CLINICAL UPDATE

Advances in the Treatment of CMV Infection

New Insights Into Cytomegalovirus Infection After Allogeneic Hematopoietic Stem Cell Transplant

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H&O How common is CMV infection among patients undergoing allogeneic hematopoietic stem cell transplant?

MB Cytomegalovirus (CMV) reactivation occurs in approximately 50% to 70% of seropositive patients undergoing allogeneic transplant. The rate varies depending on the diagnostic method that is used to identify reactivation. Among settings in which the donor is seropositive and the recipient is negative, the incidence is 20% to 25% (Figure).

H&O What risk factors have been identified for CMV reactivation and the development of CMV infection?

MB The CMV serostatus is important, with CMV seropositivity of the recipient being the highest-risk setting. CMV donor serostatus can affect the severity of CMV infection among seropositive recipients. However, even if both the donor and the recipient are seronegative and "CMV-safe" blood is used, CMV infection occurs in approximately 1% of patients. The conditioning regimen, including T-cell depletion, can affect the risk of reactivation, the viral load kinetics, and the time to first reactivation, as well.

H&O Is there a viral threshold for treatment of CMV reactivation?

MB The exact threshold for treatment is still an area of controversy. Different thresholds have been used at different sites and clinical trials, and vary according to the severity of immunosuppression. For example, the recently completed phase 3 trials of letermovir and brincidofovir both used 137 IU/mL in high-risk patients.

> The first 3 months after allogeneic transplant are considered the high-risk period, and some patients require prolonged treatment of up to 1 year.

In low-risk patients, however, the thresholds were 274 IU/mL in the letermovir trial and 1000 IU/mL in the brincidofovir trial.

H&O How is CMV monitored in allogeneic transplant patients?

MB The most common approach to monitoring is to perform a polymerase chain reaction (PCR) assay once or twice a week to identify the virus during the high-risk period and then to use an antiviral agent if the test becomes positive at a certain level. Then treatment will

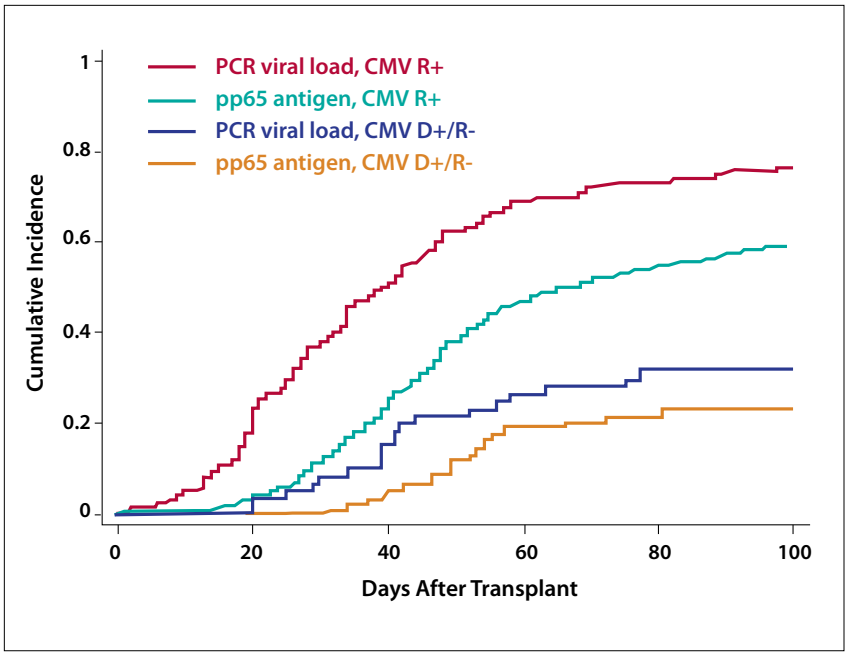

Figure. The cumulative incidence of reactivation of CMV by day 100 after hematopoietic cell transplant. CMV, cytomegalovirus; D, donor; PCR, polymerase chain reaction; R, recipient. Adapted from Green ML et al. *Biol Blood Marrow Transplant*. 2012;18(11):1687-1699. doi:10.1016/j.bbmt.2012.05.015. Permission granted through: https://creativecommons.org/licenses/by-nc-nd/4.0/.

be administered for several weeks until the PCR assay becomes negative. This strategy is called "preemptive therapy." The first 3 months after allogeneic transplant are considered the high-risk period, and some patients require prolonged treatment of up to 1 year.

H&O What signs or symptoms indicate CMV infection after allogeneic transplant?

MB The overwhelming majority of patients with blood reactivation are asymptomatic. When symptoms do occur, they vary depending on the part of the body that is affected. Gastrointestinal symptoms include nausea and epigastric pain when the infection is in the stomach or duodenum, and severe diarrhea and cramps when it is located in the lower gastrointestinal tract. Infection in the lungs can lead to signs and symptoms of pneumonia, such as cough and shortness of breath. If the eyes or central nervous system are infected, changes in vision or signs of encephalitis may occur.

H&O What is the morbidity associated with CMV infection after allogeneic transplant?

MB The morbidity includes direct and indirect effects. The direct effects are those just mentioned: gastrointestinal disease, pneumonia, and retinitis or encephalitis. The virus also has a profound impact on the immune reconstitution of the stem cell transplant recipient and increases the risk of other infections, especially fungal infections. These sequelae are termed indirect effects. All effects combined lead to a survival disadvantage that is observed in seropositive recipients.

H&O What are the management approaches?

MB Management includes the use of antiviral agents or CMV-specific T cells. CMV-specific T cells are in an earlier phase of development and usually reserved for more serious infections. As I mentioned, when CMV is detected in the blood, preemptive therapy will involve administration of an antiviral drug for 2 to 3 weeks or until the virus becomes undetectable. These treatment courses are repeated as needed during the high-risk period after transplant.

When patients already have signs and symptoms of end-organ disease, antivirals are given but usually at higher doses and for longer periods, sometimes in combination with immunoglobulin (eg, in patients with CMV pneumonia). For more complicated situations, such as refractory infections or resistant disease, therapy sometimes consists of antivirals given in combination or T-cell products. However, to date, no good evidence from randomized trials exists that demonstrates which of these approaches is superior.

In addition to the early treatment of disease, there is also a prophylactic approach, in which an antiviral drug or a vaccine is given up front to all seropositive transplant recipients. For this approach, there is a strong need for the treatment to be very well-tolerated and nontoxic. With the currently available drugs, this strategy is not frequently used. It is an option, however, when justified

by the risk-benefit ratio, for example, in situations when PCR testing is not available and/or the CMV disease risk is very high owing to the transplant protocol that is used. Newer drugs and vaccines under development may be more suited for prophylaxis.

Disclosure

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Suggested Readings

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