Systemic Antifungal Prophylaxis After Hematopoietic Stem Cell Transplantation: A Meta-Analysis

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ABSTRACT

Background: Hematopoietic stem transplant recipients are subject to increased risk for invasive fungal infections.

Objective: This meta-analysis was undertaken to explore the comparative effectiveness of systemic antifungal prophylaxis in hematopoietic stem cell transplant recipients.

Methods: We searched PubMed and The Cochrane Register of Randomized Controlled Trials up to March 2013 for randomized studies on systemic antifungal prophylaxis after hematopoietic stem cell transplantation. We performed a meta-analysis on the relative effectiveness of systemic antifungal prophylaxis on proven or probable invasive fungal infections using direct and indirect effects. Relative effectiveness was reported as odds ratio (OR) for invasive fungal infections, causative agent, empirical antifungal therapy, and withdrawals due to drug adverse events.

Results: Twenty evaluable studies provided data on 4823 patients. The risk for invasive fungal infections while on prophylaxis was 5.1% (95% CI, 3.6−6.8%). In patients receiving fluconazole, risks of proven or probable invasive fungal infections (OR = 0.24; 95% CI, 0.11−0.50; number needed to treat [NNT] = 8), systemic candidiasis (OR = 0.11; 95% CI, 0.05−0.24; NNT = 7), and overall need for empiric antifungal treatment (OR = 0.60; 95% CI, 0.44−0.82; NNT = 8) were reduced compared with patients receiving placebo. Itraconazole was more effective than fluconazole for the prevention of aspergillosis (OR = 0.40; 95% CI, 0.19−0.83; NNT = 23) at the expense of more frequent withdrawals (OR = 3.01; 95% CI, 1.77−5.13; number needed to harm = 6). Micafungin was marginally more effective than fluconazole for the prevention of all mold infections (OR = 0.35; 95% CI, 0.10−1.18; NNT = 79) and invasive aspergillosis (OR = 0.19; 95% CI, 0.03−1.11; NNT = 78) and reducing the need for empiric antifungal treatment (OR = 0.40; 95% CI, 0.13−1.21; NNT = 8). There was a relative lack of comparisons between different antifungal prophylactic strategies, including the newer azoles, voriconazole and posaconazole, in this population. Direct effects derived from single studies showed marginally significant effects for voriconazole compared with fluconazole regarding invasive aspergillosis (OR = 0.50; 95% CI, 0.20−1.20; NNT = 35) and the need for empiric treatment (OR = 0.72; 95% CI, 0.50−1.06; NNT = 15). Voriconazole compared with itraconazole (OR = 0.59; 95% CI, 0.40−0.88; NNT = 8) and posaconazole compared with amphotericin B (OR = 0.28; 95% CI, 0.06−1.24, marginal significance; NNT = 3) were better regarding empirical antifungal treatment.

Conclusions: Even when on antifungal therapy, invasive fungal infection will develop in 1 of 20 patients undergoing hematopoietic stem cell transplantation. There is evidence for the comparable effectiveness of different antifungal drugs used for prophylaxis. Fluconazole is the most widely studied agent, but micafungin might prove to be more effective. There is a relative paucity of studies for the newer azoles, although both voriconazole and posaconazole give proof of their comparative or higher effectiveness to fluconazole in single randomized studies. (*Clin Ther*. 2014;36:292–306)

Key words: fluconazole, hematopoietic, meta-analysis, micafungin, prophylaxis, transplantation.

