Use of Micafungin for the Management of a Cluster of Invasive Aspergillosis in Children with Cancer

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Authors’ contributions

This work was carried out in collaboration among all authors. Authors DC, LG and MA designed the study, wrote the protocol and wrote the first draft of the manuscript. Author FB supervised the laboratory investigation for control of mold contamination. Authors DC, DaCu, AT, AnTa and FT were in charge for patient care, collected the clinical data and performed the literature search. Author LDS performed the analysis of costs. All authors read and approved the final manuscript.

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ABSTRACT

**Background:** Progressive increase of the capacity to cure children with cancer makes their rescue from life-threatening infectious complications, such as invasive fungal infections, a compelling challenge. Local outbreak among patients at risk may occur, and the optimal strategy for their management, including prophylactic regimens, is not defined.

**Purpose:** We describe our experience in the use of micafungin to break a cluster of invasive aspergillosis in children and adolescent with cancer.

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INTRODUCTION

Invasive fungal infection (IFI), especially invasive aspergillosis (IA), is a life-threatening complication of immune suppression induced by cancer-directed chemotherapy or hematopoietic stem cell transplantation (HSCT). The reported incidence in children ranges between 2 and 21% in different studies and countries [1-5]. In Italy, recent studies report an incidence comprised between 6% and 11% [6,7]. In a nation-wide survey on a 7-year period, 127 episodes of IFI were diagnosed in 123 patients, median age of 9.7 years. The 1-year cumulative incidence was 2.5% (CI, 1.8-3.7) after frontline chemotherapy, 9.4% (CI 5.8-15.0) after relapse, and 5.3% (CI 3.9-7.1) after HSCT. Severe neutropenia was present in 98 (77%) patients. Culture-proven agents were Candida spp., mostly non-albicans, (n=28), mold (n=23), whereas three proven IFI were identified by histopathology. Favorable response to treatment within 3 months from diagnosis was observed in 77 (89%). The overall ninety-day probability of survival was 68% (CI 59-76) [8].

Moreover, the cost of treatment of IFI is very high due to duration of hospital stay, cost of drugs, and impact on cancer-directed treatment [1]. Thus, IFI remains a major issue for a pediatric hematology-oncology team, and monitoring its annual incidence and the risk of outbreak is a practice to be encouraged [9-13].

Prevention of IFI remains complex, since the conidia of Aspergillus species are in suspension in the air. Inhalation is the main route of entry of moulds, while more rarely the source of infection is a colonization of the skin or the gastrointestinal tract [14]. The use of prophylaxis of patients at risk may be considered [15] but has not been codified [16-18].

Echinocandines act as 1,3-Beta-glucan synthase inhibitors, with inhibition of the cell wall, not present in mammalian cells; so, with little human toxicity [19,20]. Micafungin has been studied in children, as a single agent or in combination with other antifungal agents, as primary or salvage regimens [20-27]. The results of therapeutic trials enrolling adults and children during HSCT, either on- or off-label, showed efficacy for both Candida and Aspergillus [23-27]. Micafungin (50 mg) has been compared with itraconazole (5 mg/kg) for the prophylaxis of IFI in HSCT recipients in a randomized, multicenter, open-label, non-inferiority trial [29]. In the 283 patients evaluable for efficacy treatment success was not different (92.6% and 94.6% in patients treated with micafungin and itraconazole) [29]. Micafungin (50 mg or 1 mg/kg if weight <50 kg) has also been compared with fluconazole (400 mg, or 8 mg/kg if weight <50 kg) for the prophylaxis of IFI in HSCT in a randomized, double-blind, multi-institutional, comparative phase III trial. Among 830 evaluable adult and pediatric patients, efficacy was superior for micafungin (80% vs. 73.5%, p=0.03) [23].

