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DEVELOPING OF VIRAL INFECTIONS IN HEMATOPOIETIC STEM-CELL TRANSPLANT (HSCT) RECIPIENTS

Boltaboyev Murodiljon Umarovich
Assistant of the Department Infectious Diseases of Fergana Public Health Medical Institute

Abstract
Transplantation of hematopoietic stem cells from bone marrow or from peripheral or cord blood for cancer, immunodeficiency, or autoimmune disease results in a transient state of complete immunologic incompetence. Immediately after transplantation, both phagocytes and adaptive immune cells (T and B cells) are absent, and the host is extremely susceptible to infection. The reconstitution that follows transplantation has been likened to maturation of the immune system in neonates. The analogy does not entirely predict infections seen in HSCT recipients, however, because the new cells mature in an old host who has several latent infections already.

Keywords: hematopoietic stem-cell transplant (HSCT), herpes simplex virus, cytomegalovirus, varicella-zoster virus, human herpes virus, Epstein- Barr virus (EPB)

Introduction

HSCT recipients are susceptible to infection with a variety of viruses, including primary and reactivation syndromes caused by most HHVs and acute infections caused by viruses that circulate in the community.

Herpes Simplex Virus: within the first 2 weeks after transplantation, most patients who are seropositive for HSV-1 excrete the virus from the oropharynx. The ability to isolate HSV declines with time. Administration of prophylactic acyclovir (or valacyclovir) to seropositive HSCT recipients has been shown to reduce mucositis and prevent HSV pneumonia (a rare condition reported almost exclusively in allogeneic HSCT recipients). Both esophagitis (usually due to HSV-1) and anogenital disease (commonly induced by HSV-2) may be prevented with acyclovir prophylaxis.

Varicella-Zoster Virus: reactivation of herpes zoster may occur within the first month, but more commonly occurs several months after transplantation. Reactivation rates are ~40% for allogeneic recipients and 25% for autologous recipients. Localized zoster can spread rapidly in an immunosuppressed patient. Fortunately, disseminated disease can usually be controlled with high doses of acyclovir. Because of frequent dissemination among patients with skin lesions, acyclovir is given prophylactically in some centers to prevent severe disease. Low-doses of acyclovir (400 mg orally, three times daily) appear to be effective in pre venting reactivation of VZV. However, acyclovir can also suppress the development of VZV-specific immunity. Thus, its administration for only 6 months after trans plantation does not prevent zoster from occurring when treatment is

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stopped. Some data suggest that administration of low doses of acyclovir for an entire year after transplantation is effective and may eliminate most cases of posttransplantation zoster.

