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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 × 10⁹ 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 pre-paid 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 ≥ 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.

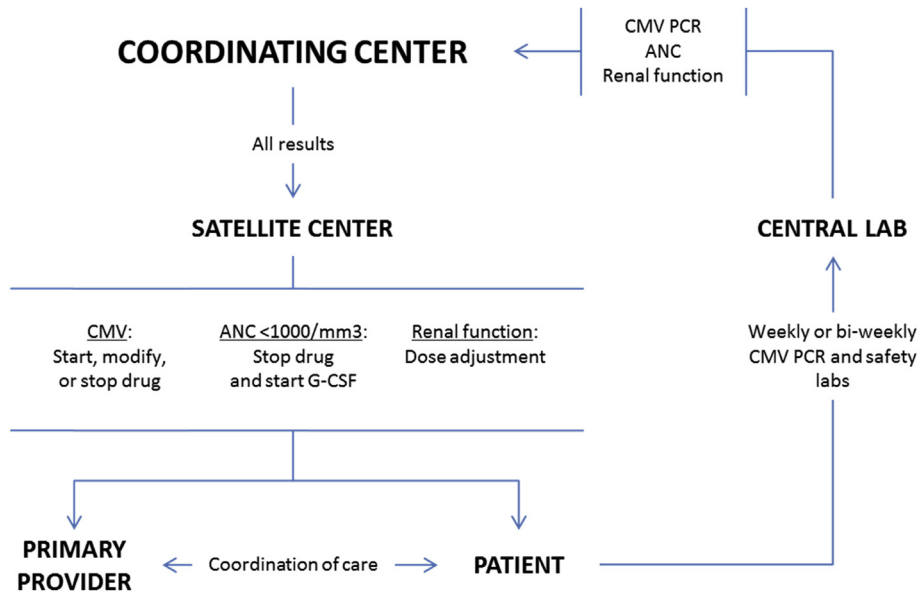


Fig. 1. Study communication. CMV = cytomegalovirus; PCR = polymerase chain reaction; ANC = absolute neutrophil count; G-CSF = granulocyte colony stimulating factor.

2.4.3. Adjustment for renal function

Blinded study drug (valganciclovir, placebo) and open label drugs (ganciclovir, valganciclovir, foscarnet) were adjusted based on the patient's estimated creatinine clearance according to manufacturer recommendations.

2.5. Statistical analysis

We compared the time from the first CMV PCR positive test to start of antiviral therapy, as well as time between discovery of neutropenia and G-CSF administration, between the study period before and after January 2004, when anti-viral medication and G-CSF protocols changed, using the Mann-Whitney *U* test. *P* values less than 0.05 were considered significant.

3. Results

3.1. Geographical distribution of subject locations

A total of 184 study participants across 141 cities and 5 time zones were randomized and received at least one dose of study drug. Demographics are shown in Table 1, and geographic distribution is displayed in Fig. 2.

3.2. Turnaround time of blood samples delivered by overnight shipment

Out of 4169 expected surveillance samples, a total of 3832 CBCs (92%) with differential, blood chemistry panels and CMV DNA samples for PCR were received and processed during the study period. Reasons for missed samples were not collected or recorded systematically. In general, samples were missed due to hospitalization, dependent care responsibilities, subject health issues and reentry of the subjects into employment and other responsibilities following recovery. Travel was also a possible reason for missing a sample, but we made every effort to help subjects locate clinics for blood draws when they were away from home and provided kits for the draws. Transit time was defined as the time of collection from the subject to the time of the sample being received by the coordinating center. A total of 158 subjects (86%) were collected at off-

Table 1

Patient characteristics (n = 184).

Characteristic	Value
Age (median)	49.70 years
Gender	
Male	104 (56.52%)
Female	80 (43.48%)
Race	
White	165 (90.76%)
Black	1 (0.54%)
Asian/Pacific Islander	7 (3.80%)
Native American	1 (0.54%)
Other/Unknown	8 (4.35%)
Ethnicity	
Hispanic	5 (2.72%)
Non-Hispanic	176 (95.65%)
Unknown	3 (1.63%)

site locations (defined as locations other than the coordinating site, Seattle) and delivered by overnight carrier. Among all samples, 63% were received within 1 day, an additional 34% within 2 days, and the remaining 3% more than 2 days after collection, with a median transfer time of 1 day (range 0–7 days) (Fig. 3a). Most samples (>85%) were drawn and shipped Monday to Wednesday, as requested. Samples were delayed past 48 h due to shipment on a Friday or Saturday, when extreme weather interfered with overnight couriers, or due to non-Monday federal holidays. Delays were not a result of federal holidays on Mondays or the terrorist attack of September 11, 2001 and subsequent alterations to air travel in the US.