Micafungin has been licensed for use in children in Europe since April 2008 for treatment of invasive candidiasis and prophylaxis of Candida infections in patients with anticipated prolonged and severe neutropenia (absolute neutrophil count <500 cells/µl for 10 or more days), or in allogeneic HSCT recipients [30]. In the U.S., micafungin is indicated in patients aged ≥4 months for: (1) treatment of candidemia, acute disseminated candidiasis, Candida peritonitis,
and abscesses; (2) treatment of patients with esophageal candidiasis; (3) prophylaxis of Candida infections in patients undergoing HSCT. Although micafungin is not approved for treatment of IA by the FDA, it is recommended by the IDSA as an alternative therapy (B-II) for adults with the caveat that the dosage has not been established [25]. Furthermore, it has been widely used for prophylaxis of IFI in children in different clinical situations and premature infants [25,27-32]. Safety, efficacy and micafungin serum concentrations were investigated in children at high risk for IFI, intolerant or with contraindications to polyenes and triazoles, receiving prophylactic micafungin (3-4 mg/kg twice weekly). The results indicated that micafungin could be a convenient, safe and efficient alternative for antifungal prophylaxis in children at high risk for IFI [33]. Recently, sequential systematic anti-mold prophylaxis, initially with micafungin and thereafter with voriconazole, resulted in very low incidence of invasive mold infections in patients undergoing allogeneic hematopoietic stem cell transplantation [34].

Micafungin has low interactions, in particular it does not interact with drugs whose metabolism is mediated via the cytochrome P450; thus it has a good compatibility with most others drugs [35].

Over a three-month time interval, during fall (October to December), we recorded in our pediatric hematology-oncology ward a total of 14 cases of IA; 4 were possible and 10 probable, according to the guidelines of the European Organization for Research and Treatment of Cancer/Mycoses Study Group [28]. Affected were children with various types of cancer, including not only those traditionally at high-risk of IFI (acute leukemia or lymphoma), but also some considered at lower risk (Langerhans Cell Histiocytosis, Ewing sarcoma, Astrocytoma). This number of events compared unfavorably with the historical control of about two cases of IFI per year in the patient population on treatment in our ward during the previous five years. Thus, it strongly suggested the occurrence of an outbreak, involving patients at both high and low risk of IFI. All patients had been recently hospitalized; thus, exposure to an environmental risk appeared the most likely explanation for the unusual clustering of cases. Based on the above findings, we designed a global strategy aimed at breaking this cluster by: i) investigation of the potential sources of contamination (water and air pipelines, cleaning procedures); ii) pharmacological prophylaxis for patients requiring hospitalization during neutropenia.

In this paper, we describe the results of this program, aimed at breaking the observed cluster of IFI by prevention of further cases of IFI in our ward.

2. MATERIALS AND METHODS

2.1 Study Design

Prospective, non-randomized, open label study of pharmacological prophylaxis of IA in a population of children and adolescent with cancer, who were at risk because not only they were neutropenic, but especially because they were admitted and treated in a hospital environment in which an IA outbreak had been recently identified.

2.2 Setting

Meyer Children Hospital is an academic, teaching institution, serving as a referral center for a 2-million population of inhabitants (Tuscany); additionally, about 30% of the total patients with cancer are received from outside the referral area. The in-patients unit includes 12 beds in either single or double-bedded rooms; the outpatient Day-Hospital dedicated area includes eight beds, working on a 12-hour/day, 6-day/week schedule. The total number of newly diagnosed patients exceeds 100 patients per year. The HSCT unit includes five single-bed rooms equipped with HEPA filters and positive air-pressure. About 40 transplant procedures have been completed yearly.

2.3 Patients and Definition

During a four-month time interval (December to April), all patients admitted in the ward received prophylaxis during the entire hospitalization if they had severe neutropenia (<500/mm^3) regardless of the underlying disease.

Specific informed consent, including the off-label use of micafungin for pharmacological prophylaxis, was obtained in all cases.

2.4 Environmental Surveillance

Volumetric air samples from the ward and the Transplant unit are collected on a yearly basis,
and additionally upon suspicion of an outbreak, for quantitative and qualitative identification of filamentous fungi. Active sampling was carried out using a volumetric sampler (Air Ideal 1 m³ in 10 minutes); passive sampling was performed by exposure of settle plates for 4 hours. Sabouraud dextrose agar and Tryptic Soy Agar plates were incubated for 3 days at 22.5±2.5°C and then for 2 days at 32.5±2.5°C. The plates were examined on day 2 and then read on day 5 for fungal growth. Colonies of *Aspergillus* species growing on the plates were isolated and identified by morphological procedures.

