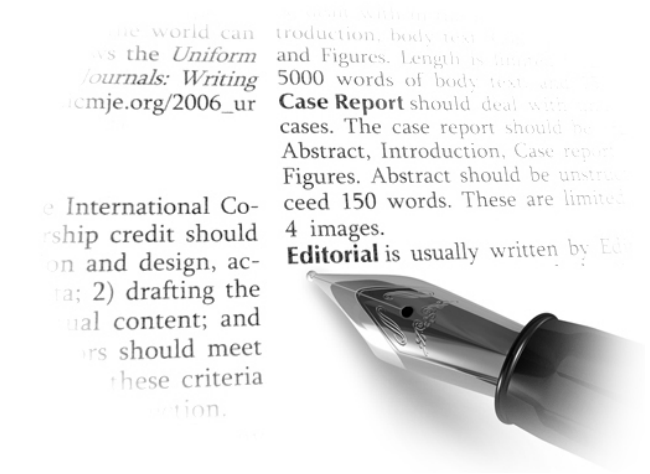

BLOOD RESEARCH
Volume 52 · Number 3 · September 2017
https://doi.org/10.5045/br.2017.52.3.151

Editorial

Invasive fungal infection (IFI) in pediatric leukemia: better outcome with ACT

Ok Sarah Shin, Ph.D.

Department of Biomedical Sciences, College of Medicine, Korea University, Seoul, Korea

Invasive fungal infection (IFI) is a major cause of morbidity, mortality, and economic burden for patients with hematological malignancies. Although fungi rarely cause disease in healthy immunocompetent hosts, fungal infections in immunocompromised hosts can lead to devastating outcome. Hematopoietic stem cell transplant recipients and patients with acute leukemia are particularly vulnerable populations for IFI due to their underlying immunosuppressed conditions [1]. The disease severity and pattern of IFI are usually determined by host immunity and susceptibility factors.

Innate immune cells, such as dendritic cells and neutrophils, play a critical role in host defense mechanisms against fungal pathogens. In addition to the activation of innate immune effectors via cytokines or chemokines, the adaptive immune responses to fungal pathogens are essential in the recognition and elimination of fungal pathogens and the development of protective immunity. For example, IFN-γ secreting Th1 cells were reported to establish a protective immune response and thereby to limit fungal burden in patients with *Aspergillus fumigatus* and *Candida albicans* [2]. Many different fungal species including *Candida albicans* have co-evolved with their hosts over long time. This co-existence indicates a complex mechanism of immune surveillance in the host and of fungi's sophisticated strategies to evade and suppress host immunity.

Acute lymphoblastic leukemia is the most common cancer diagnosed in children and the incidence of IFI in children appears to have increased over the past few decades. Although the treatment outcome for pediatric leukemia have greatly improved with advances in chemotherapy and supportive care, mortality rates of IFI patients still remain relatively high [3]. Given the substantial morbidity and mortality linked to IFI, the use of antifungal agents in combination is often considered. Antifungal combination therapy (ACT) in primary and salvage therapy has been widespread in recent years despite limited data supporting its efficacy and varying results from multiple studies [4]. ACT approaches are thought to enhance the rate or extent of fungal killing via synergistic effect, broaden the spectrum of anti-fungal activity and minimize the emergence of resistance. However, more extensive studies are needed to prove improved efficacy of ACT against multiple fungal infections such as IFI.

In this issue of **Blood Research**, Lee *et al.* [5] reported a retrospective single institution study to determine the safety and efficacy of ACT (including voriconazole and caspofungin) in pediatric leukemia patients with IFI. Caspofungin (CAS) is known as an anti-fungal agent to damage fungal cell walls by inhibiting β-1,3-D-glucan synthase, whereas voriconazole (VRC) inhibits the synthesis of fungal cell membranes. Among the twenty two patients that were included in this study, 20 patients responded to combination therapy and among them, 19 patients showed a complete response. For 100 day treatment of ACT, 3 patients failed to complete the ACT, and 100-day IFI-free

survival rate was 86.3%. Additionally, the authors claim that voriconazole and caspofungin combination therapy was well tolerated, except for two patients who showed elevated liver enzyme levels. Although several previous studies including *in vitro* and animal model studies have suggested that voriconazole and caspofungin combination therapy is more effective than the monotherapy [6-9], the authors present for the first time that ACT with voriconazole and caspofungin combination can result in promising outcome for pediatric leukemia patients.

As the authors have pointed out about the limitation of this study in the discussion, this result is a retrospective study with the small number of cases from a single institute, thus a large-scale prospective study on ACT may be required to further confirm the efficacy of ACT in pediatric leukemia patients. Furthermore, the results will be more conclusive if further studies would include a microbiological method to confirm non-aspergillosis fungal infection.

The growing incidence of IFI in cancer patients continues to cause serious concern. More importantly, the treatment of underlying malignancies with chemotherapies and newly discovered drugs can negatively affect the protective immune responses in these patients [10]. Moreover, the outcome of IFI in cancer patients largely depends on the type of cancer and its treatment efficacy. Thus, it is important for clinicians to evaluate the general risks of IFI in a particular patient and the specific local risks within the context of hospital practices, patient populations and local infection control effectiveness from a diagnostic and preventative viewpoint. Clinical trials have aimed to establish the efficacy of ACT relative to monotherapy, but such attempts have been limited by several factors, such as high costs, difficulties in patient enrollment, extended duration of study. Thus, prompt diagnosis that would allow for the early initiation of ACT and optimization of current antifungal therapy by therapeutic drug monitoring can shed further light on the improved outcome of patients with IFI.

REFERENCES

1. Romani L. Immunity to fungal infections. Nat Rev Immunol 2011;11:275-88.
2. Stuehler C, Khanna N, Bozza S, et al. Cross-protective TH1 immunity against Aspergillus fumigatus and Candida albicans. Blood 2011;117:5881-91.
3. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am 2015;62:61-73.
4. Martín-Peña A, Aguilar-Guisado M, Espigado I, Cisneros JM. Antifungal combination therapy for invasive aspergillosis. Clin Infect Dis 2014;59:1437-45.
5. Lee KH, Lim YT, Hah JO, Kim YK, Lee CH, Lee JM. Voriconazole plus caspofungin for treatment of invasive fungal infection in children with acute leukemia. Blood Res 2017;52:167-73.
6. Lellek H, Waldenmaier D, Dahlke J, et al. Caspofungin plus posaconazole as salvage therapy of invasive fungal infections in immunocompromised patients. Mycoses 2011;54(Suppl 1):39-44.
7. Raad II, Zakhem AE, Helou GE, Jiang Y, Kontoyiannis DP, Hachem R. Clinical experience of the use of voriconazole, caspofungin or the combination in primary and salvage therapy of invasive aspergillosis in haematological malignancies. Int J Antimicrob Agents 2015;45:283-8.
8. Candoni A, Caira M, Cesaro S, et al. Multicentre surveillance study on feasibility, safety and efficacy of antifungal combination therapy for proven or probable invasive fungal diseases in haematological patients: the SEIFEM real-life combo study. Mycoses 2014;57:342-50.
9. Castagnola E, Cesaro S, Giacchino M, et al. Fungal infections in children with cancer: a prospective, multicenter surveillance study. Pediatr Infect Dis J 2006;25:634-9.
10. Perfect JR, Hachem R, Wingard JR. Update on epidemiology of and preventive strategies for invasive fungal infections in cancer patients. Clin Infect Dis 2014;59(Suppl 5):352-5.