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ORIGINAL RESEARCH REPORT

Evaluation of cytomegalovirus reactivation and tolerability in seropositive umbilical cord transplant patients after implementation of an intensive prevention strategy

Matthew Rinehart [a,*], Erica Hochard [a], Michelle Rockey [a,b], Sunil Abhyankar [c], Siddhartha Ganguly [c], Tara Lin [c], Joseph McGuirk [c], Leyla Shune [c], Anurag Singh [c], Omar Aljitawi [c]

[a] Department of Pharmacy, University of Kansas Hospital, Kansas City, KS, USA
[b] University of Kansas School of Pharmacy, Lawrence, KS, USA
[c] Department of Blood and Marrow Transplant, University of Kansas Hospital, Kansas City, KS, USA

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Abstract
Objective/Background: Cytomegalovirus (CMV) causes significant morbidity and mortality in CMV immunoglobulin G+ patients undergoing umbilical cord blood transplants (UCBT). Our study aimed to describe the incidence of CMV reactivation and burden of disease, as well as the tolerability of an intensive prevention strategy as compared to historical prevention.
Methods: This was a retrospective chart review of 33 CMV seropositive patients that underwent UCBT. The intensive prevention strategy in UCBT consisted of 5 mg/kg/d ganciclovir intravenously or 900 mg valganciclovir by mouth daily initiated at the beginning of the conditioning regimen until Day −2. Then, from Day −1 to Day +100, patients received 2 g valacyclovir by mouth three times daily, and from Day +101 to Day +365, 800 mg acyclovir by mouth twice daily. Historical standard prevention was 800 mg acyclovir by mouth twice daily initiated at the beginning of the conditioning regimen until Day +365.
Results: Thirty-three patients were included from 2008 to 2014. There were no differences in the adverse effects experienced between the two regimens ($p = .4$), and. CMV reactivation

* Corresponding author at: Department of Pharmacy, University of Kansas Hospital, 3901 Rainbow Boulevard, Mailstop 4040, Kansas City, KS 66160, USA.
E-mail address: mrinehart@kumc.edu (M. Rinehart).

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occurred significantly later with intensive prevention (p = .003). The median CMV viral titer at reactivation was lower in the intensive versus the historic prevention (1,800 copies/mL and 2,700 copies/mL, respectively), but was not significantly different. CMV disease occurred significantly less often in the intensive group (p = .039).

Conclusion: The results from this study indicated that the intensive prevention strategy was well tolerated, significantly delayed CMV reactivation, and patients had less CMV disease.

Introduction

Cytomegalovirus (CMV), a member of the herpes virus family, is a ubiquitous environmental virus affecting roughly 50—85% of adults in the United States [1]. Once exposed to CMV, the host becomes a lifelong carrier, as the virus enters a dormant state within cells and evades detection and clearance by the immune system. CMV is a known cause of significant morbidity and mortality in CMV immunoglobulin G+ patients that undergo hematopoietic stem cell transplantation, but it is especially dangerous in umbilical cord blood transplants (UCBT). This is due to longer engraftment times, which render patients susceptible to the development of significant infectious complications [1—4]. CMV reactivation is most likely to occur during the first 100 days of the transplant course, but can also occur as late as 1 year later [1]. Reactivation of the latent virus during immunosuppression may lead to detectable viremia and progress to CMV diseases, such as pneumonia or gastritis. Rarely, CMV reactivation causes hepatitis, retinitis, encephalitis, or even graft failure [1]. Seropositive CMV patients that do not receive prophylaxis against reactivation have reactivation rates between 70% and 100% after UCBT [1—3].

The literature available is limited regarding optimal prophylaxis for CMV-seropositive patients undergoing UCBT. There has been only one study by Milano et al. [11] published in 2011. In this study, patients underwent either a standard or intensive prevention strategy. The medications and timing of administration of these agents can be seen in Table 1. CMV screening in the intensive cohort was performed more frequently and earlier post-transplant, with a lower threshold to begin preemptive therapy than in the standard prophylaxis group. The intensive strategy resulted in a statistically significant reduction in the hazard ratio for CMV reactivation, cases of CMV disease by the end of Year 1 post-transplant, and fewer days on CMV-specific antiviral therapy [11].

After the publication of this study in 2011, our institution, the University of Kansas Hospital (UKH; Kansas, SK, USA), developed a similar intensive prevention strategy for CMV-seropositive patients undergoing UCBT. The regimen and monitoring parameters are further described in S ection ''Materials and methods" and can be seen in Table 1. This report includes a review of safety and efficacy outcomes for patients treated using this intensive strategy.

The main purpose of this retrospective study was to evaluate the tolerability and adverse effects associated with the intensive prevention strategy adopted by our institution. The secondary outcomes evaluated included the incidence of CMV reactivation and disease in seropositive UCBT patients after implementation of the intensive strategy. The findings of this study will add to the current knowledge base, as there is limited data concerning CMV prevention during UCBT in seropositive patients.

Materials and methods

This was a retrospective chart review of 33 patients who underwent UCBT at the UKH. The study was approved by the UKH Institutional Review Board. Patients that received the intensive prevention strategy (December 2011—December 2014; n = 16) were compared with patients who received the standard regimen (January 2008—November 2011; n = 17). Patients who underwent UCBT during this period were retrospectively identified and screened for inclusion. Patients were followed from the beginning of the preparative regimen until Day +365 or until the patient was lost to follow-up or death. Patients ⩾17 years of age, CMV seropositive prior to UCBT, and who had received prophylaxis for CMV were included in the study. Patients were excluded if they had received prior anti-CMV therapy or were CMV seronegative prior to UCBT.

The intensive prevention strategy for CMV-seropositive patients was 5 mg/kg/d ganciclovir intravenously or 900 mg valganciclovir by mouth daily initiated at the beginning of conditioning until Day −2. From Day −1 to Day +100, patients received 2 g valacyclovir by mouth three times daily and from Day +101 to Day +365, and 800 mg acyclovir by mouth twice daily. Prior to the initiation of this intensive prevention strategy in December 2011, patients received the standard prevention of 800 mg acyclovir by mouth twice daily from the beginning of the conditioning regimen until Day +365. CMV monitoring was completed biweekly via polymerase chain reaction (PCR) from Day +20 until Day +100, then weekly until Day +365. PCR testing was performed with Luminex MultiCode CMV reagents (Luminex, Austin, TX, USA) and a Roche LightCycler CMV Quant Kit (Roche, Basel, Switzerland). CMV DNA levels were considered positive upon reaching 300 copies/mL. Levels between 300 copies/mL and 499 copies/mL were reported as <500 copies/mL. Once levels were ⩾500 copies/mL, levels were reported in 100 copies/mL intervals. Renal toxicity was defined as a serum creatinine increase of ⩾0.5 mg/dL (Table 1).

Statistical analysis

Categorical data was analyzed using either Fisher's exact test or Pearson's chi-square test where appropriate, and

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