

Viral Infections Post Allogeneic Hematopoietic Cell Transplantation (Allo HCT)

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ABSTRACT

Abbreviations: ATG: Antithymocyte Globulin; TCD: T Cell Depletion; RIC: Reduced Intensity Conditioning; MUD: Matched Unrelated Donor Transplants; UCBT: Umbilical Cord Blood Transplant; DUCBT: Double Cord Blood Transplant; MRD: Matched Related Donor; GVHD: Graft-Versus-Host Disease

Introduction

Serious viral infections usually occur within the first six months following allogeneic hematopoietic transplant (AlloHCT) [1]. Following AlloHCT, EBV DNAemia can be detected in 31% of T-cell replete and 65% T-cell depleted (TCD) graft recipients. The incidence of PTLD is 224, 54 per 100,000 transplants during the first and second year following (AlloHCT) [2,3]. The risk factors for EBV PTLD include a high degree of HLA mismatch; ex vivo or in vivo T-cell depletion; and the intensity and duration of immunosuppression used for prophylaxis or treatment of graft versus host disease (GVHD) [3,4].

EBV PTLD develops in approximately 1% of patients post (AlloHCT). It is highly related to EBV reactivation. Risk factors that associate with high incidence of EBV-related PTLD include older age at transplant, T cell depletion-containing conditioning regimens, antithymocyte globulin (ATG) use, and grafts derived from unrelated or HLA-mismatched donors. PTLD can also develop in patients who received autologous stem cell transplants, but the frequency is much lower than AlloSCT [3-7] PTLD in AlloSCT cases occurs in younger age group, with shorter duration of onset as compared to (SOT) solid organ transplantation. EBV PTLD occurs more commonly in pediatric patients than in adults. The higher incidence in children is thought to result of being EBV-naive recipients. PTLDs can arise during post-transplant period

after both myeloablative and nonmyeloablative alloSCT. The degree and duration of immunosuppression plays a major role in the development of PTLD. Cytotoxic T cells provide a defense mechanism against EBV-infected B cells in immunocompetent individuals. However, T cell function is impaired post allogeneic transplant which leads to the development of PTLD. In vivo T cell depletion (TCD) with antithymocyte globulin (ATG) or Alemtuzumab (AL) is commonly used in AlloSCT. TCD facilitates engraftment and reduces the incidence and severity of GvHD. As reduced intensity conditioning (RIC) and matched unrelated donor transplants (MUD) are now being performed more frequently, ATG and AL have become integral components of preparative regimens. Delayed T cell reconstitution following T cell depletion accounts for infectious complications including PTLD which is associated with increased mortality [5,6].

EBV PTLD can occur later in the most severely immunocompromised patients with additional risk factors such as donor and recipient mismatch, graft manipulation with T cell depletion as well as the degree and duration of immunosuppression. Prevention of PTLD involves limiting the duration and degree of immunosuppression, while still maintaining the adequacy of the donor graft. Achieving a balance of reduction in immunosuppression and preventing graft rejection or graft-versus-host disease can be challenging. Anti-viral prophylaxis may also play a role in preventing PTLD.

The use of anti-viral agents such as acyclovir, valganciclovir, and ganciclovir are common for HSV, CMV, and EBV prophylaxis, though data is very limited for prevention of EBV PTLD [4-7].

Other Viral Infections

Other viral infections that occur early post-transplant include CMV, HHV6, BK and adenovirus, and usually correspond to degree of immunosuppression post-transplant [6,8]. However, the current literature lacks information on outcomes of viral infections as well as the influence of graft sources, such as comparison of outcomes between umbilical cord blood transplant (UCBT) and haploidentical transplant (haplo) with post-transplant cyclophosphamide (PTCy) [14]. These infections usually occur within in early post-transplant period prior to effective immune reconstitution [1-3]. Despite advances in antimicrobial therapy, severe infections still remain a major cause of death after alternative donor HCT [7-9].