3.3. Start of preemptive antiviral treatment

Preemptive treatment for CMV was initiated 46 times (N = 36 patients) a median of 1 day (range 0–28) after the CMV DNAemia above the threshold was detected. Although there was a noticeable delay of 3 or more days in treating 7% of the episodes, no CMV disease occurred directly related to the delay. One patient was treated with foscarnet as the initial treatment due to neutropenia that started at the same time as CMV reactivation; treatment began within 2 days. We compared time-to-treat after receipt of CMV PCR



Fig. 2. Geographical distribution of subjects on study in the United States. Counts within each state represent the number cities with individuals enrolled throughout the course of the study. Star indicates the location of the coordinating center in Seattle, Washington. Dots indicate location of participating centers (University of Texas MD Anderson Cancer Center, Houston, Texas, Memorial Sloan Kettering Cancer Center, New York, New York, University of Florida, Gainesville, Florida, Mayo Clinic, Rochester, Minnesota, City of Hope National Medical Center, Duarte, California, University of Michigan, Ann Arbor, Michigan, and Duke University, Durham, North Carolina).

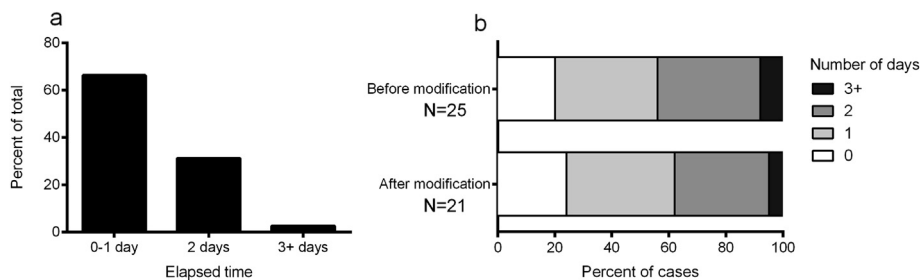


Fig. 3. **a.** Elapsed time between blood collection and specimen receipt at coordinating center. Median elapsed time was 1 day (range: 0–7 days) ($N = 3832$). **b.** Elapsed time to treatment initiation in response to CMV PCR positive result stratified based on original protocol and modified protocol initiated on 1 January 2004. 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 1000 IU/mL. One patient experienced an extended delay of 28 days due to concern for possible relapse of primary disease. ($N = 46$ episodes in 36 patients). CMV = cytomegalovirus; PCR = polymerase chain reaction.

results before and after the protocol modification in 2004 allowing for treatment with oral valganciclovir as opposed to intravenous ganciclovir and found no difference (Fig. 3b; $p = 0.65$ for all episodes; $p = 0.51$ for first episode per patient only).

3.4. Start of G-CSF for neutropenia

Neutrophil counts were monitored by study personnel. We compared those treated prior to January 2004, when G-CSF was only recommended but not an integral part of the protocol, to those treated after the protocol was amended to include routine administration of G-CSF. The standardization of G-CSF treatment led to increased use of G-CSF in the post-modification valganciclovir group (11% of patients pre-modification vs. 27% post-modification) [1], but did not affect the time to start therapy. Time to start G-CSF for an ANC $< 1.0 \times 10^9$ cells/L was the same before and after protocol modification ($p = 0.98$ for all episodes; $p = 0.88$ for first episode per patient only), and occurred within 1 day in 71% and 2 days in an additional 18% of episodes (Fig. 4a).

Study drug was discontinued when the patients became

neutropenic; G-CSF was administered for neutropenia as described above. The median time from identification of neutropenia to discontinuation of study drug was 1 day (range 0–6), and 80% of the time study drug was discontinued on the same day of the result or within 1 day (Fig. 4b). Five of the 7 instances where study drug was not stopped until 3–4 days after the identification of neutropenia involved patients located in a time zone 3 h ahead of the coordinating center, so that notification to the primary care provider to stop study drug was not made until the morning after neutropenia was found.

