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An open-label trial of the prophylactic administration of voriconazole in patients who undergo allogeneic hematopoietic stem cell transplantation: study protocol

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ABSTRACT

Invasive fungal infections, especially those caused by *Aspergillus*, can be fatal in patients who have undergone allogeneic hematopoietic stem cell transplantation. Fluconazole, itraconazole and micafungin can be used to prevent fungal infections in patients undergoing allogeneic hematopoietic stem cell transplantation, but fluconazole is not effective against *Aspergillus*, and itraconazole has less tolerability from gastrointestinal toxicity. Micafungin is approved for prophylaxis at a dose of 50 mg/day, less than a therapeutic dose. Voriconazole, the current preferred agent for invasive *Aspergillus* infection, is available in both oral and intravenous preparations, and has recently been approved for prophylaxis in Japan. Some US and European studies have reported on the prophylactic use of voriconazole, but the efficacy and safety of this has not been confirmed in Japan. Hence, this prospective study of voriconazole as prophylaxis against invasive fungal infections in patients who have received allogeneic hematopoietic stem cell transplantation is being performed to evaluate its efficacy and safety, including incidence rate of proven/probable invasive aspergillosis and other fungal infections, and adverse event(s) due to voriconazole administration. We are also investigating potential interactions between voriconazole and immunosuppressive drugs by monitoring the blood concentration of a calcineurin inhibitor in Japanese patients. Further, this study aims to improve the clinical outcomes of allogeneic hematopoietic stem cell transplantation recipients.

Keywords: invasive fungal infection, voriconazole, allogeneic hematopoietic stem cell transplantation

INTRODUCTION

Fungal infections can be fatal in patients who have undergone allogeneic hematopoietic stem cell transplantation (allo-HSCT). Among these infections, the incidence of invasive aspergillosis is high, with rates of 11–14% reported within the first year after transplantation.[1-2] The prognosis is poor, with post-onset mortality rates of 67–87%.[3] Hence, it is important to prevent these infections. Antifungal drugs for primary prophylaxis in allo-HSCT patients that have been approved for insurance coverage include fluconazole (approved in March 1989), itraconazole (approved in

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March 1993), and micafungin (approved in January 2007). However, fluconazole is ineffective against *Aspergillus*, and while itraconazole has been shown to prevent aspergillosis, patients may experience problems with tolerability due to its many gastrointestinal and other toxicities. Micafungin is approved for prophylaxis at a dose of 50 mg/day, but it is unclear whether it can prevent aspergillosis. In Europe and the United States, posaconazole can be administered preventively and its efficacy has been demonstrated; however, this drug has not been approved for use in Japan and questions remain regarding its ability to prevent invasive aspergillosis. In August 2015, the indications for voriconazole, which has shown efficacy against invasive aspergillosis, were expanded to include preventive administration. There have been reports from overseas on the prophylactic use of voriconazole,[4-5] but its efficacy and safety has not been confirmed in Japan.

A joint, multicenter, randomized trial on the preventive administration of voriconazole compared with itraconazole was performed in Europe and the United States.[6] At 180 days after transplantation, no significant differences were observed in the incidence of invasive fungal infections (2.1% vs. 1.3%, respectively) or survival rates (80.9% vs. 81.9%, respectively). However, the rate of continuing to take voriconazole preventatively was significantly higher than that of itraconazole (53.6% vs. 39.0%, $p < 0.01$). Moreover, a higher percentage of subjects transitioned from itraconazole (than from voriconazole) to another antifungal agent (29.9% vs. 41.9%, respectively, $p < 0.01$). This trial suggests that with voriconazole, fewer patients need to transition to another antifungal agent and preventative administration can be continued for longer periods. Based on these results, European guidelines recommended the use of voriconazole as preventative treatment. When administering voriconazole, it is necessary to monitor side effects such as liver dysfunction and visual disorders. Because it strongly inhibits the metabolic enzyme cytochrome P450 in the liver, interactions with immunosuppressants and other drugs require careful observation.[6] Hence, this prospective study of voriconazole as prophylaxis against invasive fungal infections in allo-HSCT patients is being performed to evaluate its efficacy and safety, and to investigate potential interactions with immunosuppressive drugs in Japanese people.

METHODS / DESIGN

Study design

This is a single-center, open-label, single-arm prospective study. This study has been registered in the Clinical Trial Registry (UMIN-CTR) (UMIN000027218).

Eligibility criteria

Inclusion criteria

1. Patients scheduled to undergo their first allo-HSCT at Nagoya Medical Center during the period from March 1, 2017 to February 28, 2019.
2. Provision of written informed consent by the patient to participate in this study.
3. Aged 20 years or older at the time of providing informed consent.
4. Either not taking voriconazole at the time of providing consent, or taking voriconazole but without evidence of proven/probable invasive fungal infection.
5. Eastern Cooperative Oncology Group performance status of grade 0–3.

Exclusion criteria

1. Patients with proven/probable invasive fungal infection at the time of acquisition of informed consent (patients can be registered if cure is confirmed at the time of participation in the study and an antifungal drug is not being used for therapeutic purposes).

Table 1 Child-Pugh classification

Measure \ Score	1 point	2 points	3 points
Neurological symptoms	Absent	Transient or mild	Hepatic coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (%)	>70	40–70	<40

Class	A	5–6 points
	B	7–9 points
	C	10–15 points

2. Patients with a history of hypersensitivity to the components of voriconazole.
3. Patients with creatinine clearance < 30 mL/min at the time of participation in the study.
4. Patients with a Child-Pugh classification score of grade C (Table 1).
5. Patients with a complication from cardiac disease (including an arrhythmia) that requires treatment.
6. Patients with a mental health disorder, psychiatric symptoms, or cognitive impairment.
7. Patients who are pregnant, possibly pregnant, or are breastfeeding.
8. Patients who are taking or scheduled to be administered a prohibited drug concomitantly with voriconazole.
9. Patients taking antiretroviral drugs to treat human immunodeficiency virus infection.
10. Patients deemed unsuitable for participation in this study by the principal investigator or other investigators.

