Combination antifungal therapy and surgery for the treatment of invasive pulmonary aspergillosis after hematopoietic stem cell transplantation

Simone Cesaro,[1] Marta Pillon,[1] Elisabetta Calore,[1] Rita Alaggio,[2] Piergiorgio Gamba,[3] Silvia Bergamo,[1] Chiara Mainardi,[1] Tiziana Toffolutti,[4] Anna Pegoraro,[1] Chiara Messina[1]

[1]Pediatric Hematology Oncology, Department of Pediatrics, Padova; [2]Department of Pathology, University of Padova; [3]Pediatric Surgery, Department of Pediatrics, Padova; [4]Pediatric Radiology, Department of Pediatrics, Padova, Italy

Abstract

An 8-year old boy, affected by severe aplastic anemia, developed a probable pulmonary invasive aspergillosis (IA) early after a second unrelated allogeneic hematopoietic stem cell transplant (HSCT). He was treated promptly with the combination of liposomal amphotericin B and caspofungin. Despite the initial stabilization, the patient deteriorated and the antifungal therapy was switched to voriconazole and caspofungin. The patient gradually improved and was discharged home on day +29 post-HSCT on oral voriconazole. On day +119, a sudden episode of hemoptysis occurred and a right superior lobectomy was decided to remove the residual aspergilloma. The patient is now alive and well more than 24 months from HSCT. This case demonstrated that antifungal combination therapy and surgery are valid options to cure pulmonary IA even in patients at high-risk and severely immunosuppressed.

Introduction

Despite the introduction of liposomal formulations of amphotericin B, broad spectrum triazoles, and antifungals with a new mechanism of action such as the echinocandins, the mortality from IPA remains high in HSCT patients.[1] The optimal treatment of IPA in HSCT patients has not been established. Current recommendations do not distinguish between neutropenic leukemic and HSCT patients, voriconazole and liposomal amphotericin B being mainly indicated as first-line therapy.[2] For a patient refractory to initial monotherapy, switching to another class of drug, i.e. caspofungin or another echinocandin, or the use of combination antifungal therapy are both considered valid options although there are limited data to guide this choice.[3]

We report a case of successful treatment of disseminated IPA in a boy affected by severe aplastic anemia who underwent a second unrelated allogeneic HSCT for primary graft failure. The successful outcome was obtained by an intensive medical treatment (combination therapy with rotation of antifungals) and delayed lung surgery.

Case Report

An 8-year old latin-american boy was diagnosed with severe aplastic anemia and was treated with 2 courses of immunosuppressive therapy (IST) without obtaining a hematological response. Fourteen months after diagnosis, he underwent an unrelated cord blood transplant that was HLA class I double mismatched. Conditioning was based on fludarabine, cyclophosphamide, and rabbit antilymphocyte serum, and mini-total body irradiation, 1×200 cGy/day.[4] GVHD prophylaxis was based on cyclosporin and a short course of methotrexate (MTX). Unfortunately, the patient had a primary graft failure. A second allogeneic HSCT was scheduled as soon as a HLA mismatched unrelated donor was identified in the international registries. The interval between the first and second HSCT was 5 months. In the 8 weeks before the second HSCT the patient was treated extensively with broad-spectrum antibiotics because of two severe infective episodes: a sepsis by *Staphylococcus warneri* and, two weeks later, a sepsis by *Stenotrophomonas malthophilia* resulting in bilateral sinusitis and necrotizing dental abscess extending to the hard palate. Given the persistent aplasia the patient was started on prophylaxis with voriconazole beginning 6 weeks before the second HSCT.

Conditioning regimen for the second HSCT was fully myeloablative with thiothepa, 2×5 mg/kg/day (day -6), cyclophosphamide, 4×50 mg/kg/day, and rabbit antithymocyte globulin (ATG Fresenius-S, Munich, Germany), 4×20 mg/kg/day, (from day - 5 to day - 2). As prevention of post-transplant EBV-related lymphoproliferative disease, the patient received also rituximab before stem cell infusion at the dose of 375 mg/m^2.

