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Original Article

Antifungal Combination Therapy for Invasive Fungal Infections in Pediatric Leukemia Patients: An Observational Cohort Study

Pediatrik Lösemi Hastalarında İnvaziv Mantar Enfeksiyonları için Antifungal Kombinasyon Tedavisi: Gözlemsel Bir Kohort Çalışması

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ABSTRACT

Objective: The role of combination regimens in the treatment of invasive fungal infections (IFIs) in hematologic malignancies remains unclear. We aimed to demonstrate data about combined antifungal therapy (CAT) in pediatric leukemia patients with IFI.

Method: Between January 2014 and December 2018, a total of 33 IFI episodes in 28 leukemia patients were analyzed retrospectively.

Results: The study patients had acute lymphoblastic leukemia (n=19), acute myeloblastic leukemia (n=9), leukemia relapse (n=21; 75%) and remission (n=7; 25%). The patients were classified as having possible (n=26; 78.8%), probable (n=5; 15.1%) and proven IFI (n=2; 6.1%). Liposomal amphotericin B (LamB) was the most preferred agent (50%) in monotherapy. Mean duration of monotherapy was 12.84±4.28 (5-24) days. LamB plus voriconazole (54.5%) was the most commonly preferred CAT. Mean duration of CAT was 42.36±36.4 days, and this combination regimen was not changed throughout the treatment period (p=0.571). Total and IFI-related mortality rates were 60.7% vs 46.4%, respectively. Mortality rates were significantly higher in patients with relapse (p=0.006). Complete response was obtained in 81.8% of surviving patients. Side effects of CAT were observed at quite a low level.

Conclusion: CAT has been found to be safe in the treatment of IFI episodes of pediatric leukemia. Uncontrolled underlying disease is the most important factor affecting the mortality rates in IFI.

Keywords: Pediatric, leukemia, invasive fungal infection, combined antifungal therapy

ÖZ

Amaç: Hematolojik malignitelerde invaziv fungal enfeksiyonların (İFE) tedavisinde kombinasyon rejimlerinin rolü belirsizliğini korumaktadır. Bu çalışmada, lösemili pediyatrik İFE hastalarında kombine antifungal tedavi (KAT) ile ilgili verilerin sunulması amaçlamıştır.

Yöntem: Ocak 2014 ile Aralık 2018 arasında, lösemili 28 hastada toplam 33 İFE atağı geriye dönük olarak analiz edildi.

Bulgular: Hastaların (19'u akut lenfoblastik lösemili ve 9'u akut miyeloblastik lösemili), 21'inde (%75) lösemi relapsı ve 7'sinde (%25) remisyon mevcuttu. İFE, 26 (%78,8) atakta mümkün, 5 (%15,1) atakta olası ve 2 (%6,1) atakta kanıtlı idi. Monoterapide en çok tercih edilen ajan (%50) lipozomal amfoterisin B (LamB) idi. Ortalama monoterapi süresi 12,84±4,28 (5-24) gündü. KAT'da en sık kombinasyon tercihi LamB artı vorikonazol (%54,5) idi. Ortalama KAT süresi 42,36±36,4 gündü ve kombinasyon rejimi tipine göre değişmiyor idi (p=0,571). Toplam mortalite oranı ve İFE'ye atfedilebilir ölüm oranı %60,7'ye karşılık %46,4 idi. Relaps olan hastalarda mortalite oranı anlamlı olarak daha yüksekti (p=0,006). Hayatta kalan hastaların %81,8'inde tam yanıt alındı. KAT kullanımına bağlı yan etkiler oldukça düşük düzeyde gözlendi.

Sonuç: Pediyatrik löseminin İFE ataklarında KAT güvenli bulunmuştur. İFE'de mortalite oranını etkileyen en önemli faktör kontrolsüz altta yatan hastalıktır.