### 2.5 Prophylactic Regimen and Monitoring Policy

Micafungin (Mycamine®, Astellas Pharma US, Inc. Northbrook, IL 60062 USA) 1 mg/kg, ≤50 mg [16,17] was administered i.v. over 1 hour, daily until discharge. Any other antifungal prophylaxis was suspended during hospitalization.

All in-patients were monitored by galactomannan assay (GM) twice weekly during admission (positive cut-off: O.D. Index >0.5); then weekly after discharge, for at least 90 days. First positive GM result was repeated; if confirmed, it triggered lung CT. Upon detection of specific imaging, this was considered as a failure of prophylaxis and voriconazole was introduced for treatment of IFI.

The primary endpoint of the study is the incidence of IFI by yeast and filamentous fungi, and the secondary endpoint the number of positive GM tests.

### 3. RESULTS

#### 3.1 Study Population

During the 120 days of the study, 27 patients became eligible for the prophylaxis. Their age ranged between 2 months and 21 years (median, 9 years); the cancer types were acute lymphoblastic (n=4) or myeloid (n=3) leukemia, non-Hodgkin lymphoma (n=3), osteosarcoma (n=6), Ewing sarcoma (n=4), medulloblastoma (n=3), neuroblastoma (n=2), other tumors (n=2). Three patients underwent autologous HSCT during the study. One patient (who had a previous admission shortly before the study start), was excluded because of break-through IFI, diagnosed on day 2 from admission. Thus, 26 patients were evaluable for this study. They accounted for 38 episodes of admission, with a median duration of 7 days (range, 2-23 days).

#### 3.2 Results of Outbreak Control Strategy

Overall, four of the 26 patients had a total of five positive GM results: of them, 3 tested negative at the confirmation test and were thus considered as false positive, attributable to interference with concomitant medication(s). The remaining patient had a second positive GM result, which triggered chest CT scan; since he had pulmonary symptoms, empiric therapy with voriconazole was started. Yet, it was withdrawn upon evidence of H1N1 virus infection, together with negativity of the GM at the third sequential test.

None of the patients reported any side effect related to micafungin administration. Finally, after a minimum follow-up of 90 days, none of the 26 study patients had developed IFI.

Environmental Surveillance evidenced no relevant contamination, with a range from 0 to 3 UFM/m³ of *Aspergillus* species at repeated testing. No variations were detected after cleaning procedures.

#### 3.3 Cost of Pharmacological Prophylaxis

The micafungin cost was of €156.65 for each vial containing 50 mg. The cumulative dose of drug received by individual study patients ranged between 16 and 506 mg, based on weight and duration of the admission. Thus, during a total of 313 days of admission for the 27 patients, the total cost was estimated as €30,451, with a mean cost per patient of €1,133.

### 4. DISCUSSION

Upon detection of an outbreak of IFI affecting 14 patients on treatment in our pediatric hematology-oncology ward, although none of them had died, we considered appropriate to react immediately with a specific strategy aiming to breaking this cluster. For the patients' safety, further to auditing the technical equipment related to water and air handling for the ward area, and to exploring potential additional sources of contamination, we also decided to implement an antifungal prophylaxis.