3.5. Dose adjustments of study drug

Ganciclovir or valganciclovir dose adjustment for renal function was implemented 203 times within a median of 1 day (range 0–5) upon obtaining the result. Of these renal adjustments, more than 80% occurred within 2 days (range 0–6 days; Fig. 4c), but 5% of dose adjustments were not made until 4 days after the results were available and 1.5% of adjustments were made 5 or more days after the physician was notified. Of 37 cases with a delay of 2 days or

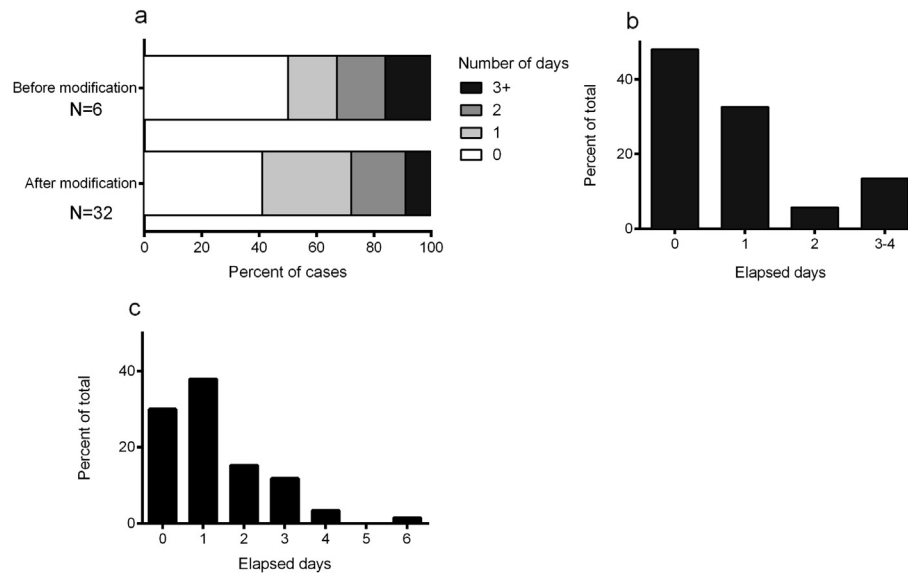


Fig. 4. a. Elapsed time from identification of neutropenia ($ANC < 1000/mm^3$) to start of G-CSF stratified on original protocol and modified protocol initiated on 1 January 2004 which made the use of G-CSF for treatment of neutropenia standard ($N = 38$ episodes in 27 patients). ANC = absolute neutrophil count; G-CSF = granulocyte colony stimulating factor. b. Elapsed time from neutropenia ($ANC < 1000/mm^3$) to discontinuation of study drug ($N = 52$). ANC = absolute neutrophil count. c. Elapsed time prior to adjusting study drug dose based on creatinine clearance results ($N = 203$).

more, however, only 1 developed neutropenia after a delay of 4 days.

4. Discussion

Despite the perception that conducting multicenter randomized clinical trials according to GCP standards in the late period after HCT is logistically infeasible, we demonstrate that it is possible to overcome many of these challenges. We received 92% of scheduled blood samples from 36 states without major problems. Only 3% of samples were received more than 2 days after collection with an overall median transfer time of 1 day. The transit time of all samples met the recommended parameters of 72 h for the stability of CBC specimens at 4 °C [2]. Sample delivery was most affected by non-Monday holidays and extreme weather conditions.

In the randomized trial [1], preemptive therapy was as successful as prophylaxis in prevention of CMV disease but each had its own challenges for management of patients. Preemptive therapy required diligent follow-up to ensure viral testing was performed, results were provided quickly, and treatment was provided quickly when indicated. Prophylaxis with valganciclovir, a medication associated with myelotoxicity and one that requires dose adjustment in the setting of renal insufficiency, required diligent monitoring of ANC and serum creatinine; quick dose adjustment and the provision of G-CSF likely reduced the frequency and impact of severe drug-related neutropenia.

Over 50% of subjects with CMV DNAemia greater than the threshold were treated within one day of receipt of results. Given that the doubling time of CMV is one to two days on average and that immunosuppression plays a role in the *in vivo* replication dynamics [3], the ability to deliver care quickly is paramount, although the doubling time may be longer late after HCT due to partially reconstituted CMV-specific immunity.