Anahtar kelimeler: Pediyatrik, lösemi, invaziv mantar enfeksiyonu, kombine antifungal tedavi

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INTRODUCTION

Although many novel antifungal agents are in use, invasive fungal infections (IFI) continue to cause high morbidity and mortality rates in pediatric patients with hematologic malignancies[1,2]. Successful treatment of IFI is required to ensure the survival of this pediatric population. Currently, there are four classes (azoles, polyenes, pyrimidine analogues, and echinocandins) of drugs used in the treatment of IFI in children[3]. Appropriate use of available antifungals in this vulnerable population is important for the treatment of IFI[2]. However, safety and efficacy data including antifungal activity, pharmacokinetic properties, and toxicity of the antifungal agents in children still needs to be reinforced by trials[3,4]. Monotherapy is often preferred for the treatment of fungal infections in pediatric patients[4]. In some serious fungal infections where monotherapy is insufficient, the combination of antifungals remains on the agenda as a potential treatment strategy[5]. Since serious fungal infections need to be cured during the treatment of primary diseases, children with hematologic malignancies are the group of patients in whom combination regimens are frequently considered and tried to be applied[4,5].

Antifungal combination therapies are used in patients with hematologic malignancies in consideration of potential gains such as preventing resistance problems, increasing treatment efficacy and reducing side effects[5,6]. Combined antifungal therapy (CAT) is not a new notion, it is even used effectively in the treatment of some well-defined infections[7]. Unfortunately, the role of combination regimens in the treatment of IFI in patients with hematologic malignancies remains controversial[8]. Despite insufficient evidence, there are preclinical studies indicating that combination regimens are effective in treatment-resistant fungal infections[9-11]. However, these studies could not be transferred to the clinical practice, and quite few data are available for their clinical use. The limited data on this treatment regimen with scarce number of relevant prospective studies, and even more scanty data in pediatric patients, are obtained as a result of clinical experience[6,8,12-15]. In a few recent pediatric reports, it has been stated that CAT is preferred as a treatment option in progressive IFI or as a salvage treatment in patients with poor prognosis with anticipated achievement of satisfactory results[16-19]. The combinations of four groups of antifugal agents, acting through different molecular pathways and different cellular targets have been customized to the preference and priority of clinicians as there is no definitive accepted recommendation[8,9]. In the absence of sufficient evidence and suggestions; we aimed to demostrate experimental data on the use of CAT in pediatric IFI patients with hematologic malignancies, including the results of its efficacy and toxicity.

MATERIALS and METHODS

A retrospective study was conducted at University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital from January 2014 until December 2018. Patients under 18 years of age with a hematologic malignancy (acute lymphoblastic or myeloblastic leukemia) diagnosed as having IFI were enrolled in the study. Basic demographic data, underlying conditions, duration of neutropenia (absolute neutrophil count <500 cells/μL), radiological findings, antifungal medications, treatment-related clinical and laboratory side effects, and outcomes were noted. Galactomannan (GM) enzyme immunoassay (Platelia Aspergillus, BioRad, France) analyzes with plasma samples were performed twice weekly in the presence neutropenic fever and IFI episodes, and serum GM levels of ≥0.5 ng/mL were considered positive for IFI. All patients received prophylactic antifungal agents such as fluconazole or voriconazole according to their primary disease protocol (ALL IC BFM 2009, AML-BFM 2004 INTERIM, and ALL-REZ BFM 2002), and the risk or history of IFI. Diagnosis of IFI was defined according to the criteria of the European Organization for Research and Treatment of Cancer/IFIs Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group (EORTC/MSG)[20]. Patients were grouped according to the proven, probable, or possible diagnosis of IFI. Empirical antifungal treatment was initiated if fever persisted for more than 96 hours after initiation of empirical antibacterial treatment in consideration of relevant guidelines[21,22]. If there were symptoms, signs, laboratory or radiological findings suggestive of IFI, antifungal therapy was initiated earlier than the onset of the above-mentioned treatment. CAT was initiated based on the severity of patient's IFI and clinician's own subjective decision. The day of diagnosis was defined as the day that the clinician confirmed diagnosis of IFI, and initiated the antifungal treatment. Response to treatment was defined according to criteria of EORTC/MSG[20]. Overall response and survival rates estimated for the duration of 12 weeks were recorded. Research ethics committee approval was obtained for the study

from the University of Health Sciences, Ankara Child Health and Diseases Hematology-Oncology Training and Research Hospital Clinical Research Ethics Committee of the institution (decision number: 2013-057, date: 19.11.2013).