Cytomegalovirus, the onset of CMV disease (interstitial pneumonia, bone marrow suppression, graft failure, hepatitis/colitis) usually begins 30–90 days after transplantation, when the granulocyte count is adequate but immunologic reconstitution has not occurred. CMV disease rarely develops earlier than 14 days after transplantation and may become evident as late as 4 months after the procedure. It is of greatest concern in the second month after transplantation, particularly in allogeneic HSCT recipients. In cases in which the donor marrow is depleted of T cells (to prevent GVHD or eliminate a T-cell tumor), the disease may be manifested earlier. The use of alemtuzumab to prevent GVHD in nonmyeloablative transplantation has been associated with an increase in CMV disease. Patients who receive ganciclovir for prophylaxis, preemptive treatment, or treatment (see below) may develop recur rent CMV infection even later than 4 months after transplantation, as treatment appears to delay the development of the normal immune response to CMV infection. Although CMV disease may present as isolated fever, granulocytopenia, thrombocytopenia, or gastrointestinal disease, the foremost cause of death from CMV infection in the setting of hematopoietic stem-cell trans plantation is pneumonia. With the standard use of CMV-negative or filtered blood products, primary CMV infection should be a risk in allogeneic transplantation only when the donor is CMV seropositive and the recipient is CMV-seronegative. Reactivation disease or superinfection with another strain from the donor is also common in CMV-positive recipients, and most seropositive patients who undergo hematopoietic stem-cell transplantation excrete CMV, with or without clinical findings. Serious CMV disease is much more common among allogeneic than autologous recipients and is often associated with GVHD. In addition to pneumonia and marrow suppression (and, less often, graft failure), manifestations of CMV disease in HSCT recipients include fever with or without arthralgias, myalgias, hepatitis, and esophagitis. CMV ulcerations occur in both the lower and the upper gastrointestinal tract, and it may be difficult to distinguish diarrhea due to GVHD from that due to CMV infection. The finding of CMV in the liver of a patient with GVHD does not necessarily mean that CMV is responsible for hepatic enzyme abnormalities. It is interesting that the ocular and neurologic manifestations of CMV infections are uncommon in these patients. Management of CMV disease in HSCT recipients includes strategies directed at prophylaxis and preemptive therapy (suppression of silent replication) and at treatment of disease. Prophylaxis results in a lower incidence of disease at the cost of treating many patients who otherwise would not require therapy. Because of the high fatality rate associated with CMV pneumonia in these patients and the difficulty of early diagnosis of CMV infection, prophylactic IV ganciclovir (or oral valganciclovir) has been used in some centers and has been shown to abort CMV disease during the period of maxi mal vulnerability (from engraftment to day 120 after trans plantation). Ganciclovir also prevents HSV reactivation and reduces the risk of VZV reactivation; thus acyclovir prophylaxis should be discontinued when ganciclovir is administered. The foremost problem with the administration of ganciclovir relates to adverse effects, which include dose-related bone marrow suppression (thrombocytopenia, leukopenia, anemia, and pancytopenia). Because the frequency of CMV pneumonia is lower among autologous HSCT recipients (2–7%) than among allogeneic HSCT recipients (10–40%), prophylaxis in the former group will not

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become the rule until a less toxic oral antiviral agent becomes available. Promising new drugs that are now being assessed in clinical trials include maribavir, a benzimidazole ribonucleoside that inhibits a viral protein kinase activity (UL97). Like prophylaxis, preemptive treatment, which targets patients with polymerase chain reaction (PCR) evidence of CMV, entails the unnecessary treatment of many individuals (on the basis of a laboratory test that is not highly predictive of disease) with drugs that have adverse effects. Currently, because of the neutropenia associated with ganciclovir in HSCT recipients, a preemptive approach-that is, treatment of those patients in whose blood CMV is detected by an antigen or nucleic acid amplification test-is used at most centers. This approach is almost as effective as prophylaxis and causes less toxicity. Quantitative viral load assays, which are not dependent on circulating polymorphonuclear leukocytes, have sup planted antigen-based assays and are used by most centers. A positive test (or increasing viral load) prompts the initiation of preemptive therapy. When prophylaxis or pre-emptive therapy is stopped, late disease may occur, although by then the patient is often equipped with improved graft function and is better able to combat disease. Treatment of CMV pneumonia in HSCT recipients (unlike that in other clinical settings) involves both IV immune globulin (IVIg) and ganciclovir. In patients who cannot tolerate ganciclovir, foscarnet is a useful alternative, although it may produce nephrotoxicity and electrolyte imbalance. When neither ganciclovir nor foscarnet is clinically tolerated, cidofovir can be used; however, its efficacy is less well established, and its side effects include nephrotoxicity. Case reports have suggested that the immunosuppressive agent leflunomide may be active in this setting, but controlled studies are lacking. Maribavir is under investigation for treatment as well as pro phylaxis. Transfusion of CMV-specific T cells from the donor decreased viral load in a small series of patients; this result suggests that immunotherapy may play a role in the treatment of this disease in the future.

Human Herpesviruses 6 and 7. HHV-6, the cause of roseola in children, is a ubiquitous herpesvirus that reactivates (as determined by quantitative plasma PCR) in ~50% of HSCT recipients 2–4 weeks after transplantation. Reactivation is more common among patients requiring glucocorticoids for GVHD and among those receiving second transplants. Reactivation of HHV-6 (primarily type B) appears to be associated with delayed monocyte and platelet engraftment. Although encephalitis developing after transplantation has been associated with HHV-6 in cerebrospinal fluid (CSF), the causality of the association is not well defined. In several cases, plasma viremia was detected long before the onset of encephalitis; nevertheless, patients with encephalitis did tend to have very high viral loads in plasma at the time of CNS illness. HHV-6 DNA is sometimes found in lung samples after transplantation. However, its role in pneumonitis is also unclear. Although HHV-6 has been shown to be susceptible to foscarnet (and possibly to ganciclovir) in vitro, the efficacy of antiviral treatment has not been well studied. Little is known about the related herpesvirus HHV-7 or its role in posttransplantation infection.

