Micafungin prophylaxis for acute leukemia patients undergoing induction chemotherapy

Trial Registration: Clinicaltrials.gov NCT02440178, registered May 12, 2015
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Methods

Study Design

In this prospective, single-arm, open-label study (Clinicaltrials.gov number, NCT02440178), we enrolled patients with newly diagnosed acute leukemia (AML, acute lymphoblastic leukemia [ALL], and acute biphenotypic leukemia [ABL]) who received intensive induction chemotherapy at Seoul National University Hospital (SNUH) and Seoul National University Bundang Hospital from September 2015 through June 2017. All patients enrolled in the study provided written informed consent. Inclusion criteria were as follows: 1) ≥ 18 years old; 2) Acute leukemia diagnosed by bone marrow examination; 3) intensive induction chemotherapy; 4) Eastern Cooperative Oncology Group performance status score ≤ 2; and 5) serum creatinine and bilirubin levels < 1.5 times the upper limit of the reference range for our laboratory. Exclusion criteria were as follows: 1) suspected fungal infection 30 days before initiation of induction chemotherapy; 2) history of hypersensitivity to echinocandin; 3) diagnosis of other malignancy in the previous 5 years; 4) previous chemotherapy, radiation, or immunosuppressive treatment; 5) immunodeficiency disease; 6) pregnant or breastfeeding; 7) uncontrolled seizures or mental illness; 8) acute myocardial infarction, uncontrolled arrhythmia, or low ejection fractions (< 40%); 9) previous organ transplantation; and 10) interstitial lung disease.

Patients received 50 mg micafungin intravenously once daily from the initiation of

induction chemotherapy to recovery of neutrophil count (absolute neutrophil count > 500/μg for three consecutive days), suspected fungal infection, or occurrence of drug-related toxicity. The primary end point was incidence of invasive fungal infection, and the secondary end points were adverse events of prophylactic micafungin and mortality during induction chemotherapy. Patients were followed up for 6 and 12 weeks after the initiation of induction chemotherapy for the occurrence of fungal infection and survival, respectively.

The determination of sample size

The previous study showed that the incidence of fungal infections was about 29.2% in prophylactic fluconazole group and 13.8% in posaconazole group. We hypothesized that the incidence of fungal infections in the prophylactic micafungin group was reduced by 15.4% (assuming that the incidence is similar to that of the prophylactic posaconazole group) from that of prophylactic fluconazole group. Therefore, a sample size of 65 patients was required for this study based on a statistical power of 80% and a significance level of 5%, including a dropout rate of 10%.

Diagnosis of invasive fungal infection

For all patients, baseline chest x-rays were obtained within 7 days after the initiation of induction chemotherapy. *Aspergillus* infection was diagnosed according to the criteria for invasive pulmonary aspergillosis of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. An invasive fungal infection was defined as “proven” by a positive culture for fungus with symptoms and signs of a fungal infection, as “probable” by direct or indirect detection (galactomannan antigen or serum *β*–D-glucan) with clinical and radiographic findings, or as “possible” if

sufficient clinical evidence for fungal infection was present without mycological evidence.

Statistical Analysis

Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Cumulative incidence of fungal infection and the time from initiation of micafungin treatment to a switch to another antifungal agent were evaluated by Kaplan–Meier analysis. All analyses were performed using SPSS for Windows, version 23.0 (IBM; Armonk, NY, USA); All statistical tests were two-sided, and significance was defined as $P < 0.05$.

Ethical Considerations

This study was approved by the institutional review board at Seoul National University Hospital (IRB; H-1412-022-631) and was conducted in accordance with the guidelines of the Declaration 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

Micafungin Prophylaxis During 1st Induction Chemotherapy for De Novo Acute Leukemia

2. Principal Investigator

Professor Youngil Koh, Department of Hematology and Oncology

3. Background

In acute leukemia, neutropenia persists for a long time during inducing chemotherapy, which leads to the occurrence of invasive fungal infection. The need for prophylactic antifungal agents has been continuously demanded, and micafungin is currently used as a prophylactic antifungal agent in pretreatment for hematopoietic stem cell transplantation. Although micafungin is currently used for the treatment of fungal infections, it has not been established as a preventive agent in induction therapy for acute leukemia.

4. Investigational drugs

Micafungin

- Efficacy/Effect:

1) Treatment of esophageal candidiasis

2) Prevention of fungal infection in hematopoietic stem cell transplant recipients

5. Precautions for use:

1) Warning

Severe hypersensitivity has been reported. If hypersensitivity occurs, administration of this drug should be stopped immediately and appropriate treatment will be needed.

2) Other clinically significant adverse events are as follows.

① Vascular and lymphatic disorders: coagulation disorders, hemolysis, hemolytic anemia, pancytopenia, thrombotic thrombocytopenic purpura

② Cardiac abnormalities: arrhythmias, cardiac arrest, cyanosis, myocardial infarction, tachycardia

③ Hepatobiliary disorders: hepatocellular damage, hepatomegaly, jaundice, liver failure

④ General adverse reactions and administration site abnormalities: thrombus at the administration site

⑤ Infection and invasion of pathogens: infection, pneumonia, sepsis

⑥ Metabolic and nutritional abnormalities: acidosis, anorexia, hyponatremia

⑦ Musculoskeletal, connective tissue, bone abnormalities, joint pain

⑧ Nervous system abnormalities: convulsions, brain disease, intracranial hemorrhage

⑨ Kidney and urinary disorders: anuria, hemoglobinuria, oliguria, acute renal failure, renal tubular necrosis

⑩ Respiratory, chest and septal abnormalities: apnea, dyspnea, hypoxia, pulmonary embolism

⑪ Skin and subcutaneous tissue abnormalities: erythema multiforme, skin necrosis

6. Clinical trial period

Subjects will receive this drug from the day they start induction therapy to the day they recover from neutropenia. The research team will evaluate the incidence of fungal infection up to 6 weeks and survival up to 12 weeks after initiation of induction therapy.

7. Clinical trial method

If you participate in this study, you will receive a free supply of micafungin. Patients received 50 mg micafungin intravenously once daily from the initiation of induction chemotherapy to recovery of neutrophil count (absolute neutrophil count > 500/μg for three consecutive days), suspected fungal infection, or occurrence of drug-related toxicity. Chest imaging and fungal serology will be performed once a week. If necessary, culture tests for body fluids such as sputum and blood may be performed. The drug is discontinued when the neutrophil count exceeds 500 or exceeds 3000 for 3 days or more. In addition, a blood test to evaluate fungal infection at the 6th week is needed.

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. Continuous 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