In a study that compared 48 recipients of single UCBT with 144 recipients of unrelated BM or PB Allo HCTs, a Spanish group showed that the UCBT group had a higher risk of developing an infection, but infection-related mortality (25%) was similar in the two groups at 3 years [7-9]. HLA mismatch did not affect outcome in the UCBT group. The Minnesota group has demonstrated comparable rates of CMV infection between double cord blood transplant (dUCBT) and matched related donor (MRD) transplantation [7-9]. Cord blood contains fewer T cells than other stem cell sources, and cord blood lymphocytes have specific immunologic characteristics, such as different response pattern to cytokines and a greater proportion of naive T cells. In haploidentical transplant recipients, there is more NK cell alloreactivity, with therapeutic advantage after transplantation [12]. In a prospective analysis of immune reconstitution in dUCBT recipients and matched unrelated donor (MUD) recipients, Jacobson et al found that CD3 recovery was significantly delayed in the dUCBT group compared with the MUD group for as long as 6 months after allo HCT, including naive (CD45RO-) and memory (CD45RO+) CD4 T cells, regulatory (CD4CD25) T cells, and CD8 T cells [7-9]. These unique properties of UCB may contribute to a high risk of infection reported in some studies. Novel strategies are now being developed to combat viral infections including the virus-specific or trivirus-specific (adenovirus, Epstein-Barr virus, and cytomegalovirus) cytotoxic T lymphocytes [11-13]. Early diagnostic information regarding viral infections is critically important in the current era of emerging new therapies for viral infections.

CMV Infection

CMV infection occurs in 50%-80% of the population and CMV virus is maintained in a latent reservoir in mononuclear leukocytes. Containment of CMV in its latent state affects a large proportion of host immune repertoire. In young adults, 1%-2% of CD4 and CD8 T cells are CMV-reactive, which rise to up to 30%-40% in the elderly. For the majority of CMV-infected individuals, asymptomatic reactivation is effectively countered by innate and

adaptive immunity. In the immunocompromised AlloSCT patients, unconstrained viral replication and dissemination can lead to CMV disease, and increased mortality due to end-organ damage. The efficacy of conventional antiviral therapies including ganciclovir and foscarnet is limited in the setting CMV disease with end-organ involvement [15].

CMV-seropositive patients will experience CMV dissemination after AlloSCT, particularly in the context of transplant using T cell-depleted or matched unrelated donor (MUD) grafts. In CMV-seronegative patients, CMV infection is prevented through selection of CMV-seronegative grafts, but 20%-40% of CMV-seronegative patients who receive CMV-seropositive grafts develop primary CMV infection. Untreated, 50% of alloSCT patients with CMV reactivation will develop CMV disease. The current clinical practice uses close surveillance monitoring of CMV DNA burden by quantitative PCR. Preemptive antiviral pharmacotherapy and prophylactic therapy strategies are used to reduce the incidence of CMV disease after HSCT. Novel antiviral pharmacotherapies including maribavir, letermovir, brincidofovir are under clinical trial development but have not yet clearly demonstrated superiority/lesser toxicity in comparison with conventional agents [15].

Immunotherapeutic strategies to hasten T cell recovery after alloSCT remains a compelling alternative option as an adjunct to drug treatments. CMV-seropositive patients in receipt of T cell-depleted CMV-seronegative donor or cord blood grafts are at highest risk from CMV-associated morbidity and mortality. Patients with severe graft-versus-host disease (GVHD) and drug-induced T cell dysfunction are also at high risk of CMV-related morbidity. Recovery of CMV-specific CD4 responses is also critical to effective antiviral responses, and restoration of both antigen-specific CD4 and CD8 T cell populations to deliver long-term control of CMV is critical in this scenario [11-13].

Adenovirus Viral Infections

Adenovirus (AdV) is a member of the adenoviridae. AdV infections are much more common in pediatric patients (20%-26%) than in adults (9%) undergoing AlloSCT. In the severely immunocompromised patients, Adv can cause severe respiratory viral disease, hepatitis and colitis. Other complications include hemorrhagic cystitis and adenoviral keratoconjunctivitis. Adv infection can cause subclinical viremia, viremia with disease symptoms, and disseminated disease. The incidence of disseminated disease is 1%-7% with mortality of 8%-26%. Rapidly increasing or persistent viremia is associated with the occurrence of severe adenoviral disease both in children and in adults. Monitoring of the viral load by quantitative blood Adv (PCR) is far superior with high sensitivity. A study in adult AlloHCT recipients has reported an infection rate of 2.5% with pneumonia occurring in 24% of cases as the most common cause of death. Viral gastrointestinal shedding prior to transplant is found to be associated with increased risk of viremia after HCT [10].

