Advances in Preventing Cytomegalovirus Disease in Stem Cell Transplant Recipients

a report by

Karen K Biron[1] *and* **Per Ljungman**[2]

1. Past President, International Society for Antiviral Research (ISAR);

2. Past President and Secretary, European Group for Blood and Marrow Transplantation (EBMT)

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Prevalence of Cytomegalovirus

Infection with the human herpesvirus cytomegalovirus (CMV) is a common occurrence, with an estimated 40–85% of the population in Europe and North America infected and harbouring the virus in a dormant form.[1] The incidence of infection increases with age and is more common in women than in men, but infection rates depend on various factors, including global location and socioeconomic class.[2,3] Although not highly contagious, transmission of CMV occurs through close contact with bodily fluids from an infected individual.

Pathophysiology of Cytomegalovirus

The majority of immunocompetent individuals will experience few, if any, symptoms upon exposure to CMV.[3] Some individuals may experience sore throats or symptoms similar to those of infectious mononucleosis,[4,5] with fever and mild hepatitis. Like all herpesviruses, CMV has the characteristic ability to remain latent in the body during an infected individual's lifespan. The virus frequently re-emerges when an individual is immunosuppressed for health or medical reasons.

All patients undergoing conventional allogeneic haematopoietic stem cell transplants (SCTs) experience significant immunodeficiency and most also become neutropenic – factors that significantly contribute to serious post-transplantation complications and infections.[6] Many transplant recipients are already seropositive through previous exposure to the virus, and these seropositive patients are considered at high risk of CMV disease. In addition, transmission from seropositive donors to seronegative recipients is also an important risk factor for CMV disease. CMV infection in immunosuppressed or immuno-compromised patients is a serious threat, associated with high rates of morbidity and mortality.[7,8] Pneumonia and enteritis are the more common clinical manifestations of CMV disease in allogeneic haematopoietic SCT recipients. In CMV-seropositive recipients, active CMV infections occur in 70–80% of patients. Before antiviral intervention was introduced, 20–35% developed CMV disease. Active infection will develop in approximately 15% of seronegative individuals receiving stem cells from a seropositive donor.[9] Even with the administration of antiviral treatment, CMV pneumonia remains associated with a significant risk of mortality.[10,11]

Current Management Approaches

Two antiviral strategies are used in the management of CMV disease risk in transplant recipients. One strategy is pre-emptive antiviral intervention, in which high-risk patients are monitored via sensitive diagnostic assays for the presence of CMV viraemia, antigenaemia or DNA-aemia, and therapy is initiated upon detection of primary or reactivated CMV infection.[12] Another strategy, known as universal prophylaxis, administers an antiviral drug to all patients at risk of CMV infection, as assessed from the pre-transplantation seropositive status of the donor or recipient. The start of antiviral chemoprophylaxis is determined by the agent chosen. Drugs without marrow toxicity (acyclovir, valacyclovir, foscarnet) can be started before SCT, while ganciclovir is started after engraftment and continued for the first three months after transplantation, with the goal of preventing CMV disease. Neither strategy has been shown to be a superior CMV management approach for the prevention of CMV disease.[12]

Studies into the prevention of CMV disease in SCT patients with pre-emptive therapy have shown a reduction in the incidence and mortality rate of CMV disease. Some physicians prefer pre-emptive therapy because it specifically treats the subpopulation of the entire patient cohort that is most at risk of CMV disease, thereby decreasing the risk of side effects and the overall treatment costs. Universal prophylaxis is also effective in preventing CMV disease. However, the lack of good prophylactic drug options on the market is a major drawback to the prophylactic approach: existing drugs are either too poor in efficacy or too toxic for use in a standard prophylactic manner.

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Ganciclovir is effective for the prevention of CMV disease as well as for the treatment of patients with serious and life-threatening CMV infections. Ganciclovir is currently the most commonly used treatment for stem cell or bone marrow transplant patients, but also commonly induces the adverse effects of nephrotoxicity and myelosuppression – which encompasses neutropenia, granulocytopenia and thrombo-cytopenia – thereby limiting its use in patients with already suppressed bone marrow function.[13] Foscarnet was shown in a randomised study to have similar efficacy and toxicity to ganciclovir and is a good alternative, especially in myelosuppressed patients. Cidofovir given weekly can be used as a third-line treatment, especially in patients with CMV disease not responding to ganciclovir or foscarnet, but its use is hampered by renal toxicity.

The availability of effective antiviral drugs for CMV and, in particular, ganciclovir as pre-emptive therapy has changed the field substantially, and has improved treatment options. However, the currently available drugs are limited by a number of drawbacks in addition to toxicity. Ganciclovir and foscarnet both require twice-daily intravenous administration. Ganciclovir can also be administered through intravitreal implant to patients with ocular disease (CMV retinitis). However, the orally available prodrug valganciclovir is a valyl ester formulation of ganciclovir with bioavailability approximately 10 times that of oral ganciclovir, and undergoes rapid hydrolysis to ganciclovir in the body. Although no controlled study has been performed in SCT recipients, valganciclovir seems to be similar to ganciclovir in terms of efficacy, tolerability and adverse effects.[14]

> Pre-clinical pharmacokinetic and toxicological studies have demonstrated that maribavir has good oral bioavailability and a favorable safety profile.

Furthermore, CMV clinical isolates resistant to both ganciclovir and foscarnet have been reported due to mutations in the viral DNA polymerase gene UL54. Resistance mutations in the protein kinase gene UL97 are also common in patients undergoing long-term ganciclovir therapy.[7]

Ultimately, any new anti-CMV agents in development should be orally bioavailable for convenience, with superior efficacy and an improved safety profile.

