Recommendations for Broader Coverage Antifungal Prophylaxis in Childhood Acute Myeloid Leukemia: ASH Evidence-Based Review 2011

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A 16-year-old female diagnosed with acute myeloid leukemia (AML) with inversion 16, a favorable prognostic indicator, has persistent neutropenia after her fourth cycle of dose-intensified chemotherapy. She was recently admitted for treatment with empiric antibiotics for febrile neutropenia, and an astute intern noticed a new lesion on her right foot with a dark necrotic center. A biopsy of the lesion showed spreading hyphae, consistent with *Aspergillus*. Despite her compliance with fluconazole fungal prophylaxis, computed tomography imaging revealed disseminated aspergillosis involving her lungs, liver, and kidneys. Amphotericin was started, but systemic fungemia and the development of multiorgan failure resulted in her death. You are in the difficult position of having to explain to her parents that she died in remission from chemotherapy-related complications. All of those involved in this unfortunate scenario wonder if something could have been done to prevent her death.

Introduction

Increasing intensity of therapy for acute myeloid leukemia (AML) with the goal of improving overall survival has resulted in periods of prolonged severe neutropenia after chemotherapy. In a recent report from the Children's Oncology Group (COG), the infectious death rate associated with modern AML therapy was 11%, with more than half of these related to *Aspergillus* and *Candida* species.[1] Another COG AML trial reported a mean of 50 days to absolute neutrophil count recovery after the final 2 chemotherapy cycles.[2] Prolonged neutropenia places patients at high risk for life-threatening infections such as invasive fungal infection (IFI), so the appropriate selection and timing of prophylactic antimicrobial agents have become a critical component to therapy in this vulnerable population. IFI contributes significantly to cancer treatment–related mortality, with an estimated case fatality rate of 13%,[3] although invasive aspergillosis is associated with a childhood mortality rate of approximately 50%.[4] Due to the intensity of AML therapy, children with AML constitute the highest-risk population for IFI, similar to patients undergoing stem cell transplantation.[5]

In a multinational meta-analysis of 38 trials involving 7014 treatment and control subjects with chemotherapy-induced neutropenia, Bow et al found that antifungal prophylaxis effectively reduced the incidence of both IFI and fungal infection–related mortality.[6] There are scant data to support optimal times for the initiation and discontinuation of fungal prophylaxis. The most common organisms identified in chemotherapy-related IFI are *Candida* and *Aspergillus* species. In a recent survey of 2 pediatric consortiums on antifungal practices in AML, 77% of COG institutions and 91.3% of Berlin-Frankfurt-Muenster (BFM) institutions routinely administer antifungal prophylaxis; however, the BFM group was much more likely to include antimold coverage (63.5% of COG centers use fluconazole vs 28.3% of BFM centers).[7] Although a widely used prophylactic agent in children with high-risk malignancies, fluconazole is not effective against all species of *Candida* and lacks activity against *Aspergillus,* which comprises up to one-half of IFI cases in this patient population.[1] In a review of 1047 IFI cases in children diagnosed with malignancy (the majority of whom had AML), 20% of IFIs were attributed to yeasts and 80% to molds, with a notable trend in IFI etiology toward non–albicans candidemia and non-aspergillus molds.[8] Given the significant contribution of IFI to treatment-related mortality in childhood AML and the availability of newer antifungal agents with broader coverage, we performed a literature search to determine the strength of evidence supporting alternative approaches to antifungal prophylaxis in this population.

Combining the MESH terms "leukemia, myeloid, acute," "prevention and control," "anti-infective agents," and "mycoses" resulted in 20 PubMed citations. Limits were then set to include children (age 0-18 years), human studies, and manuscripts with English translation, resulting in a reduction to 6 citations. Further limits were set to include only randomized controlled trials (RCTs) or meta-analyses, resulting in 2 citations, one of which was excluded because it was a pharmacokinetic study. A prospective study was among the excluded 4 citations and was included. Of the other 3 citations excluded, all were single- or multi-institution retrospective reviews. We then searched using the MeSH term "leukemia, myeloid, acute" limited to "human," "English," and "published in last 5 years" (4376 citations) to ensure that no studies were missed due to misclassification, and discovered an additional RCT, leaving 3 articles concerning primary prevention of IFI in children or adolescents with AML (Table 1).

