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A multicenter, longitudinal, interventional, double blind randomized clinical trial in hematopoietic cell transplant recipients residing in remote areas: Lessons learned from the late cytomegalovirus prevention trial

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ABSTRACT

Purpose: The logistics of conducting double-blinded phase III clinical trials with participants residing in remote locations are complex. Here we describe the implementation of an interventional trial for the prevention of late cytomegalovirus (CMV) disease in hematopoietic cell transplantation (HCT) subjects in a long-term follow-up environment.

Methods: A total of 184 subjects at risk for late CMV disease surviving 80 days following allogeneic HCT were randomized to receive six months of valganciclovir or placebo. Subjects were followed through day 270 post-transplant at their local physician's office within the United States. Anti-viral treatment interventions were based on CMV DNAemia as measured by polymerase chain reaction (PCR) (>1000 copies/mL) and granulocyte colony stimulating factor (G-CSF) was prescribed for neutropenia (absolute neutrophil count (ANC $< 1.0 \times 10^9$ cells/L). Blood samples for viral testing and safety monitoring were shipped to a central laboratory by overnight carrier. Real-time communication was established between the coordinating center and study sites, primary care physicians, and study participants to facilitate starting, stopping and dose adjustments of antiviral drugs and G-CSF. The time required to make these interventions was analyzed.

Results: Of the 4169 scheduled blood specimens, 3832 (92%) were received and analyzed; the majority (97%) arriving at the central site within 2 days. Among subjects with positive CMV DNAemia (N = 46), over 50% received open label antiviral medication within one day. The median time to start G-CSF for neutropenia was <1 day after posting of laboratory results (range 0–6; N = 38). Study drug dose adjustments for abnormal renal function were implemented 203 times; within one day for 48% of cases and within 2 days for 80% of cases.

Conclusion: Complex randomized, double-blind, multicenter interventional trials with treatment decisions made at a central coordinating site can be conducted safely and effectively according to Good Clinical Practice (GCP) guidelines over a large geographic area.

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1. Introduction

Because many patients are managed by their local primary care providers after hematopoietic cell transplantation (HCT), often distant from the transplant center, timely communication and coordination of care in a clinical trial context according to Good Clinical Practice (GCP) standards can be challenging. The complicated logistics of managing a trial requiring real-time changes in patient care based on laboratory results from a distance means that such studies are rarely, if ever done. Indeed the paucity of high-quality treatment and prevention studies in this setting has plagued the field for decades. We recently reported the findings from an investigator-initiated, multicenter, double-blind placebo-controlled, randomized Phase III trial comparing valganciclovir prophylaxis to polymerase chain reaction (PCR)-guided preemptive therapy for the prevention of late cytomegalovirus (CMV) disease in post-allogeneic HCT patients surviving at least 80 days from transplant [1], which was specifically designed to allow for the expansion of the study drug label to include prophylactic use. The study demonstrated that complex clinical trials utilizing both private and academic-based care settings can be successfully carried to fruition and provided a model for the cooperation necessary for the successful completion of the trial. Here we present the specifics that enabled this long-term, double-blinded phase III clinical trial to be successfully conducted across 36 U.S. states with real-time treatment and dose adjustment of study medications based on laboratory monitoring.

2. Methods

2.1. Trial design

The detailed design of the clinical trial is reported elsewhere [1]. Briefly, a multi-center randomized, double-blind, placebo-controlled study of valganciclovir for the prevention of late CMV infection was conducted in CMV seropositive subjects undergoing allogeneic HCT between 2001 and 2008. Seven sites participated in this study with the Fred Hutchinson Cancer Research Center (Fred Hutch) as the coordinating center. Over the course of the study, 184 subjects were randomized and formed the intent-to-treat population. Randomization to receive study drug (valganciclovir or placebo) occurred between day 80 and day 120 post HCT (Supplementary Fig. 1). The active study period during which study drug was administered and real-time decisions were made occurred between randomization and day 270 post-transplant.