INTRODUCTION

In a single calendar year (2010), more than 30,000 patients received hematopoietic stem cell transplantation

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(HSCT) in Europe and more than 17,000 in the United States, as reported by The European Group of Blood and Marrow Transplantation[1] and the Center for International Blood and Marrow Transplant Research, respectively.[2] These figures represent a near 10-fold increase and 5-fold increase compared with the number of HSCTs in 1990,[1,2] and reflect the increasing number of patients exposed to risks associated with HSCT, including invasive fungal infections (IFIs).[3,4] The Transplant-Associated Infection Surveillance Network (TRANSNET) database reports cumulative annual incidence of IFIs at 7.7, 8.1, 5.8, and 1.7 per 100 transplants for matched-unrelated allogeneic HSCT, mismatch-related allogeneic HSCT, matched-related allogeneic HSCT, and autologous HSCT, respectively. In addition, the estimated 1-year survival in HSCT after invasive candidiasis is only 33%, and even lower (25%) after invasive aspergillosis.[5] The multicenter Prospective Antifungal Therapy Alliance registry has also indicated a high mortality rate, with a 12-week mortality of 49% after diagnosis of invasive candidiasis.[6]

Because of the high impact of invasive fungal infections in this population, the Infectious Disease Society of America's guidelines recommend antifungal prophylaxis for high-risk patients. This indication includes patients receiving HSCT and patients with anticipated neutropenia of longer than 7 days. The azole group of antifungal agents (ie, fluconazole, itraconazole, voriconazole, and posaconazole) and echinocandin antifungals are considered acceptable options. Specific mention is made for mold prophylaxis, despite the lack of solid evidence, recommending the use of an agent with anti-mold activity in patients with previous invasive aspergillosis, anticipated neutropenia that is longer than 2 weeks, or prolonged neutropenia before the HSCT.[7] Similarly, the European Guidelines recommend fluconazole in HSCT prophylaxis during the early neutropenic phase, provided that it is combined with adequate mold-directed surveillance (including imaging studies and/or galactomannan assay). These guidelines also recommend that an anti-mold agent be reserved for patients with graft-versus-host disease (GVHD), with posaconazole being the preferred option.[8] These recommendations are based on evidence provided by a small number of randomized controlled trials (RCTs) combining a systemic drug with another comparator drug or with placebo. There is little evidence on the relative effectiveness of all these available treatment options, with the exception of comparisons with placebo or nonsystemic antifungal agents.[9,10] In this context, we systematically reviewed the literature for all available RCTs for antifungal prophylaxis in this population and performed a meta-analysis to evaluate the risk of proven or probable IFIs in this population and the relative effectiveness of antifungal prophylaxis.

METHODS

Data Sources and Searches

We searched PubMed (from inception to March 2013) and The Cochrane Register of Randomized Controlled Trials (from inception to March 2013). Last access was on March 19, 2013. PubMed search terms included: *randomized* AND *prophylaxis* AND (*antifungal** OR *ketoconazole* OR *fluconazole* OR *itraconazole* OR *voriconazole* OR *posaconazole* OR *micafungin* OR *caspofungin* OR *anidulafungin* OR *amphotericin*). The Cochrane Database was searched for RCTs using combinations of the terms *prophylaxis* AND [name of drug], where each drug name was entered one by one. We included a manual search of bibliography for additional articles, as well as a search of the references of relevant guidelines to the topic. We complemented the literature search by including the American Society of Hematology (2004–2012) and European Hematology Association (2006–2013) proceedings for additional randomized trials. We also searched ClinicalTrials.gov to report ongoing trials on the topic. No language restriction was imposed.

Study Selection

An RCT on HSCT, including allogeneic, autologous, or both procedures, was considered eligible provided that: (1) it randomized prophylactic systemic antifungal agents or (2) randomized a systemic antifungal compared with placebo or no prophylaxis. Studies that provided data to calculate the odds ratios (ORs) and the corresponding CIs for at least one of the following outcomes were included: (1) proven or probable IFIs, (2) invasive candidiasis, (3) invasive aspergillosis, (4) all mold IFIs, (5) withdrawals related to adverse events, (6) need for empirical antifungal therapy, (7) overall mortality (deaths reported among enrolled patients), and (8) mortality attributed to IFIs (deaths due to IFI among enrolled patients).

An RCT was excluded if it had no extractable data on HSCT, compared different dosing or different