Prophylaxis and Treatment of Cytomegalovirus Infection after Solid Organ Transplantation

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Summary

Cytomegalovirus (CMV) infection occurs in the majority of patients following solid organ transplantation. The mainstay of treatment for symptomatic CMV infection in this patient population is intravenous ganciclovir and, to a lesser extent, foscarnet. Methods of preventing CMV infection include: (i) protective matching; (ii) use of CMV-seronegative, filtered or leucocyte-poor blood products; (iii) active immunisation with a vaccine; (iv) passive immunisation with immunoglobulins; (v) prophylaxis with antiviral agents such as interferons, aciclovir (acyclovir), ganciclovir or foscarnet; and (vi) pre-emptive therapy.

Protective matching is not feasible due to the scarcity of donor organs. CMV-seronegative, filtered or leucocyte-poor blood products should be used, at least in seronegative recipients. A live attenuated CMV vaccine has been shown to be of limited efficacy in preventing CMV disease in renal transplantation recipients; however, a subunit vaccine is in development. Prophylaxis with immunoglobulins has been shown to be effective in some solid organ transplantation populations; however, the cost of such an approach is considerable. Of the antiviral agents, intravenous ganciclovir is the only agent that has been shown to have some degree of prophylactic efficacy in the majority of solid organ transplantation recipients. However, the cost and need for intravenous access make intravenous
ganciclovir a suboptimal prophylactic agent. Several newer drugs, including oral agents, are currently being studied in this mode. Pre-emptive therapy, based either on the early detection of CMV or the targeting of patients with risk factors for CMV, appears to be a promising new approach.

Cytomegalovirus (CMV) infection occurs in the majority of solid organ transplant recipients,[11] primarily in the first 3 post-transplantation months when immunosuppression is most intense. As an example, symptomatic CMV disease occurs in 8, 29, 25 and 39% of kidney, liver, heart and heart-lung transplantation recipients, respectively.[12] CMV may be transmitted to transplant recipients via infected donor organs or cellular blood products; the former is the primary source of CMV infection after solid organ transplantation.[13]

Three major patterns of CMV transmission are observed in solid organ transplantation recipients. Primary infection occurs when a CMV-seronegative individual receives cells latently infected with the virus from a seropositive donor, followed by viral reactivation. Secondary infection or reactivation infection occurs when endogenous latent virus is reactivated in a CMV-seropositive individual post-transplantation. Thirdly, superinfection or reinfec­tion occurs when a seropositive recipient receives latently infected cells from a seropositive donor and the virus that reactivates post-transplantation is of donor origin.

In immunosuppressed solid organ transplant recipients, CMV has 3 major effects. (i) It causes infectious diseases syndromes, including fever, malaise, arthralgias, leucopenia and thrombocyto­penia, as well as organ involvement including pneumonitis, hepatitis, gastrointestinal involvement and retinitis, among others. (ii) It has been implicated in causing increased immunosuppression, which may explain the frequent association of CMV with other opportunistic infections, such as fungal and Pneumocystis infections.[14] (iii) It has been associated with allograft rejection in the form of early-onset allograft rejection in renal transplant recipients,[5] and chronic allograft rejection (allograft atherosclerosis) in cardiac transplant recipients.[6] CMV infection, therefore, has a potential impact on both patient and graft outcome following solid organ transplantation.

Following primary infection with CMV, long term cellular and humoral immunity usually develop, but CMV remains latent or persistent within the host. Immunosuppression administered follow­ing transplantation may lead to uncontrolled viral replication and consequently symptomatic CMV in­fection. A patient without prior immunity to CMV who receives an organ with latent or persistent vi­rus (primary infection) is at higher risk of uncontrolled replication than a patient who had prior im­munity to CMV pretransplant (secondary infection or reinfection). Likewise, the higher the degree of immunosuppression, the higher the risk of uncontrolled viral replication. For these reasons, certain patient characteristics place transplant recipients at risk for CMV infection. These include characteristics such as the CMV serology of the donor and the recipient (the seronegative recipient of an organ from a seropositive donor is at highest risk), the use of antilymphocyte preparations, and fulminant hepatitis at the time of transplantation (in liver transplant recipients).[7·8] Identifying such risk factors should potentially enable pre-emptive stra­tegies in solid organ transplant recipients.

The treatment and to some extent the prevention of CMV infection have evolved dramatically in the last 10 years. This is due to the introduction of effective antiviral agents with low toxicity in the con­text of the newer diagnostic techniques discussed in section 1, and will be the subject of the remain­der of this review.

1. Diagnosis

The diagnosis of CMV infection in tissue has traditionally been based on the recognition of cyto­megalic inclusion bodies,[9] CMV may also be de-