Other Upper Respiratory Infections

The conditioning regimen have an impact on the incidence of respiratory virus infections, but patients with myeloablative and non-myeloablative conditioning have similar incidences for respiratory virus infections. However, in contrast to patients receiving non-myeloablative conditioning, LRI are significantly increased during the first 100 days post myeloablative ASCT [11,12].

Treatment of Respiratory Viral infections Post ASCT

A recent study described lower overall survival for patients with respiratory virus infection accompanied by bacterial co-infection causing increased mortality. The risk factors for increased mortality included lymphopenia, CMV DNAemia requiring antiviral therapy at the time of viral LRI and need for oxygen support. Over the past years, more respiratory infections in HCT recipients have been reported due to the use of new diagnostic methods including multiplex PCR with higher sensitivity, specificity and rapid turnaround time compared to convention viral culture and direct fluorescence antibody assays. Early diagnosis and treatment are important to improve outcomes of patients with viral URIs and LRIs [11,12].

CMV-specific T cell lines. An alternative to CMV-specific T cell clones is the use of CMV-specific T cell lines. In a clinical study, a single infusion of CMV-specific CD4 T cells showed plasma CMV clearance in 63% of patients. The HLA-A2-restricted pp65 peptide NLVPMVATV (NLV) is also being used but major disadvantage of the HLA-A2-restricted NLV peptide approach is the restriction of benefit to HLA-A2+ patients only. There are compelling data to suggest that virus-specific transferred T cells can engraft and expand and have the potential to mediate clinical responses [13-15].

Multi Virus Specific T Cell Lines (Multi-VST)

Multi-VST lines represent an interesting option to target multiple viral infections using adoptive cell therapy. Such lines can be manufactured either with APC systems using overlapping peptide pools from multiple viruses, or with other gene transfer approaches by the use of an adenoviral vector encoding the CMV-associated pp65 antigen to transduce APCs (MoDCs and EBV-transformed lymphoblastoid cell lines [LCLs]) before coculture with PBMCs or naive cord blood. This method delivers both MHC class I-dependent processing and expansion of CMV-reactive CD8 T cells, and MHC class II-dependent processing and presentation of adenovirus/EBV/CMV-associated peptides to drive expansion of virus-specific CD4 T cells. The adenoviral transfer vector promotes anti-adenoviral T cell specificity (bisppecific cytotoxic T lymphocytes [CTLs]), and if EBV-transformed B cells are used in lieu of MoDCs, then additional EBV-specificity is generated (trisppecific CTLs) [13-15].

A clinical study of trisppecific CTLs administered prophylactically after demonstrated CMV-specific reactivity in 70% of patients with no increase in the incidence of GVHD. In this study, CMV- and

EBV-specific T cell numbers rose in the absence of viral reactivation, but adenoviral-CTL expansion was only observed in the context of adenoviral infection. More recent studies have used nucleofection to introduce DNA plasmids encoding multiple immunogenic antigens from CMV, EBV, and adenovirus into APCs, or have used viral antigen-derived 15-mer peptide libraries (pepmix) with APCs to deliver a product with a broader CMV-reactive T cell repertoire [13-15].

Conclusion

Increased number of viral infections both systemic and upper respiratory tract occur post allogeneic transplant due to ineffective immune reconstitution. Early diagnosis and treatment are critically important to reduce morbidity and mortality associated with these infections post ASCT. Viral infections cause morbidity and mortality in immunosuppressed following AlloSCT recipients due to inability of host immune system to limit viral replication and dissemination, and loss of T cell function is central to this effect. Immunotherapeutic strategies to accelerate reconstitution of virus-specific immunity and to hasten T cell recovery after HSCT remain a compelling alternative to drug treatments. CMV- and EBV-directed virus-specific T cells (VSTs) are being used in the settings of both SOT and AlloHST with profound immunosuppression. Emerging evidence supports the use of VSTs for treatment of broader range of viral targets, including varicella-zoster virus, adenovirus, and BK virus [11-15].

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