2.2. Communication between sites, primary providers and participants

Maintaining communication between the coordinating site and primary physicians was critical to the success of this study and to ensuring timely interventions. Subjects were tested once weekly by PCR for CMV DNA in plasma, neutropenia (absolute neutrophil count (ANC) $< 1.0 \times 10^9$ cells/L) and renal insufficiency (serum creatinine >2.5 mg/mL). Blood was drawn at the subject's local medical facility and shipped overnight (Federal Express) using prepaid packages and study-provided kits to the coordinating center for testing at the University of Washington clinical laboratories. The primary care provider for each patient was contacted by site personnel with laboratory results as they became available (Fig. 1). Monthly contact with the subject during the treatment phase was maintained by the study coordinator at the local sites and consisted of status checks of CMV infections, other infections, hospitalization, adverse events, medication history, study drug compliance and any requests for drug supply or laboratory supplies. Data, including clinical and laboratory records, were maintained in a secure online database. Hardcopies of case report forms were also available for review.

2.3. Metrics evaluated

To evaluate the logistical aspects of conducting an interventional trial for the prevention of late CMV disease in HCT subjects in a long-term follow up environment, we examined the geographic distribution of subjects, time required to receive overnight shipment of blood specimens and the turnaround time for clinical interventions based on laboratory results.

2.4. Interventions

We analyzed the performance characteristics of several key interventions. Clinical interventions consisted of (a) start of preemptive antiviral treatment for a positive CMV quantitative PCR result $\geq$ 1000 IU/mL (b) interruption of study drug administration and start of granulocyte colony stimulating factor (G-CSF) for any neutropenic episode defined by ANC $< 1.0 \times 10^9$ cells/L and (c) adjustment of study medication dose based on renal function. Subjects were monitored on a weekly basis with plasma CMV DNA PCR testing and complete blood count (CBC) with differential and blood chemistry panels through day 270.

2.4.1. Initiation of preemptive antiviral treatment for a positive CMV DNAemia

If subjects developed PCR DNAemia (>1000 copies/mL) or CMV disease (reactivation of previously latent infection or newly acquired infection with evidence of organ involvement), they were treated with intravenous ganciclovir (5 mg/kg) or open-label valganciclovir (900 mg) twice daily for one week or until DNAemia declined followed by open-label once daily valganciclovir (900 mg); foscarnet (90 mg/kg twice daily) was used instead if indicated due to neutropenia. Intravenous (IV) ganciclovir was given for initial treatment of CMV disease and in situations when no oral medication could be administered. In January 2004, the protocol was modified to allow the use of open label valganciclovir as an alternative to IV ganciclovir for the treatment of CMV reactivation to prevent possible treatment delays associated with the logistics of IV therapy. Patients were given a supply of valganciclovir and instructed by the study coordinator to discontinue study drug and start open-label treatment when CMV DNAemia exceeded the threshold. These patients were subsequently monitored by PCR and retreated if CMV tests resulted positive through day 270. Foscarnet 60 mg/kg IV twice daily induction for at least 1 week was given for patients with neutropenia, followed by 90 mg/kg maintenance daily until the PCR result was negative.

2.4.2. G-CSF initiation for neutropenia

Neutrophil counts were monitored while subjects received study drug through day 270. If the ANC dropped below 1.0×10^9 cells/L, study drug was held, and G-CSF could be prescribed per physician discretion based on ANC levels. G-CSF was recommended until the ANC was $>1.0 \times 10^9$ cells/L. The protocol allowed up to 14 days of G-CSF support at which time a bone marrow biopsy was recommended to establish a diagnosis. During periods of neutropenia, monitoring of ANC was performed locally every other day and the results were faxed to the enrolling site. Blood draws for ANC were also shipped to the central site twice weekly while the patient was neutropenic. In January 2004, the protocol was amended to standardize the use of G-CSF for the treatment of neutropenia at an ANC $< 1.0 \times 10^9$ cells/L in all participants.