Posaconazole prophylaxis during anti-thymocyte globulin treatment for hypoplastic myelodysplastic syndrome(HMDS)/ aplastic anemia(AA) patients

Trial Registration: Clinicaltrials.gov NCT03318159, registered Jul 23, 2017

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Methods

Study Design

In this prospective, open label, single arm study(Clinicaltrials.gov no. NCT03318159), we enrolled patients with diagnosed hypoplastic myelodysplastic syndrome(HMDS) and aplastic anemia(AA) patients who received anti-thymocyte globulin(ATG) treatment at Seoul National University Hospital(SNUH) and Seoul National University Bundang Hospital from Aug 2018 through Jun 2023. All patients enrolled in the study provided written informed consent. Inclusion criteria were as follows : 1) ≥18 years and <75 years old, 2) hypoplastic myelodysplastic syndrome(HMDS) or aplastic anemia(AA) diagnosed, 3) anti-thymocyte globulin(ATG) treatment, 4) no QTc prolongation on initial ECG, 5) Serum creatinine and AST/ALT levels ≤ 2 times the upper limit of the reference range for laboratory and 6) Serum bilirubin levels ≤ 1.5 times the upper limit of the reference range for laboratory. Exclusion criteria were as follows : 1) Suspected fungal infection within 30 days of ATG treatment, 2) history of allergic to –triazoles, 3) diagnosis of other malignancy in the previous 5 years, 4) previous chemotherapy, radiation, or immunosuppressive treatment, 5) pregnant or breastfeeding, male or female patients of reproductive potential who are not employing an effective method of birth control, 6) active HBV and HCV patiens and HIV positive patients, 7) history of receiving organ transplantation, 8) QTc prolongation is identified on baseline ECG of who have Torasdes de pointes syndrome and 9) on ergotamine alkaloids, CYP3A4(terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine) or HMG-CoA reductase inhibitors.

Patients received 300mg Posaconazole orally twice daily on day 1 and 300mg once daily for 4weeks from day 2. Posaconazole should start on the same day as ATG, but if it's not possible to start on the same day, it's allowed to start within +/- 3 days.

The primary end point was the incidence of proven/probable/possible fungal infection through 4-week post-treatment period, and the secondary end points were overall survival, any fungal infection.

Patients were followed up for 6 months from the end of prophylactic treatment for the occurrence of additional fungal infection and survival, respectively.

The determination of sample size

The incidence rate of invasive fungal infection is estimated to be 80% in childhood aplastic anemia patients undergoing ATG treatment (Pediatric Hematology and Oncology, 31:1, 20-28, 2014). Allowing for up to a rate of 30%, based upon a sample size of n=20 patients per group, this study will ensure that a two-sided test with $\alpha = 0.05$ has 80% to detect the difference. We aim to recruit double the minimally required sample size.

Statistical Analysis

Categorical variables were compared using Student t-test or Pearson's chi-square test as appropriate. $P < 0.05$ are considered statistically significant. Overall survival were evaluated by Kaplan-Meier analysis.

Ethical Considerations

This study was approved by the institutional review board at Seoul National University Hospital(IRB; 1706-207-866) and was conducted in accordance with the guidelines of the Declatation of Helsinki for biomedical research. Informed consent was obtained from all participants.

Informed consent

The information is prepared to explain the contents of this research. If you have any questions, please ask the principal investigator or other investigator.

1. Clinical Trial Title

Posaconazole prophylaxis during anti-thymocyte globulin treatment for hypoplastic myelodysplastic syndrome(HMDS)/ aplastic anemia(AA) patients

2. Principal Investigator

Professor Youngil Koh, Department of Hematology and Oncology

3. Background

In the case of aplastic anemia and dysplasia syndrome, which are continuously pancytopenia due to bone marrow dysfunction, there is a high risk of invasive fungal infection by themselves. Furthermore, the risk of fungal infection can be higher due to the anti-thymocyte globulin effect when treated. In particular, these fungal infections occur immediately after treatment, and the risk is reported to exceed about 15-20%. Therefore, it is clinically recommended to prevent antifungal drugs, but it has not been established yet, and for that reason, the best agent have not been known. Therefore, in this study we want to check whether the preventive use of posaconazole, a broad-spectrum antimicrobial agent that is already widely used, can reduce the probability of fungal infection and increase the successful treatment rate.

4. Investigational drugs

Posaconazole

- Efficacy/Effect :

1) Treatment of patients with invasive aspergillosis who are refractory to amphotericin B or itraconazole or intolerant to these treatments

2) Prevention of invasive fungal infections

5. Precautions for use

Major advedse event associated with the most frequently reported treatment in relation to medication include nausea, vomiting, diarrhea, fever, and elevated bilirubin.

6. Clinical trial period

Subjects will receive this drug from the day start of anti-thymocyte globulin treatment to 4weeks

of drug. The research team will follow up for 6months the time of completion of the 4weeks medication.

7. Clinical trial method

If you participate in this study, you will receive a free supply of posaconazole. Patients received prescribed dose posaconazole twice a day on the first day of anti-thymocyte globulin treatment and once a day on the second day for a total of 4 weeks. If necessary, culture test for body fluids such as sputum and blood may be performed. The sample process will be performed in the treatment and examination process for regenerative anemia and dysplasia of the bone marrow, which will not be conducted in this study except for posaconazole administration.

8. Benefits for study subjects

By reducing the frequency of fungal infections, you can benefit from hospital stay and cost of treatment.

9. Expenses and Compensation

Participation in this clinical trial may provide you with a free supply of antifungal drugs, but may not have any other benefit. For the evaluation of fungal infection, chest imaging tests, blood tests, and culture tests for body fluids are needed. These tests are performed depending on the patient's condition.

10. Requirements for study subjects

There are no special requirements for study subjects. If you are discharged from the hospital after treatment, you must visit the hospital for evaluation of fungal infection at the 6th and 12th weeks from the date of induction chemotherapy.

11. Voluntary participation/discontinuation of study

Participation in clinical trials is entirely up to you. If you do not agree to participate in the clinical trial, it does not matter at all. In addition, even after consenting to participate in the trial, you can withdraw your consent to participate in the clinical trial at any time if you wish, and there will be no disadvantage or damage.

12. Continous provision of new research-related information

If the investigator becomes aware of any new facts during the study, the investigator will inform you or your representative of the facts at any time.

13. Damage and compensation

Although this drug is currently marketed and used, unexpected side effects may occur. Compensation will be determined in accordance with regulations related to Seoul National University Hospital and separate compensation agreements with insurance companies. Damage compensation can be compensated up to a maximum of 500 million per accident and 100 million per person.

14. Confidentiality

All records of your identity obtained in this research will be kept confidential, and even when the results are published, your personally identifiable information will be kept confidential.

15. Contact person

If additional information is needed regarding the clinical trial and the rights and interests of the subject, or in case of damage related to the clinical trial, contact: 02-743-7617 (research nurse), other emergency contact information, if you have any questions about the research, etc.) IRB (Institutional Review Board, Medical Research Ethics Review Board): 02-2072-0694 Clinical Research Ethics Center Contact: 02-2072-3509