The choice of the drug to be used in this situation was not very easy. According to the ‘European Conference on Infections in Leukemia’ (ECIL)
recommendation [36], primary antifungal prophylaxis against IFI should be considered in high risk patients (BII) using fluconazole (CI), the only one with EMA authorization including prophylaxis for candida in children [37]. Yet, despite being the only licensed drug for this purpose, fluconazole is not active against mould and thus, an off-label use of another drug appeared to be necessary. Itraconazole (BI) is associated with interactions with several drugs; liposomal amphotericin (BII) is also associated with potential toxicity; posaconazole (BI for children >12 years) has a poorly predictable intestinal absorption requiring PK monitoring [36]. Micafungin is expected to cover not only the yeast but also the filamentous fungi and in particular Aspergillus species, and has been successfully used for treatment of IA. [21,22,35-37] The guidelines provided by The National Comprehensive Cancer Network® (NCCN®) [38] and the ECIL [36] assign to this drug a C1 level of evidence for the prophylaxis of IFI in patients undergoing allogeneic HSCT. So we decided to use micafungin for pharmacological prophylaxis, despite it was not licensed for this specific use in our country. This decision was shared with the Institutional Hospital Infection Board (C.I.O.), which approved, and then widely explained to the parents of all patients, who gave their informed consent. The dose we selected, equivalent to 50.86 mg micafungin sodium, has proven effective in PK studies and in clinical studies against IA [23].

In this limited and mono-institutional experience, pharmacological intervention with “prophylactic” aim was associated with termination of the outbreak, i.e. no new cases of infection. No additional intervention had been made on other potential risk factors. In addition, the secondary endpoint gave very positive results, with only four samples testing positive at initial GM assay; of them, three were not confirmed at repeated assay. The only patient with a second positivity, triggering lung CT scan, had pulmonary symptoms and was thus safely put under empiric therapy; yet, this was then withdrawn upon the diagnosis of H1N1 infection.

Our neutropenic patients, exposed to an obvious environmental risk, were allowed to carry on their therapeutic program without any reduction of the dose-intensity. The i.v. route of administration allowed reaching protective blood levels within a very short time, and the nurses considered the single daily dose convenient. Thus, this type of “prophylaxis” turned out to be very feasible. Our investigation did not provide any explanation for the outbreak episode. No environmental cause could be identified. Thus, we suspect that the episode might be related to seasonal variations of temperature and humidity, as well as the crucial effect of wind speed and washout caused by rainfall, that may influence the timing and magnitude of airborne spore counts with occasional variations. All these factors have been related to a higher incidence of moulds clusters during autumn [13,17,39,40], the same season during which we observed our outbreak. The minimum concentration of Aspergillus required to cause infection in an immunocompromised host remains unknown; even concentrations below 1 CFU/m³ have been reported to be sufficient to cause epidemics. Yet, these concentrations are normally present in the air outside of the hospital, thus paradoxically making any discharge a potential risk for the immune compromised host [12,13,17].

The progress of medical care has to be matched with its sustainability. Under the pharmaco-economic point of view, this prophylaxis also had an extremely favorable cost/benefit ratio. The total cost of the drug was of about €30,000, with about €1,133 per patient; this has to be matched with no new cases of IA observed. Even the cost of undue hospitalization(s) for additional cases, together with extended antifungal therapy, would have largely exceeded this cost. The median total hospital charges for a pediatric patient with IA were $49,309 in USA [1]; in another study in Italy, the mean cost per patient of the IA treatment only has been calculated for adult patients in €21,086 only for drug treatment, not accounting for the hospitalization costs [41].

This study has limitations: first, since for ethical reasons, it was not controlled, we have no evidence that the “environmental” risk of IFI had remained persistently high throughout the entire study duration. Second, it is mono-institutional and the number of patients exposed is quite small, also including some patients with cancer types usually considered at lower risk for IA. Yet, patients at lower risk for IA had also been involved in the preceding outbreak, and all patients to be treated were selected based on profound neutropenia.

5. CONCLUSION

In conclusion, we faced a cluster of IA, a life-threatening event for patients treated in a
pediatric hematology-oncology ward. Since treatment of cancer cannot be suspended without jeopardizing its dose-efficacy, the team must be trained to react rapidly in terms of patient protection and environment re-assessment. Our choice of prophylaxis with micafungin, although its use was off-label, turned out to be safe, feasible and very effective in apparently breaking (or at least being associated with break of) the cluster of IA in our ward. The cost-benefit evaluation of the prophylaxis also suggests a very favorable profile.

CONSENT

The study was widely explained to the parents of all patients, who gave their written informed consent.

ETHICAL APPROVAL

The Institutional Hospital Infection Board (C.I.O.) approved the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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