In summary, all 3 studies included both children and adults with AML. Torres et al concluded that voriconazole was a well-tolerated and effective prophylaxis against IFI.[9] Ito et al demonstrated equal efficacy and tolerability for both fluconazole and itraconazole in preventing IFI.[10] Cornely et al demonstrated superiority of posaconazole compared with either fluconazole or itraconazole in preventing IFI and in improving overall survival, although they noted more

Table 1. Evidence for the use of broader antifungal prophylaxis agents in childhood AML

Study	Design	N	Median age, y (range)	Diagnosis	Objective	Outcome
Torres et al[9]	PC	127	43 (2-74)	AML or SCT	To determine safety and efficacy of voriconazole	72.9% without proven, probable, or suspected fungal infection
Ito et al[10]	RCT	218	53 (16-80) 58 (16-80)	AML or MDS	To demonstrate non-inferiority of itraconazole compared with fluconazole	Itraconazole group: 4 possible, 0 probable IFI Fluconazole group: 8 possible, 3 probable IFI
Cornely et al[11]	RCT	602	53 (13-82) 53 (13-81)	AML or MDS	To compare safety and efficacy of posaconazole to fluconazole or itraconazole	Posaconazole group: 2% IFI Fluconazole or itraconazole group: 8% IFI

PC indicates prospective cohort; SCT, stem cell transplantation for leukemia; and MDS, myelodysplastic syndrome.

adverse events (primarily gastrointestinal) in the posaconazole group.[11] To review the objectives of childhood AML trials currently under way, we surveyed www.clinicaltrials.gov for studies actively recruiting children with de novo AML. Of the 18 studies listed, 4 were observational, 13 were chemotherapy trials, and 1 was a supportive care RCT. This RCT is a phase 3 COG study (ACCL0933) investigating caspofungin versus fluconazole in preventing IFIs in children and young adults with newly diagnosed or relapsed AML, and will provide critically important information as to the use of caspofungin in this high-risk patient population.

Current antifungal prophylaxis practice in childhood AML therapy is associated with unacceptable rates of IFI. As described in the illustrative case history above, overwhelming fungal infections may develop in patients with otherwise favorable-risk disease. Such occurrences are even more common in patients with high-risk features. Even if not fatal, fungal infections can delay treatment and interfere with stem cell transplantation or the utilization of novel agents. Newer agents such as voriconazole, posaconazole, micafungin, caspofungin, and anidulafungin provide broader antimold coverage and may be of benefit in this population. However, due to pharmacokinetic differences between adults and children and to the potential for drug interactions, further studies specific to pediatric populations are required. The 2010 update of clinical practice guidelines from the Infectious Diseases Society of America recommends posaconazole for all AML patients $\geq$ 13 years of age, citing benefit to prophylaxis when rates of aspergillosis exceed 6%[12] (no recommendations were made for children $<$ 13 years of age due to a lack of evidence). Echinocandins and voriconazole are listed as possible alternatives based on limited evidence. This benefit is less well-established after induction, and consideration must be given to drug bioavailability, method of administration, and interference with metabolism of chemotherapeutic agents, including drug interactions with targeted agents such as those being investigated by COG in the current AML trial.

Based upon this review, we conclude that voriconazole may be safely and efficaciously used in childhood AML, itraconazole may be used in older adolescents, and posaconazole provides superior protection against IFI than either fluconazole or itraconazole in children $\geq$ 13 years of age. However, the paucity of quality evidence in this field and the absence of RCTs that include children $<$ 13 years of age highlight the need for prospective studies and RCTs investigating the use of these agents as antifungal prophylaxis in childhood AML. We suggest that antifungal prophylaxis with broad antimold coverage be given at minimum during induction chemotherapy to children with AML who are $\geq$ 13 years of age (grade 2B) and also to children who are $<$ 13 years of age (grade 2C).[13]

Disclosures

Conflict-of-interest disclosure: The authors declare no competing financial interests. Off-label drug use: None disclosed.

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