Successful Treatment of Lung *Aspergillus terreus* Infection After a Second Hematopoietic Stem Cell Transplant in a Patient With Myelodysplastic Syndrome

Yu Zhang,† Junfa Chen,† Lili Qian,‡ Xuejing Yang,‡ Jianping Shen†

Department of Hematology and the Department of Laboratory, First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

Acknowledgements: The authors have no conflicts of interest to disclose and received no funding for this study.

Corresponding author: Jianping Shen, Department of Hematology, First Affiliated Hospital of Zhejiang Chinese Medical University, 54# Youdian Road, Hangzhou, 310006, China

Phone: +86 13516811728 E-mail: sjping88@163.com

Experimental and Clinical Transplantation (2017) DOI: 10.6002/ect.2016.0319

### Case Report

A 24-year-old man was diagnosed with myelodysplastic syndrome (MDS, RAEB-II) in May 2015. He had an intermediate karyotype (+8) and pancytopenia. The bone marrow showed 14% blast cells, which was categorized as very high risk (6.5 points) according to the Revised International Prognostic Scoring System. The patient needed a transplant; however, no human leukocyte antigen (HLA)-identical sibling or unrelated donor was available. The patient’s father, who was HLA half-matched, agreed to donate stem cells. The treatment approach before transplant consisted of omacetaxine mepesuccinate (2 mg intravenously [IV], once daily from day 1 to day 7), cytarabine (25 mg subcutaneously, twice daily from day 1 to day 7), and aclarubicin (20 mg IV, once daily on days 1, 3, and 5) every 28 days for 1 course and 25 mg/m² IV decitabine once daily for 5 days every 28 days for 2 courses.

In August 2015, the patient received a haplo-identical hematopoietic stem cell transplant (HSCT; peripheral blood + bone marrow) with a myeloablative conditioning regimen based on cytarabine (4 g/m²/d IV for 2 days), busulfan (3.2 mg/kg/d IV for 3 days), cyclophosphamide (3.6 g/m²/d IV for 2 days), and antilymphocyte globulin (10 mg/kg/d IV for 4 days). Graft-versus-host disease prophylaxis consisted of cyclophosphamide, methotrexate, and short-term methotrexate. The patient received 8.46 × 10⁶ CD34-positive cells/kg. On day 21 after transplant, granulocytes and platelets were not engrafted into the patient. The bone marrow puncture report suggested extremely low bone marrow proliferation. Primary engraftment failure was considered, possibly associated with donor-specific antibodies (DSAs). Peripheral blood specimens from both the patient and the parents were sent for DSA detection. The results suggested that there were strongly positive anti-HLA-I antibodies in the patient’s body. Analysis of specific sites (detection performed using HLA-I, HLA-II, and major histocompatibility complex class I polypeptide-related sequence A single antigen magnetic bead reagents) showed that they were strongly positive DSAs. In addition, the patient did not have specific antibodies against the mother’s HLA (Table 1). We immediately performed the
second transplant using the mother as the donor (using peripheral blood) and added a single unit of cord blood (third-party blood from the Shanghai cord blood bank, Shanghai, China).

Before transplant, immunoglobulin (0.4 g/kg/d IV twice per week from day 7 pretransplant onward), plasmapheresis (day 6 and day 3 pretransplant), rituximab (375 mg/m²/d IV on day 2 pretransplant), and CD25 monoclonal antibody (20 mg/d IV on day 1 pretransplant and day 4 posttransplant) were administered to reverse the graft rejection and reduce the antibody load. Cyclophosphamide (50 mg/kg/d IV on day 3 posttransplant) was provided as a posttransplant graft-versus-host disease prophylaxis regimen. On d01, the patient was transfused with 27.5 mL of cord blood (6/6 matched), and the mononuclear cell count was 11.6 × 10⁸/L. On the 2 days of infusion (d01 and d02), the patient was transfused with 397 mL of peripheral blood stem cells from the mother. The CD34-positive count was 5.5 × 10⁶/kg, and the mononuclear cell count was 17.7 × 10⁸/kg.

After the second transplant, granulocytes were implanted on day 11, and platelets were implanted on day 13. The bone marrow puncture report on day 20 suggested that bone marrow proliferation was active, and a short tandem repeat (STR) report of the patient’s peripheral blood on day 30 suggested that the degree of chimerism between the patient and the patient’s mother was 98.56%.

Cytomegalovirus (CMV) serology results for the donor and the recipients were positive before the first and second transplant procedures. We used ganciclovir (5 mg/kg IV daily from day 8 to day 2) before the first transplant and then acyclovir (1 g orally 3 times daily) for CMV prophylaxis after the first and second transplant procedures. The donor’s CMV DNA tests continued to be negative during hospitalization. At 3 months before the first transplant, the patient had a fever during chemotherapy, and a lung computed tomography (CT) revealed that both lungs had scattered and patchy areas of high-density shadows. The patient’s Aspergillus antigen index test was 1.13 (reference < 0.5), without alveolar lavage and lung biopsy. We administered an itraconazole intravenous drip for 14 days and sequential oral administration for 14 days, after which the patient had a normal lung CT. His galactomannan test dropped to 0.31, and antifungal treatment was stopped.