Epstein-Barr Virus. Primary EBV infection can be fatal to HSCT recipients; EBV reactivation can cause EBV–B-cell lymphoproliferative disease (EBV-LPD), which may also be fatal to patients taking immunosuppressive drugs. Latent EBV infection of B cells leads to several interesting phenomena in HSCT recipients. The marrow ablation that occurs as part of the HSCT procedure may sometimes eliminate latent EBV from the host. Infection can then be reacquired immediately after transplantation by trans fer of infected donor B cells. Rarely, transplantation from a

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seronegative donor may result in cure. The recipient is then at risk for a second primary infection. EBV-LPD can develop in the recipient's B cells (if any survive marrow ablation) but is more likely to be a consequence of outgrowth of infected donor cells. Both lytic and latent EBV replication are more likely during immunosuppression (e.g., they are associated with GVHD and the use of antibodies to T cells). Although less likely in autologous transplantation, reactivation can occur in T-cell–depleted autologous recipients (e.g., patients being given antibodies to T cells for the treatment of a T-cell lymphoma with marrow depletion). EBV-LPD, which can become apparent as early as 1–3 months after engraftment, can cause high fevers and cervical adenopathy resembling the symptoms of infectious mononucleosis but more commonly presents as an extranodal mass. The incidence of EBV-LPD among allogeneic HSCT recipients is 0.6–1%, which contrasts with figures of ~5% for renal transplant recipients and up to 20% for cardiac transplant patients. In all cases, EBV-LPD is more likely to occur with high-dose, prolonged immunosuppression, especially that caused by the use of antibodies to T cells, glucocorticoids, and calcineurin inhibitors (e.g., cyclosporine, FK506). PCR can be used to monitor EBV production after hematopoietic stem-cell transplantation. High or increasing viral loads predict an enhanced likelihood of devel oping EBV-LPD and should prompt rapid reduction of immunosuppression and search for a focus of disease. If reduction of immunosuppression does not have the desired effect, administration of a monoclonal antibody to CD20 (rituximab or others) for the treatment of B-cell lymphomas that express this surface protein has elicited dramatic responses and currently constitutes first-line therapy for CD20-positive EBV-LPD. However, long term suppression of new antibody responses accompanies therapy, and recurrences are not infrequent. Additional B-cell–directed antibodies, including anti-CD22, are under study. The role of antivirals is uncertain because no available agents have been documented to have activity against the different forms of latent EBV infection. Preventing lytic replication in these patients would theoretically produce a statistical decrease in the frequency of latent disease by decreasing the number of virions available to cause additional infection. In case reports and small animal studies, ganciclovir and/or high-dose zidovudine together with other agents has been used to eradicate EBV-LPD and CNS lymphomas, another EBV-associated complication of transplantation. Both interferon and retinoic acid have been employed in the treatment of EBV-LPD, as has IVIg, but no large prospective studies have assessed the efficacy of any of these agents. Several additional drugs are undergoing preclinical evaluation. Standard chemotherapeutic regimens have been used as a last resort, even though patients' tolerance and long term results have been disappointing. EBV-specific T cells generated from the donor have been used experimentally to prevent and to treat EBV-LPD in allogeneic recipients, and efforts are underway to increase the activity and specificity of ex vivo–generated T cells.

All in all, to receiving antibiotic prophylaxis, transplant recipients should be vaccinated against likely pathogens. In the case of HSCT recipients, optimal responses cannot be achieved until after immune reconstitution, despite previous immunization of both donor and recipient. Recipients of allogeneic HSCTs must be reimmunized if they are to be protected against pathogens. The situation is less clear-cut in the case of autologous transplantation. T and B cells in the peripheral blood may reconstitute the immune response if they are transferred in adequate numbers.

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