How to Improve the Design of Trials of Antifungal Prophylaxis among Neutropenic Adults with Acute Leukemia

Francesco Menichetti
Infectious Diseases Unit, Cisanello Hospital, Pisa, Italy

The risk for invasive fungal infections in patients with acute leukemia is generally low (4%–8%), and the routine use of fungal prophylaxis is not warranted except in specific high-risk groups that should be identified among this population. In a prophylactic study with a new agent, fluconazole or itraconazole oral solution represent good choices for the comparator because they are proven better than placebo or oral nonabsorbable antifungal agents in reducing the risk of invasive fungal infections in patients with acute leukemia. Because prophylaxis is most valuable when the risk of infection is high, patients with well-understood risk factors (severe mucosal disruption caused by chemotherapy, impaired cell-mediated immunity caused by steroids or fludarabine, use of a central venous catheter, and colonization by *Candida* species) should be selected. The end points for antifungal prophylactic trials should focus on proven and probable invasive fungal infections. Superficial and mucosal fungal infections do not represent a primary end point for these studies. Poor compliance should be considered as an interruption of treatment due to side effects and should be included in the criteria for failure. Fungus-related mortality should be evaluated as a failure of prophylaxis, whereas overall mortality may be influenced by many other cofactors. Differences in gastrointestinal toxicity of antifungal agents may limit the use of double-blind designs in some situations.

The risk of invasive fungal infections in patients with acute leukemia ranges from 4% to 8% [1–3] and is lower than the rate of 16%–18% observed in patients who have undergone hematopoietic stem cell transplantation [4, 5]. Thus, the relevance of fungal prophylaxis in patients with acute leukemia has been less apparent, and the routine use of prophylaxis has not been thought to be warranted. However, antifungal prophylaxis might be warranted for patients with acute leukemia who have well-understood risk factors (severe mucosal disruption caused by chemotherapy, impaired cell-mediated immunity caused by steroids or fludarabine, use of a central venous catheter, and colonization by *Candida* species), and we need carefully conducted studies involving such higher-risk patients, who may represent 50% of the population with acute leukemia. Given these complexities, several important issues in the design of clinical trials of fungal prophylaxis for patients with acute leukemia must be considered during the design of future trials.

WHAT SHOULD BE THE COMPARATOR FOR NEW DRUGS?

Fluconazole was shown to be better than placebo in reduction of systemic fungal infections in patients with acute leukemia [1, 2], and this reduction was mainly related to a decrease in invasive candidiasis. Itraconazole oral solution was also able to reduce invasive candidiasis in patients with acute leukemia [3]. The impact of fungal prophylaxis with itraconazole on invasive aspergillosis was less clear; suggestions of efficacy [6–8] are not supported by the results of other randomized clinical trials [3, 9, 10]. Nonabsorbable antifungal agents have been thought valuable in the prevention of invasive fungal infections in patients with acute leukemia [11], but with the limitation of low tolerability.
In choosing a comparator for a new drug in a trial of fungal prophylaxis, one should thus consider invasive candidiasis as the main target among patients with acute leukemia. The local prevalence ofazole-resistant strains of Candida other than Candida albicans and the specific risk factors for invasive aspergillosis (local epidemiology and chemotherapy-induced impairment of cell-mediated immunity) should also be considered. Testing of a hypothesis of noninferiority to fluconazole (or itraconazole oral solution in settings in which aspergillosis is judged a significant risk) seems to be the right choice for a prophylactic trial among patients with acute leukemia.

**WHAT DOSE AND SCHEDULE OF PROPHYLACTIC REGIMEN SHOULD BE EVALUATED?**

In the majority of prophylactic trials among patients with acute leukemia [1, 2] or those undergoing hematopoietic stem cell transplantation [3, 4], fluconazole has been used at a dose of 400 mg/day, either intravenous or oral. However, in a large, transplantation [3, 4], fluconazole has been used at a dose of 400 mg/day, either intravenous or oral. However, in a large, comparative clinical trial that enrolled >800 patients with acute leukemia, the rate of systemic fungal infections was 2.6% in patients treated with fluconazole at 150 mg/day by mouth and 2.5% in those treated with oral amphotericin B suspension [11].

The oral absorption of itraconazole when given in capsule form is erratic, especially in patients with hematologic malignancies, and itraconazole oral solution may require up to 10–15 days to produce therapeutic blood levels [11, 12]. Thus, with itraconazole, it is advisable to start with the intravenous formulation for 2 days to reach therapeutic blood levels and then shift to the oral formulation [12].

**WHICH INCLUSION CRITERIA WOULD PROVIDE A HIGH ENOUGH INCIDENCE OF INVASIVE FUNGAL INFECTIONS TO WARRANT PROPHYLAXIS?**

To select a population of patients with acute leukemia with a higher risk of invasive fungal infections, one should consider several important factors. The type and status of underlying disease may influence the risk: patients with acute myelogenous leukemia are at a higher risk than are those with acute lymphoblastic leukemia; patients with relapsed disease are at higher risk than are those with newly diagnosed disease for a lower marrow reserve, intensive chemotherapy, and potential fungal colonization; and patients with lack of remission are persistently neutropenic [13]. The type of antileukemic chemotherapy also seems to play a key role in determining the risk of invasive fungal infections—severe mucosal disruption caused by gut-damaging chemotherapy (a remission-induction regimen with high-dose cytosine arabinoside plus etoposide in acute non-lymphocytic leukemia or the use of idarubicin) and impairment of cell-mediated immunity related to steroids or fludarabine therapy may help to select a subgroup of patient at higher risk for fungal infections [14].