For the first transplant, the patient received itraconazole (200 mg orally twice daily on days 1 and 2; 200 mg once daily from day 3 onward) for empirical prevention therapy. On day 7, the patient developed a fever, which reached 38.9°C. Pulmonary CT did not show any obvious abnormality (Figure 1A). His body temperature was controlled after meropenem treatment (1 g IV 3 times daily).

For the second transplant, the patient also received itraconazole for empirical prevention therapy. On day 8, the patient also developed a fever, which reached 39.4°C, as well as cough and chest pain. Pulmonary CT suggested diffuse left pleural thickening combined with a mass shadow (Figure 1B). Treatment was changed to cefoperazone/sulbactam (cefoperazone-to-sulbactam ratio of 2:1, 3 g IV twice daily), tigecycline (50 mg IV twice daily, with the first dose doubled), and voriconazole (6 mg/kg IV twice daily on day 1 and 4 mg/kg IV twice daily from day 2 onward). On day 17, the patient still had a fever, reaching 40.0°C, with aggravated cough and chest pain. The patient was treated with amphotericin B, which was gradually increased to 0.6 mg/kg IV once daily. The patient’s body temperature and cough and phlegm symptoms did not improve.

On day 23, a CT-guided lung lesion puncture was performed (Figure 1C). The direct smear showed fungal spores and hyphae (Figure 2A). Colonies with round shapes, soft textures, villous shapes, light

<table>
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<tr>
<th>Classification</th>
<th>Result</th>
<th>Specificity</th>
<th>MFI</th>
<th>Molecular Specificity</th>
<th>Interpretation</th>
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<tr>
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<td>Positive</td>
<td>Cw10</td>
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<td>C*0304</td>
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</tbody>
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Abbreviations: DSAs, donor-specific antibodies; MFI, mean fluorescence intensity

Figure 1. Changes in Pulmonary Computed Tomography Images
brown colors, and radial grooves formed on the Sabouraud agar (Figure 2B). Under the microscope, the conidiophore head showed a dense cylindrical shape, the hyphae had septa and were transparent, and the outer wall was rough (Figure 2C and 2D). Fungal DNA was extracted to perform polymerase chain reaction amplification of the internal transcribed spacer region. After sequencing and comparison and analysis using blast in GenBank, the specimen was confirmed to be *Aspergillus terreus*. The treatment was changed to piperacillin/tazobactam (4.5 g IV 3 times per day), tigecycline (50 mg IV twice daily), micafungin (5 mg/kg IV once daily), and posaconazole (400 mg orally twice daily).

The patient’s body temperature returned to normal on day 25, and the cough and chest pain symptoms significantly improved. Antifungal therapy is summarized in Figure 3. At final follow-up (day 305 posttransplant), MDS is in complete remission status, and antibacterial drugs were terminated, with only posaconazole (200 mg orally twice daily) maintained.

**Discussion**

Myelodysplastic syndrome is a very heterogeneous group of myeloid disorders characterized by peripheral blood cytopenias and increased risk of transformation to acute myelogenous leukemia. In higher-risk groups, the available therapies include intensive chemotherapy and allogeneic stem cell transplant. Our patient was newly diagnosed with very high-risk MDS; in the absence of an HLA-matched donor, haploidentical HSCT was an appropriate choice. Unfortunately, the patient developed graft failure posttransplant. Risk factors for graft failure include donor/recipient HLA disparities, use of an unrelated donor, use of cord blood as a stem cell source, T-cell depletion of the graft, use of reduced-intensity conditioning regimens, low numbers of transplanted cells, and the presence of DSAs. Preformed DSAs present at the time of transplant correlated with graft failure, especially in mismatched and haploidentical HSCT patients. Therefore, we changed the donor to the patient’s mother to perform the second transplant and used a series of methods to reverse the DSA-mediated graft rejection and reduce the antibody load. The grafts were implanted successfully, and the STR report showed that the degree of chimerism was 98.5%.

Invasive fungal infections pose the most serious infectious risk to patients with hematologic malignancies and in those undergoing HSCT. A timely diagnosis is essential in promptly initiating antifungal therapy to optimize clinical outcomes. With the use of percutaneous puncture biopsy under CT direction, we isolated a pathogenic organism and determined that it was *Aspergillus terreus* via microculture and gene sequencing. *Aspergillus terreus* is an emerging opportunistic fungus whose clinical incidence has recently increased. Treatment commonly fails, and the mortality rates are higher than those of other *Aspergillus species*. *Aspergillus terreus* infections have prompted clinical interest because of their lack of response to amphotericin B and the relatively high percentage of clinical isolates with acquired resistance to azoles, particularly voriconazole. Isavuconazole has demonstrated potent
in vitro antifungal activity against most *Aspergillus* species, including *Aspergillus terreus* strains that were resistant to amphotericin B. Unfortunately, isavuconazole is not available in China. The in vitro activity of posaconazole against *Aspergillus terreus* is greater than itraconazole and voriconazole; therefore, we used posaconazole to treat this patient. In consideration of the high intersubject variability determined by the drug’s degree of absorption, we used micafungin combined with posaconazole. The combined treatment of posaconazole and micafungin had a good efficacy in this case and provided valuable information for the selection of treatment with the second transplant after primary engraftment failure and *Aspergillus terreus* infection during the HSCT process.

References