On day 0, the patient was infused with a total number of nucleated cells of 7.8×10^8/kg.

The twice-weekly monitoring of serum galactomannan (GM) showed a progressive increase from 0.6 on day - 6 to 2.1 on day +1, this latter day being characterized also by the appearance of high fever (39°C), cough, and bronchial breath sound to the left lung. An urgent CT scan of the lungs showed 3 radiological lesions with ground glass ring consistent with probable IPA involving the left superior lobe, the left inferior lobe, and right inferior lobe. A combination therapy with liposomal amphotericin B (Ambisome® Gilead, Milan, Italy), 3 mg/kg/day, and caspofungin, 1×70 mg/m^2 followed by 1×50 mg/m^2/day, was started. In the following week both fever and patient clinical findings remained stable whereas the serum GM cut-off index continued to rise to 4.5. Blood cultures and viral search (cytomegalovirus, adenovirus, respiratory syncitial virus, Epstein-Barr virus, Human Herpes virus 6) remained always negative. On day + 11, the patient deteriorated with higher fever, polypnea, hypoxemia, important pleural pain to left hemithorax. The lung CT scan showed a further extension of lung involvement with parenchymal consolidation extending to almost all the left lung and pleural effusion (Figure 1). GM cut-off index further increased to 8. The antifungal combination therapy was switched to voriconazole and caspofungin, and G-CSF was started (day +13). The patient gradually improved and the fever disappeared as well as the oxygen dependence. The neuthrophil engraftment was on day + 18. Caspofungin was suspended and the patient was discharged home on day + 29 on oral voriconazole with a GM cut-off

Correspondence: Simone Cesaro, Pediatric Hematology Oncology, Policlinico G.B. Rossi, Azienda Ospedaliera Universitaria Integrata, p.le L.A. Scuro, 10, 37134, Verona, Italy.
Tel. +39.045.812.4931 - Fax. +39.045.812.4909.
Email: simone.cesaro@ospedaleuniverona.it

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index lower but still abnormal, 2.09. In the following months, the clinical conditions continued to improve as demonstrated by a further lung CT scan on day + 60 whereas the GM cut-off index persisted abnormal, though decreasing: 2.6-2.9 in the second month, and 1.07 in the third month. On day +119, the patient presented with a sudden episode of hemoptysis. The lung CT scan showed persistence of a consolidation area at the right superior lobe with involvement of the bronchi (between the dorsal portion of the left superior lobar bronchus and the anterior portion of the left inferior lobar broncus). It was decided to perform a left superior lobectomy to prevent the risk of sudden fatal hemorrhages. The histological examination was consistent with aspergilloma (Figure 2). The GM cut-off level became persistently negative after surgery. The patient continued on voriconazole as secondary prophylaxis. Repeated lung CT scans and GM serum determinations confirmed the complete resolution of pulmonary aspergillosis. At 26 month after HSCT, the patient is alive and well, with full donor engraftment, and enjoys a normal life.

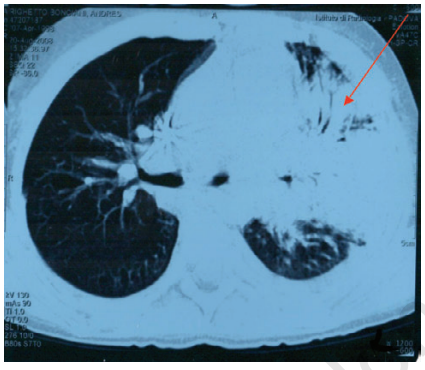

Figure 1. Diffuse parenchyma involvement with consolidation to almost all left lung and pleural effusion.