New Candidate for Cytomegalovirus Disease Prevention

Ganciclovir and cidofovir are, respectively, nucleoside and nucleotide analogues. Ganciclovir requires initial monophosphorylation by the CMV UL97, while both require additional phosphorylation by cellular enzymes for activation before they can act as competitive inhibitors against their corresponding substrates at the CMV DNA polymerase binding site. If incorporated into CMV DNA, the drugs can block chain elongation.[7] Foscarnet, a pyrophosphate analogue, occupies the pyrophosphate binding site on CMV polymerase and prevents incoming dNTPs from being incorporated into viral DNA.[7] Because ganciclovir, cidofovir and foscarnet all target DNA synthesis in the viral life cycle at the level of DNA polymerase, cross-resistance can occur at the level of mutation in the CMV DNA polymerase.

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Maribavir is a benzimidazole riboside compound that has been shown in biochemical and genetic studies to inhibit the CMV protein kinase pUL97, the same kinase responsible for initiating the antiviral activity of ganciclovir.[2,16] Distinct from the existing anti-CMV drugs, maribavir has a novel mechanism of action mediated through the UL97 protein kinase that restricts viral DNA synthesis, assembly and even virion maturation events beyond. Maribavir is a potent and selective competitive inhibitor of ATP binding in the kinase's catalytic region. The protein kinase pUL97 is highly conserved across clinical strains of CMV, and has highly conserved homologues across other herpesviruses, implying that the kinase is essential for survival of the virus and disease pathogenesis.[7,16–20] When pUL97 is inhibited, whether via maribavir or a laboratory-generated deletion mutation, the efficiency of viral DNA replication is severely impaired, with observed defects in encapsidation and nuclear egress, ultimately reducing the viral yield.[16,18–20]

In vitro studies have shown that maribavir is more potent against CMV than ganciclovir, and is less toxic to bone marrow cells.[2,15] Pre-clinical pharmacokinetic and toxicological studies demonstrated that maribavir has good oral bioavailability and a favourable safety profile. Furthermore, maribavir did not cause myelosuppression, and exhibited a lower toxicity than currently available anti-CMV drugs.[21] Phase I clinical studies testing maribavir as a prophylactic agent against CMV showed effective antiviral activity *in vivo*, and it was well tolerated across a range of doses, the most commonly reported adverse event being taste disturbance.[22,23] Results from phase II studies affirmed the drug's strong antiviral activity, marking a statistically significant reduction in the rate of CMV reactivation in SCT recipients in all three dosage groups (100mg BID, 400mg QD, 400mg BID).[24] The promising early data with maribavir will be confirmed in ongoing studies. Currently, international phase III studies are under way to evaluate the efficacy, safety, tolerability and prophylactic use of maribavir administered for the prevention of CMV disease in SCT and solid-organ transplant (SOT) patients.[24,25] Due to the drug's promising anti-CMV activity, the US Food and Drug Administration (FDA) granted fast-track status to maribavir in February 2006 for preventing CMV infection in bone marrow transplant and SOT patients. In November 2007, the European Medicines Agency (EMEA) designated maribavir as an orphan drug for CMV patients with impaired cell-mediated immunity.

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In vitro studies have shown that maribavir is active against all known CMV strains resistant to the commonly administered anti-CMV drugs in the clinic.[24] CMV resistance to ganciclovir arises most commonly through mutations in the CMV UL97 gene;[7,20] cross-resistance to

maribavir due to ganciclovir resistance mutations in UL97 has yet to be observed in laboratory studies, possibly because the drugs interact with different domains of pUL97. In addition to the UL97 gene target, resistance of laboratory-generated maribavir variants has also been mapped to the CMV UL27 locus, a gene that encodes for a protein of unknown function.[29] The benefit of maribavir being part of a new class of compound with a completely novel mechanism of action is that, in addition to the favourable safety and resistance profiles, maribavir presents patients with the option of switch therapy.

With a mechanism differing from that of the currently available first- and second-line anti-CMV agents, orally bioavailable maribavir is a promising new compound in prophylaxis against CMV reactivation and infection. Preliminary clinical data have shown the drug to have a convenient dosing schedule, as well as high tolerability and efficacy. Furthermore, there are no known cross-resistances between maribavir and the commonly used anti-CMV drugs to date.

Considerations for Future Research

If the current clinical trials conclude that maribavir is effective and safe, it would be logical to investigate the use of maribavir in other disease management settings and for the treatment of other established diseases. Maribavir is currently available only in oral formulation; it may be worth developing the compound for intravenous administration should that option be one day required.

Other Herpesviruses

The viral protein kinase pUL97 targeted by maribavir acts across many steps in the viral life cycle. In theory, this should provide a greater opportunity for the drug to act in different stages of the viral reactivation and infection cycle. These aspects have yet to be explored, but lead to the idea that maribavir may be effective for the treatment of infections caused by other herpesviruses, or perhaps any viruses that carry homologous maribavir targets. The marketed anti-CMV agents have been studied for use in treatment as broad-spectrum antiherpesvirus drugs. The activities of ganciclovir and similar guanosine analogues have been found to extend to most herpesviruses, including HHV-6.[15,26] Cidofovir has also been examined for oral treatment of poxvirus infections in addition to herpesvirus infections, although cidofovir's many activities result from the less selective nature of its inhibitory action against viral and host cell polymerases.[27] Maribavir has already been shown to be active against Epstein-Barr virus (EBV), although the mechanism and exact target have not yet been identified.[28]

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The existing unmet needs have encouraged research into new drugs for CMV that will potentially have increased efficacy and target specificity, without the limitations of the existing compounds. Given maribavir's promising clinical trials thus far, this will hopefully prompt further development of new candidates against CMV infection and disease. ■

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