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Efficacy of a Viral Load-Based, Risk-Adapted, Preemptive Treatment Strategy for Prevention of Cytomegalovirus Disease after Hematopoietic Cell Transplantation

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Cytomegalovirus (CMV) surveillance and preemptive therapy is the most commonly used strategy for CMV disease prevention in hematopoietic cell transplantation recipients. In 2007, we introduced a CMV prevention strategy for patients at risk for CMV disease using quantitative PCR surveillance, with treatment thresholds determined by patient risk factors. Patients (N = 367) received preemptive therapy either at a plasma viral load of ≥500 copies/mL, at ≥100 copies/mL if receiving ≥1 mg/kg of prednisone or anti-T cell therapies, or if a ≥5-fold viral load increase from baseline was detected. Compared with patients before 2007 undergoing antigenemia-based surveillance (n = 690) with preemptive therapy initiated for any positive level, the risk-adapted PCR-based strategy resulted in similar use of antiviral agents, and similar risks of CMV disease, toxicity, and nonrelapse mortality in multivariable models. The cumulative incidence of CMV disease by day 100 was 5.2% in the PCR group compared with 5.8% in the antigenemia group (1 year: 9.1% PCR vs 9.6% antigenemia). Breakthrough CMV disease in the PCR group was predominantly in the gastrointestinal (GI) tract (15 of 19 cases; 79%). However, unlike CMV pneumonia, CMV GI disease was not associated with increased nonrelapse mortality (adjusted hazard ratio, 1.19; $P = .70$ [GI disease] vs 8.18; $P < .001$ [pneumonia]). Thus, the transition to a preemptive therapy strategy based on CMV viral load and host risk factors successfully prevented CMV disease without increasing the proportion of patients receiving preemptive therapy and attributable toxicity. Breakthrough disease in PCR-based preemptive therapy occurs at a low incidence and presents primarily as GI disease, which is more likely to be responsive to antiviral therapy.

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INTRODUCTION

Strategies using virologic surveillance and preemptive treatment have become the standard of care for the prevention of cytomegalovirus (CMV) disease after hematopoietic cell transplantation (HCT) [1,2]. However, a significant variation among transplantation centers in testing methods, frequency, and thresholds for initiating preemptive therapy remains [3,4]. As of 2003, nearly half of transplantation centers reported using a surveillance strategy based on pp65 antigen in peripheral blood leukocytes, whereas the remainder had transitioned to a strategy based on plasma or whole blood CMV DNA level measured by PCR [4]. Several cohort studies [5-12] and a few small randomized clinical trials [13-15] have compared the performance of these 2 tests for use in a preemptive treatment strategy. Although pp65 antigenemia testing has been shown to perform well in CMV disease prevention, several operational disadvantages limit its use: the test requires circulating neutrophils and, thus, is not reliable before engraftment; the samples require rapid processing to retain sensitivity; and interpretation of the slides requires highly trained

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personnel and has a high interobserver variability. In contrast, CMV DNA measurement by real-time PCR is more sensitive than pp65 antigenemia, provides more precise quantitation of CMV, can be automated, and is markedly less affected by specimen transport conditions and time [7-9].

In 2007, the Fred Hutchinson Cancer Research Center (FHCRC) changed from a preemptive strategy based on weekly surveillance of pp65 antigenemia to one based on CMV DNAemia measured by quantitative real-time PCR for patients at risk for CMV disease. The strategy was designed with 2 primary goals: (1) to ascertain a treatment threshold that was low enough to take advantage of the sensitivity of the PCR assay to identify early patients most likely to have a short doubling time [16] and those who progress to disease without high viral loads [7] and (2) to avoid increasing the overall proportion of patients treated to minimize adverse effects of therapy. We thus selected the viral load thresholds for preemptive treatment based on the patient's degree of immunosuppression, as a factor that correlates with viral replication dynamics [16]. Additionally, rapid relative increases of viral load were also chosen as an indication for preemptive treatment. The thresholds were chosen a priori with the goal of designing a surveillance strategy that could be implemented and adopted in a large transplantation center. In this study, we report the efficacy of this risk-adapted, viral load-based strategy for the prevention of CMV disease after HCT and identify characteristics and outcome of breakthrough CMV disease with contemporary preemptive strategies.

METHODS

Patient Selection

The study included patients of all ages who were at risk of CMV disease and received their first allogeneic HCT at the FHCRC between 2002 to 2005 and 2007 to 2009. Patients at risk for CMV disease were either CMV seropositive (R+; D− or D+) or seronegative patients receiving stem cells from seropositive donors (D+/R−). Patients receiving ex vivo T cell-depleted stem cell products or umbilical cord blood transplantations were excluded [17]. We excluded patients who underwent mixed CMV surveillance—sometimes tested by antigenemia, other times by PCR, during the transition period in 2006 and early 2007. During this time period, there were several ongoing clinical trials for CMV disease prevention; patients randomized to the study drug/vaccine in these studies were also excluded.

To control for secular trends in the frequency of secondary neutropenia, Gram-negative bacteremia, and mortality during the study time period, we also analyzed patients who were CMV seronegative, received stem cells from a seronegative donor (D−/R−), and underwent first allogeneic bone marrow (BM) or peripheral blood stem cell transplantation at the FHCRC between 2002 to 2005 and 2007 to 2009. Because these low-risk patients continued to undergo antigenemia-based preemptive therapy, they were not included in the analysis of CMV disease. This protocol was approved by the Institutional Review Board at the FHCRC.

Data Sources

The FHCRC prospectively collects demographic, clinical, and laboratory data from all patients undergoing HCT and the donors from the pretransplantation period through at least the first 100 days after transplantation. Clinical and laboratory data after discharge from the center are also available from the long-term follow-up database; additional pathology, radiology, and antiviral therapy data were extracted from the electronic medical records.

CMV Surveillance, Treatment, and Antiviral Prophylaxis

Patients at risk for CMV reactivation underwent weekly surveillance testing either by pp65 antigenemia or by PCR to measure plasma viral load. During the antigenemia era, surveillance testing was started after engraftment (after day 10) and continued weekly until day 100 [18]. As the PCR test does not require neutrophils, weekly surveillance was initiated about day 0. Patients who received preemptive therapy in the first 100 days or who were receiving steroids for chronic graft-versus-host disease (cGVHD) continued weekly PCR surveillance throughout the first year in both periods. Preemptive therapy with either induction-dose ganciclovir (5 mg/kg i.v. every 12 hours) or foscarnet (90 mg/kg every 12 hours; in case of neutropenia) was initiated for an antigenemia result of ≥1 positive cell per 2 slides [18] or, in the PCR era, for a CMV viral load ≥500 copies/mL or a 5-fold increase from baseline within the previous month. Patients receiving anti-T cell therapies such as alemtuzumab or antithymocyte globulin, or ≥1mg/kg prednisone equivalent were treated at a viral load of ≥100 copies/mL. For patients with CMV viral loads under the treatment threshold, twice weekly testing was recommended. Induction dosing was continued for at least 7 days at which point, if antigenemia or plasma CMV viral load were decreasing, the therapy was changed to maintenance-dose ganciclovir (5 mg/kg i.v. once daily), which would be continued for at least 2 weeks or until the repeat test was negative. After day 100, PCR surveillance was recommended in both cohorts with a preemptive treatment threshold of ≥1,000 copies/mL or a 5-times increase of viral load within 1 month. CMV plasma PCR was tested by a double-primer assay as