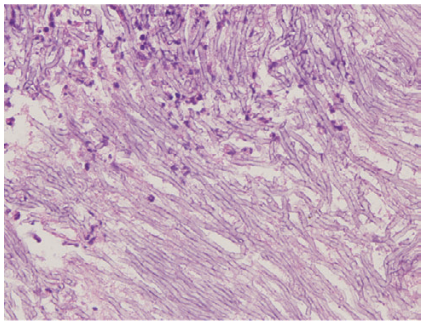

Figure 2. Septatae hyphae consistent with *Aspergillus* infection in the granuloma removed surgically.

Discussion

The introduction of new drugs or new formulations has contributed to improve the prognosis of IPA after chemotherapy whereas the success rate in HSCT patients still remains unsatisfactory: the favourable response is 32.4% with voriconazole and 47% with Ambisome®, and the corresponding figures as rescue therapy are 14% for caspofungin, and 38% for voriconazole.[5-8]

The combination of antifungal drugs, in order to obtain a synergistic effect by acting on different targets of the fungal cell components, has been proposed as an alternative to treatment with a single antifungal agent. The recent updated guidelines of the European Conference on Infectious Complications in Leukemic patients stated that combination antifungal therapy is optional in patients who need rescue treatment.[2]

Our patient presented with many factors that may have impacted negatively on survival, because he received a second myeloablative HSCT having been immunodepressed and severely neutropenic for several months. Moreover, he was treated with broad spectrum antibiotics for 2 episodes of bacterial sepsis, and the invasive aspergillosis developed despite prophylaxis with voriconazole. For all these reasons, we decided to maximize the treatment using antifungal combination therapy from the beginning. The use of Ambisome and caspofungin initially obtained a stabilization of the patient clinical parameters but the combination was changed to voriconazole and caspofungin after a subsequent clinical and radiological worsening of the patient. This fact does not certainly mean the failure of antifungal therapy because the clinical and radiological worsening is sometimes described concurrently with patient myeloid recovery or neutrophil engraftment, due to the so called inflammatory systemic response. Although the data are limited, we opted to switch to a salvage therapy with the combination of voricozole and caspofungin because it was associated to a reduced mortality in patients with IA after allogeneic HSCT.[9]

Caillot et al. showed that aggressive surgery has a role in preventing fatalities due to massive hemorrhages in patients with invasive pulmonary aspergillosis and hemoptysis.[10] Despite that, its role in the treatment of lung aspegillosis is still considered optional due to the fear of post-surgical morbidity, especially after HSCT.[2] In this patient, the surgery contributed to speed the complete eradication of residual lung lesions as demonstrated by the persistent negativity of GM and the absence of recurrent pulmonary fungal infection in the following months.

In conclusion, this case showed that both antifungal combination therapy and surgery are a valid option to treat an IPA occurring in the early phase post-HSCT in a pediatric patient. We recognize that more data are needed to assess the role of combination antifungal therapy and of surgery in this setting but the complexity and poor prognostic profile of these patients may pose problems in the design of a prospective study.

References

1. Burgos A, Zaoutis TE, Dvorak CC, et al. Pediatric Invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics 2008;121: 1286-94.
2. Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3-2009 Update. Bone Marrow Transplant 2011;46:709-18.
3. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of Aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008; 46:327-60.
4. Bacigalupo A, Sociè G, Lanino E, et al. Fludarabine, cyclophosphamide, anti-thymocyte globulin, with or without low dose total body irradiation for alternative donor transplants in acquired severe aplastic anemia (SAA): a retrospective study from the EBMT-SAA working party. Haematologica 2010;95:976-82.
5. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-15.
6. Cornely OA, Maertens J, Bresnik M, et al. Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial). Clin Infect Dis 2007;44:1289-97.
7. Maertens J, Raad I, Petrikkos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. Clin Infect Dis 2004;39:1563-71.
8. Walsh TJ, Lutsar I, Driscoll T, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. Ped Infect Dis J 2002;21:240-8.
9. Marr KA, Boeckh M, Carter RA, et al. Combination antifungal therapy for invasive aspergillosis. Clin Infect Dis 2004;39:797-802.
10. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 1997;15:139-47.