAART chemotherapy. In the conventional chemotherapy setting, HIV lymphoma responders to HAART had improved survival.¹² Other theories are that the transplant procedure itself may introduce perturbations in the HIV virus such as depletion in the HIV reservoir by the high dose chemotherapy. Genotypic status of the patient may also influence outcome. The presence of the CCR5 delta 32 gene mutation in early studies has been shown to be protective against the risk of developing lymphoma.¹³ In our initial review of the genotypic status of our HIV ASCT patients, we found approximately 40% of our patients were

heterozygous for the delta 32 gene mutation.(unpublished data). A national trial of autologous stem cell transplantation for HIV lymphoma will be conducted through the BMT CTN network. As part of this trial, the genotypic status of patients will be evaluated and we will prospectively determine if this can be correlated with disease free survival. Correlative studies will also evaluate the HIV viral reservoir pre and post transplant.

Allogeneic Transplantation

Allogeneic hematopoietic stem cell transplantation poses a greater challenge due to the need for chronic immunosuppression in an already immunosuppressed patient. Solid organ transplantation paved the way for stem cell transplantation.¹⁴ The solid organ transplants laid to rest some of the concerns about immunosuppression. The underlying HIV infection was able to be controlled if patients remained on antiretroviral therapy. Drug interactions due to cytochrome P450 inhibition by certain antiretrovirals were managed by dose adjustments of calcineurin inhibitors.

Our now extensive experience with autologous hematopoietic stem cell transplants in HIV positive patients has demonstrated that HIV infection did not delay engraftment times as long as myelosuppressive medications such as azidothymidine are avoided. Hence one can anticipate similar engraftment times in the allogeneic setting. The pattern of immune recovery remains unknown. For example, in the HIV negative allogeneic transplant, T cell recovery is first with CD8+ cells, CD4+ recovery generally can take up to six months.¹⁵ A series of two HIV positive patients who underwent nonmyeloablative transplant at Fred Hutchinson Research Center demonstrates some of the potential of allogeneic hematopoietic stem cell transplant in regards to HIV immune responses.¹⁶ The two patients underwent a preparative regimen of fludarabine and 200 cGY total body irradiation. They received HLA matched peripheral blood stem cells from an HLA matched sibling or unrelated donor. HAART was continued throughout the transplant, though adjustments in HAART were made to avoid potential drug interactions. Reconstitution of CD4 and CD8 subsets was in keeping with other nonmyeloablative transplants. Further studies were done to see if the new HIV naïve donor cells could target HIV epitope specificities. The pattern of specificities of post transplantation donor cells was different from pretransplant patterns in that new HIV-1 specific CD8+ T cell responses were generated post transplant. In the patient that achieved full donor chimerism there was a loss of detectable proviral DNA which suggests that the pool of latently infected lymphocytes died out after transplantation. Hence this experience was suggestive that allogeneic transplantation may have two fold benefits.

Larger studies will need to be done to demonstrate if the benefits of allogeneic transplant can be sustained in the myeloablative setting with its attendant potential higher mortality. The largest series was a retrospective study of thirty patients transplanted between 1987 and 2003 from the EBMT.¹⁷ The relevance of this study is limited by the fact that HAART was not available till after 1996. The transplant related mortality was higher than in the HIV negative transplant setting at 46 %. Though, four of the eight patients in the post HAART era survived versus two of 22 patients in the pre HAART era.

Allogeneic Transplantation for HIV infection

The most intriguing aspect of allogeneic hematopoietic stem cell transplantation is its potential to also control HIV infection. A case report in the New England Journal of medicine demonstrated this point. A German patients with acute myelogenous leukemia underwent allogeneic stem cell transplantation from an HLA matched unrelated donor who was homozygous for the CCR5 for the delta 32 deletion.¹⁸ HAART was administered until day-1. The patient relapsed at day 332 and underwent a second transplant from the same donor with single dose TBI conditioning. Despite the absence of HAART, there was no

rebounding of the HIV viral load post transplant. The investigators went further and also looked for the HIV virus in compartments that can harbor the virus in the absence of detectable serum virus. The intestinal lamina propria is one important reservoir. In the patient rectal biopsy did reveal that CCR5 producing macrophages were still present in the intestinal mucosa which were therefore of host origin. But despite this, the HIV-1 DNA could not be detected in the rectal mucosa. Immunologic studies demonstrated a loss of anti HIV virus specific interferon Gamma producing T cells. This was suggestive that HIV antigen stimulation was not present after the transplant. Although the patient had non CCR5 tropic X4 variants of the virus as well, his HIV viral load remained undetectable. After nearly two years of follow up the patients CD4 count has returned to normal levels with all cells demonstrating the homozygous CCR5 deleted gene.

Ideally one would envision combining the benefits of the transplantation of cells with the CCR5 gene mutation but without the risks of allogeneic stem cell transplantation. One way to get this "best of both worlds" would be the transplantation of autologous stem cells that were genetically modified to be CCR5 negative. We have conducted two trials at the City of Hope with this approach. The most recent used a lentivirus based system to transduce stem cells with a combination of three forms of anti HIV RNA. This included RNAi in the form of 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. Four patients with AIDS related lymphoma were transplanted with autologous lentiviral transduced modified stem cells and unmanipulated stem cells after high dose chemotherapy. All patients engrafted and demonstrated low levels of genetically modified cells.¹⁹ Future trials will address how to increase levels of engraftment of the genetically modified stem cells. Ideally this would then allow patients to also discontinue HAART.

Conclusions

The barrier of HIV infection as an impediment to transplant has been broken. Multiple studies have now demonstrated that autologous stem cell transplantation can be performed safely in patients with underlying HIV infection and that the procedure may lead to durable remissions in patients with high risk AIDS related lymphomas. A large consortium based trial of autologous stem cell transplantation through the BMT CTN (clinical trials network) will open later this year. This trial will also encompass correlative studies evaluating the HIV reservoir, immunologic recovery and pharmacokinetic interactions with antiretroviral therapy and chemotherapy. In addition, another BMT CTN autologous stem cell transplantation trial for lymphoma in HIV negative patients will serve as a retrospective historical control arm. Allogeneic stem cell transplantation remains a higher hurdle to overcome. There are no large studies to support this approach yet and the largest retrospective series is hindered by the fact that most of the patients were in the pre HAART era. On the other hand, the Hutter experience of allogeneic stem cell transplantation with a CCR5 negative donor shows us a glimpse of the future where transplant will be used for both control of malignancy and HIV infection.

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