The protocol was amended in January 2004 to allow for the use of open label valganciclovir as preemptive therapy in place of IV ganciclovir given the difficulty in rapidly coordinating the administration of IV therapy in an outpatient remote setting. Although more patients received valganciclovir after the protocol change,

time to receive the first dose of preemptive therapy was not shorter when patients had valganciclovir readily available at home. It may be that time to treatment was impacted mostly by delays in notification from busy local doctors, rather than arranging for IV administration. There were two outliers to starting therapy, one at 7 days and one at 28 days after receipt of positive PCR results. While the time to begin treatment was prolonged in these cases neither of these two subjects progressed to develop CMV disease. The 28 day time lapse was due to the concern of relapsed malignancy, and the 7 day time lapse was likely due to communication issues between the primary physician and the subject.

Neutropenia is an expected adverse event of ganciclovir and valganciclovir; however, the exact incidence late after HCT is not known. The use of G-CSF has been observed to reverse neutropenia with a median time to reversal of 2 days in HIV-infected subjects [4]. The majority of patients in our study started G-CSF within 2 days of discovery of neutropenia. Although more patients received G-CSF once the protocol was modified to make administration standard for neutropenia in January 2004, the change did not lead to a more rapid start of the drug. Further, most patients discontinued study drug within 2 days of discovery of neutropenia. Start of G-CSF and discontinuation of study medication was delayed in some cases due to the challenges presented by management of the trial across multiple time zones. The reversal of severe neutropenia appeared to be effective, as no statistically significant differences in invasive bacterial and fungal infections were seen between the randomization groups [1,5,6].

Study drug dose adjustment for renal function was implemented within a median of 1 day upon obtaining the result, but a number of subjects requiring a dose adjustment were not informed until 4 or 5 days after the results were available. This disappointing delay did not have an obvious explanation, but may have been due to differences in time zones and days of the week (Fridays). In any case, the delay in dosage change only resulted in neutropenia in one case. A recent survey of primary-care physicians reported failure to inform the subject of their test results in 7.1% of all visits [7]. Our study was able to ensure documentation and communication with subjects equal to and arguably better than global

community practice.

This study successfully implemented real-time management of CMV preemptive treatment in a randomized, double-blinded, placebo-controlled setting away from comprehensive cancer centers. The ability to quickly communicate with subjects and providers across the United States was limited by the technology of the time. When this study was initiated, telephone and fax were the standard method used to communicate test results, with some email. Today, email, text messaging and smart phone applications can rapidly transmit results securely and remind subjects to take medications, simplifying the logistics needed to conduct clinical trials with subjects in remote locations [8]. People are easier to reach than ever with less effort and expense on the part of coordinators, as many electronic forms of communication can be automated and are growing in acceptance. Even so, the monitoring of virologic and safety testing in this study required significant dedication from study personnel, local primary care providers and patients (Fig. 1). Designated personnel to perform vigilant and ongoing communication with subjects and providers are needed to minimize late sample delivery, particularly with regard to holidays and inclement weather, and allow therapeutic decisions to be made on a real-time basis.

This study has strengths and limitations. This study represents the first double blinded trial to successfully implement real-time management of CMV preemptive treatment, and further demonstrates prospective documentation of sample collection over time covering a very large geographic and diverse area. One limitation is that reasons for delays in study drug adjustment were not prospectively collected on the study case report forms. Another limitation is the inability to differentiate performance between patients who were managed directly from site coordinators versus those who were treated through remote providers.

Participation in long-term longitudinal interventional trials with real time management of study medication in remote settings provides subjects with access to expert medical professionals and the latest therapies. It also helps to generate data of the highest quality. This may be particularly relevant for studies of late complications after HCT, such as chronic GVHD as well as pulmonary and infectious complications [9]. In addition, patients may experience an increased sense of hope and meaning as a result of contributing to studies offering better treatment for their disease [10]. The prospect of enabling subjects to participate in a multi-center study while being treated by their local physician represents new options in healthcare delivery. Given the paucity of data on turnaround times in oncology patients, this trial provides benchmark data for future interventions. Our results show that a randomized double-blinded multicenter trial with subjects geographically located miles from the coordinating center can be conducted effectively, safely and according to GCP standards.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.conctc.2016.05.002>.

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