New Antiviral Drug Reduces CMV Disease in Bone Marrow Transplant Patients

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One of the most widely recognized achievements developed at The Hutch is bone marrow transplantation to treat cancer patients. Among the myriad issues surrounding such a complex procedure is the increased risk of infection or reactivation of cytomegalovirus (CMV) and development of CMV disease following transplantation. Current treatment strategies for CMV have severe side effects and drug resistance can develop. A recent study reported in the *New England Journal of Medicine* by senior author Dr. Michael Boeckh of the Vaccine and Infectious Disease Division and colleagues shows promising results for a new antiviral drug to treat and/or prevent CMV infection following transplantation.

Patients who undergo allogeneic hematopoietic cell transplantation, often do so as a last chance attempt to cure them of leukemia or lymphoma. During the procedure, the patient's immune system is severely weakened by chemotherapy and/or radiation before stem cells are transplanted from a healthy donor. Due to a depleted immune system and the introduction of new immune system cells that are genetically distinct from the recipient's cells, the patient is highly susceptible to many infections, as well as graft versus host disease. Infection with CMV affects this population of patients with particularly high prevalence.

Although between 50% and 80% of adults in the U.S. are infected with CMV, the virus forms a lifelong latent infection with little or no symptoms in people with a healthy immune system. However, in immunocompromised individuals, such as hematopoietic cell transplant patients, CMV infection can cause pneumonia, retinitis, gastrointestinal disease and an increased chance of death. These outcomes arise despite the administration of available antiviral agents. Furthermore, the use of current drugs is limited because of adverse effects such as toxicity to blood cells, the very cells that the transplantation was carried out to replace.

A new antiviral drug CMX001 "was originally developed as an oral treatment for smallpox, but other studies have suggested it is effective in treating a range of other viruses," explains Dr. Boeckh. "For that reason, CMX001 has been stirring considerable interest among researchers and clinicians alike." Following promising preclinical results and several initial clinical trials, the drug was tested in a large multi-center cohort of allogeneic hematopoietic cell transplant recipients in a phase II trial.

The study involved 230 allogeneic hematopoietic cell transplant patients recruited at 27 centers. Patients either received the new antiviral drug CMX001 at varying doses, or a placebo. The duration of the treatment was from 9 to 11 weeks. Following the treatment period, CMV DNA was detected in plasma by polymerase chain reaction to monitor for CMV events, defined as CMV disease or CMV DNA greater than 200 copies per milliliter. The investigators found that only 10% of patients receiving 100 mg of CMX001 twice weekly experienced a CMV event, compared to 37% in the placebo group ($p = 0.002$). The most common side effect of the treatment was diarrhea, which was most common and often serious in the patients receiving the highest dose of CMX001 (200 mg twice weekly). However, for patients receiving 100 mg twice weekly instances of diarrhea were milder in nature and did not result in an increased rate of withdrawals from the study.

"The results of this study are very encouraging for the field of hematopoietic cell transplantation, as CMX001 could prevent or treat a large number of potentially fatal viral infections for which we don't currently have good treatment," adds Dr. Boeckh. The drug is also being tested for efficacy against other life-threatening viral infections including adenovirus, herpes simplex virus and monkeypox virus. The promising results shown by CMX001 bode well for this new antiviral. "This drug could potentially be a game-changer," predicts Dr. Boeckh. "The phase III study to definitively prove the efficacy of CMX001 is now ongoing."

Marty FM, Winston DJ, Rowley SD, Vance E, Papanicolaou GA, Mullane KM, Brundage TM, Robertson AT, Godkin S, Momméja-Marin H, Boeckh M. CMX001-201 Clinical Study Group. 2013. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. *N Engl J Med* 369:1227-36

Also see: Ljungman P, Hakki M, Boeckh M. 2011. Cytomegalovirus in hematopoietic stem cell transplant recipients. *Hematol Oncol Clin North Am* 25:151-69

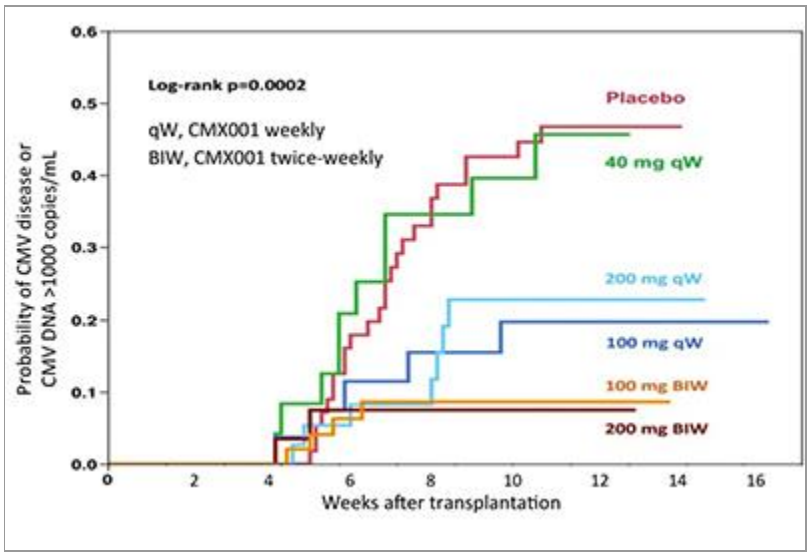

Image provide by Dr. Michael Boeckh, adapted from the original article.

Time to CMV disease or CMV plasma DNA > 1000 copies/mL according to CMX001 study groups. Twice weekly treatment of 100 mg or 200 mg CMX001 showed the strongest ability to prevent CMV disease.