Empirical Antifungal Treatment of Febrile Neutropenia

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The risk of fungal infections increases dramatically in immunocompromised patients and especially in those with profound and protracted neutropenia.

Because of the insensitivity of diagnostic methods and the poor outcomes associated with established infections, empirical antifungal therapy is used for patients with neutropenia who have persistent fever despite the administration of antibacterial agents

Although conventional amphotericin B has been considered the optimal first-line agent, its status as the preferred treatment has recently been challenged by the results of trials comparing it with lipid formulations of amphotericin B and newer antifungals.

Unfortunately, empirical treatment with conventional amphotericin B is limited be breakthrough fungal infections, acute toxic effects related to the infusion, and dose limiting nephrotoxic reactions. The development of lipid formulations of amphotericin B allows empirical antifungal therapy to be administered with potentially improved efficacy and reduced toxicity.

The antifungal agents used in the clinical trials have different targets and toxic effects. Fluconazole is effective only against certain *Candida* species, whereas itraconazole, amphotericin B and the newer agents echinocandin and voriconazole have increased activity against molds and several resistant *Candida* species. Toxic effects also vary, with echinocandin, triazoles and lipid formulations of amphotericin B having fewer toxic effects than conventional amphotericin B. So given the greater number of options, which antifungal agent is best for empirical antifungal therapy:

The results of a comparative trial evaluating the safety of Liposomal amphotericin B (AmBisome) versus amphotericin B lipid complex (Abelcet) in the empirical treatment of febrile neutropenia suggested that AmBisome at 3mg/kg/day or 5mg/kg/day presents a superior safety profile in comparison with Abelcet at 5mg/kg/day. When voriconazole was compared with AmBisome in empirical antifungal therapy in patients with neutropenia and persistent fever voriconazole failed to meet specified criteria for non inferiority to AmBisome with respect to overall response to empirical therapy.

A recent trial at caspofungin versus liposomal amphotericin B for empirical antifungal therapy of persistently febrile neutropenic patients concluded that caspofungin was as effective as L-AMB for empirical therapy of suspected fungal infection in febrile neutropenic patients. It must be emphasized that the number of high-risk patients in this study was small compared to AmBisome's previous studies and further information is needed in order to clarify caspofungin and AmBisome's response to baseline infections.

From the available data it can be concluded that till now L-AMB is the drug of choice for empirical antifungal therapy and that its use may reduce the frequency of break through fungal infections, preserve renal function, and reduce the frequency of acute infusion-related toxic effects.

References

1. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982;72:101-11
2. EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med 1989;86:668-72
3. Viscoli C, Castagnola E, Van Lint MT, et.al. Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomized clinical trial. Eur J Cancer 1996;32A:814-20
4. Malik IA, Moid I, Aziz Z, Khan S, Suleman M. A randomized comparison of fluconazole with amphotericin B as empiric anti-fungal agents in cancer patients with prolonged fever and neutropenia. Am J Med 1998;105:478-83
5. White MH, Bowden RA, Sandler ES, et.al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever neutropenia. Clin Infect Dis 1998;27:296-302
6. Walsh TJ, Finberg RW, Arndt C, et.al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. N Eng J Med 1999;340:764-71
7. Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicentre, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. Am J Med 2000;108:282-9
8. Wingard JR, White MH, Anaissie E, et.al. A randomized double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. Clin Infect Dis 2000;31:1155-63
9. Boogaerts M, Winston DJ, Bow EJ, et.al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized, controlled trial. Ann Intern Med 2001;135:412-22
10. Walsh TJ, Pappas P, Winston DJ, et.al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-34
11. T.Walsh, C. Sable, B. Depauw, G. et.al. A Randomized, Double-blind, Multicenter Trial of Caspofungin (CAS) v Liposomal Amphotericin B (LAMB) for Empirical Antifungal Therapy (EAFRx) of Persistently Febrile Neutropenic (PFN) Patients (Pt). Abstracts 43rd ICAAC, September 2003 Abstract No M-1761