Sample size

In order to obtain information on the efficacy and safety of prophylactic administration of voriconazole in Japanese, the sample size was calculated based on the precision of estimation of the primary endpoint. Assuming that the 1-year cumulative incidence rate of Aspergillus is 3%, it requires 30 patients to maintain the 95% confidence interval within 22% with a probability of 90% or more. At the Nagoya Medical Center, about 20 transplantations are performed annually. Assuming that the trial enrollment rate is 75%, the registration period is estimated to be 2 years.

Intervention

Voriconazole administration will begin 7 days before the date of transplantation and will continue for at least 100 days after transplantation. Oral administration will continue until the neutrophil count has recovered to ≥ 500/μL and immunosuppressive drugs have been terminated.

Oral administration

For patients weighing ≥ 40 kg, the voriconazole dose will be 300 mg twice daily on day 1, then 200 mg twice daily between meals from day 2. For patients weighing < 40 kg, the voriconazole dose will be 150 mg twice daily on day 1, then 100 mg twice daily between meals from day 2.

Criteria for changing the administration method, dose, or schedule

If oral intake is difficult, the intravenous form of the drug will be used. The dose for this will be 6 mg/kg twice daily on day 1, then 4 mg/kg twice daily from day 2. The patient will be transitioned to the oral drug once oral intake becomes possible. When this occurs, oral voriconazole will be given at the dose for day 2. Patients with mild to moderate reduction in liver function (Child-Pugh classification grade A or B [Table 1]) should receive the regular dose on day 1, then half of the regular dose from day 2.

Post-therapy

Oral voriconazole administration will end within 5 weeks after 100 days post-transplantation, when neutrophil levels reach 500/μL and immunosuppressants are stopped. "Within 5 weeks" is allowance from the end date and time of VRCZ in case of deviation in medication timing at outpatient clinics. Once the preventive administration of voriconazole has been terminated, any further administration of preventive antifungal agents, including voriconazole, is prohibited until one completed year post transplantation.

Endpoints

The primary endpoint is the 1-year cumulative incidence rate of proven/probable invasive aspergillosis after transplantation. The secondary endpoints are (i) continuation rate of taking voriconazole prophylaxis at post-transplantation day 100, (ii) adverse event(s), (iii) incidence rate of proven invasive fungal infections other than invasive aspergillosis during the period of voriconazole administration, (iv) relationship between blood concentrations of voriconazole and the incidence rate of proven/probable invasive fungal infection(s), and (v) effect of voriconazole administration on the blood concentration of a calcineurin inhibitor.

Statistical analysis

The analysis of efficacy will be performed on the full analysis set. The analysis sets are defined as follows.

1. Full analysis set: Subjects who fulfill the main registration criteria and who have at least one observed value after receiving voriconazole.
2. Safety analysis set: Subjects who received voriconazole at least once after registration.

Analysis of the primary endpoint

One-year cumulative incidence rate of proven/probable invasive aspergillosis after transplantation. The rate and its 95% confidence interval will be estimated based on a binomial distribution. In addition, the appearance of invasive aspergillosis over time will be estimated using the Kaplan-Meier method.

Analysis of the secondary endpoints

1. Continuation rate of voriconazole administration at day 100. The continuation rate of voriconazole and its 95% confidence interval at day 100 after transplantation will be estimated, based on a binomial distribution.
2. Adverse event(s): The number and incidence rates of each adverse event will be calculated.
3. Incidence rate of proven invasive fungal infections other than invasive aspergillosis during the period of voriconazole administration: The number and incidence rates of each fungal species causing invasive infection will be calculated.
4. Relationship between the blood concentration of voriconazole and the incidence rate of proven/probable invasive fungal infection. Blood levels of voriconazole on day 7 will be categorized, and

the number and incidence rates of invasive fungal infections will be calculated for each category. 5. Effect of voriconazole administration on the blood concentration of a calcineurin inhibitor. The calcineurin inhibitor dose before transplantation and on day 7 will be plotted for each patient.

DISCUSSION

This is a prospective study, conducted at Nagoya Medical Center, of allo-HSCT patients who receive voriconazole as preventative therapy. The study aims to evaluate the efficacy and safety of voriconazole as a prophylactic agent and to investigate its interactions with immunosuppressive drugs in Japanese people, and to improve the clinical outcomes of allo-HSCT recipients. Based on the result of the efficacy and safety obtained in this study, we will plan to conduct a multicenter joint study to compare voriconazole with other fungal drugs as the next study.

ETHICS COMMITTEE PROCEDURE AND CONSENT FOR THE STUDY

This trial was approved by the Clinical Research Ethics Committee of Nagoya Medical Center on March 9, 2017. Written informed consent is obtained from every participant in the study.

AUTHOR CONTRIBUTIONS

HI performed the final approval of the protocol and coordinate the overall trial. AK will manage the progress of and coordinate the overall trial, and will manage the storage of records. YH, HI and AK designed and examined the trial protocol. HH assisted with drafting the protocol and will be responsible for the statistical analyses. AS assisted with drafting the protocol and conducted quality control (data management and monitoring).

COMPETING INTERESTS

The authors declare that they have no competing interests.

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