**Selection of a population at higher risk for invasive candidiasis.** The presence of Candida species in >1 noncontiguous site or the colonization of the mouth or gut with Candida tropicalis are considered significant risk factors for invasive candidiasis [15–18]. Antimicrobial therapy may favor colonization, and chemotherapy-induced gut damage may facilitate the entry of fungal pathogens into the bloodstream. Given the high negative predictive value of surveillance cultures for Candida species, the selection of only colonized patients for a prophylactic trial seems to be a rational choice [19].

**Selection of a population at higher risk for invasive aspergillosis.** The risk factors for invasive aspergillosis in patients with acute leukemia include severe and prolonged neutropenia, acute myelogenous leukemia in second relapse, chemotherapy with high-dose cytosine arabinoside or other gut-damaging chemotherapy, use of steroids, no use of high-efficiency particulate air filters, nasal colonization, and previous fungal pneumonia. However, design of a prophylactic trial against invasive aspergillosis is difficult because the risk of infection is locally variable in relation to seasonal variations, building activity, changes in antitumor therapy, and variable ancillary measures (better hygiene and use of high-efficiency particulate air filters). Furthermore, the adherence to diagnostic protocol (serology, CT, and invasive procedures) is also variable.

If a rate of proven invasive fungal infections of ≥10% is considered an incidence high enough to warrant prophylaxis, the patient selection criteria for patients with acute leukemia might include expected severe (<100 cells/mm³) and prolonged (>10 days) neutropenia, gut-damaging chemotherapy (e.g., the regimen of idarubicin, cytarabine, and etoposide), the use of central venous catheters, and Candida colonization [19].

**WHAT ARE THE END POINTS FOR TRIALS OF ANTIFUNGAL PROPHYLAXIS?**

Proven and probable invasive fungal infections, according to the definitions of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases [20], represent valid end points for trials of fungal prophylaxis. Several published trials of fungal prophylaxis in patients with acute leukemia used as an end point “suspected” or “possible” fungal infections, referring to the empirical use of amphotericin B to treat neutropenic patients with fever not responding to antibiotic therapy but without any further diagnostic clues (e.g., no supplemental clinical, radiological, serological, or microbiological data indicating a fungal infection). The use of possible fungal infections as an end point of a prophylactic trial should therefore...
be discouraged. However, the need for antifungal therapy could represent a reliable end point for antifungal prophylaxis trials, provided that strict criteria for its use were defined and followed: the study design should clearly indicate whether either preemptive (for proven or probable fungal infections) or empirical (for fever of unknown origin) antifungal therapy is permitted, to limit the overuse of this strategy, and should predefine the initial empirical antibiotic regimen (including a minimum duration of therapy for the trial of antibacterials).

Superficial and mucosal fungal infection are defined as clinically and microbiologically documented infections of the oral cavity, gastrointestinal tract, vagina, or skin. The majority of published clinical trials of fungal prophylaxis have used superficial fungal infections as an end point of the study. However, there is no consistent relationship between superficial/mucosal and invasive fungal infections, their clinical consequences are entirely different, and the use of superficial infections thus does not represent a valid end point.

Colonization, especially of the gastrointestinal tract, may precede invasive fungal infections, and the influence of antifungal prophylaxis on fungal colonization may give important information regarding the selection of resistant strains. Although colonization does not seem to represent a useful primary end point for clinical trials of fungal prophylaxis, it may be useful as a criterion to select patients to include in the study.

WHAT ARE THE CRITERIA FOR FAILURE OF PROPHYLAXIS?

Apart from proven and probable invasive fungal infections and the need for antifungal therapy, the criteria for failure include treatment interruption due to side effects and mortality. Compliance is evaluated as a separate aspect of drug safety, but it should be noted that poor compliance (which occurs when a patient either misses >5 consecutive doses or takes <50% of the total number of doses) should probably be considered a failure of prophylaxis due to gastrointestinal intolerance.

Mortality in neutropenic patients with acute leukemia is influenced by several factors unrelated to fungal prophylaxis: response to antibiotic therapy, response to antifungal therapy, severity of underlying disease, and complications other than infection. The influence of fungal prophylaxis on overall and fungus-related mortality should be evaluated, but only fungus-related mortality should be considered as a failure in trials of antifungal prophylaxis.

CAN A BLIND RANDOMIZATION USE DRUGS WITH DIFFERENT GASTROINTESTINAL TOXICITIES?

A double-blind design is possible in placebo-controlled trials when the gastrointestinal toxicity of the drug is related to the concomitant presence of an additive substance that can be used alone as placebo. Itraconazole oral solution is prepared with the addition of cyclodextrin, with this carrier component being responsible for the bitter taste and gastrointestinal toxicity of the drug. By using cyclodextrin as placebo, we were able to complete a double-blind trial with itraconazole oral solution as prophylaxis in patients with acute leukemia [3].

When trials are designed to compare 2 drugs with different gastrointestinal toxicities, it is difficult to plan and maintain a double-blind design. One approach, but admittedly one that is not completely satisfactory, is evaluation of outcome by an independent observer who ignores (or is prevented from seeing) any data on the different profile of gastrointestinal toxicity of the 2 drugs.

CONCLUSIONS

Several issues need to be addressed in future clinical trials of antifungal prophylaxis among patients with acute leukemia. The key steps are a focus on patients at highest risk and use of strong end points. Attention to these details will enhance the scientific and medical value of future studies in this challenging area.

Acknowledgments

Potential conflicts of interest. F.M. is a member of the speakers’ bureaus for Pfizer, AstraZeneca, MSD, Elan, Gilead, Bayer, Vicuron, and Chiron and has served as a consultant for Wyeth, Roche, MSD, and Gilead.

References