Statistical Analysis

Statistical analysis was performed using SPSS v25.0 (IBM Corp., Armonk, New York, USA) statistical package. Categorical variables were compared by chi-square or Fisher exact tests, and summarized with frequencies. For continuous variables, median and interquartile range were calculated. Group comparisons were carried out using independent samples t-test or Mann-Whitney U tests, and Kruskal-Wallis test wherever appropriate. All tests were 2-sided with a significance level of 0.05.

RESULTS

Thirty-three IFI episodes in 28 patients were examined. Two or more episodes were recorded in four patients. Demographic and clinical characteristics of the patients, and data for IFI were listed in Table 1. None of the patients underwent hematopoietic stem cell transplantation prior to the onset of IFI. GM analysis was performed in all patients at the beginning of a febrile neutropenia attack and afterwards in case of need. During 10 (32.3%) episodes, GM analyzes yielded positive results. The median GM index of the positive episodes was 1 (0.74-9). The most common radiological findings were ground-glass opacities (75.8%), nodules (54.5%) and consolidations (24.3%). Cavitation and/or halo sign were recorded in 7 episodes. Radiological examination performed revealed the presence of pulmonary IFI in 27, hepatosplenic IFI in 2, central nervous system IFI in 1 and paranasal IFI in 1 episode.

Liposomal amphotericin B (LAmB) was the first antifungal agent used for monotherapy in 16 (50%), caspofungin in 11 (34.4%), and voriconazole in 5 (15.6%) episodes. Mean duration of monotherapy was 12.84±4.28 (5-24) days. The second antifungal was added because of insufficient response at all episodes, and voriconazole was preferred in 22 (68.7%), LAmB in 7 (21.8%), caspofungin in 2 (6.4%), and posaconazole in 1 (3.2%) patient. CAT was initiated directly in only one episode as voriconazole plus caspofungin. Preferred combination regimens, duration of therapy, treatment responses, and mortality rates are summarized in Table 2. Combination treatment with antifungal agents lasted between 15, and 67 days, and in surviving patients transition from combined regimen to monotherapy took 28-67 days. In both of the proven IFI episodes, the causative agents were *Candida* spp.

The 12-week overall and survival rates of the patients were 75% and 39.2%, respectively. The cause of death was progression of IFI in 13 patients, and the remaining 4 patients did not respond to the treatment of the underlying disease. IFI- related mortality rate was 46.4%. The IFI-related mortality rate was 76.5%. Mortality rates were significantly higher in patients with relapse, despite being treated with a specific relapse protocol, (χ^2=7.47; p=0.006). The effect of the combination regimen used on mortality was found to be statistically insignificant (z=1.3; p=0.192). Complete response (CR) to the treatment was obtained in 9 (81.8%) of 11 surviving patients. Median recovery time in patients with CR was 120 (28-210) days. Duration of neutropenia (z=0.39; p=0.695), CAT (z=1.37; p=0.173), and time to recovery (z=0.768; p=0.443) were not statistically different in the episodes with/without fatal outcomes. The effect of the selected primary antifungal agent could not be evaluated due to insufficient number of cases. Duration of neutropenia (z=0.22; p=0.821), CAT (t=0.795; p=0.446), and time to recovery (t=0.991; p=0.355) were not statistically significantly different according to relapse or remission status. There was no statistically significant relationship between IFI classification and the episodes with/without fatal outcomes (χ^2=3.726; p=0.293). Among the surviving patients, voriconazole was preferably used in 9 and posaconazole in two patients as the secondary prophylactic antifungal agents.

CAT was well tolerated in most patients. Renal dysfunction accompanied by electrolyte disturbances in one patient and increased transaminase levels in two patients were seen as adverse effects of CAT, and discontinuation of treatment was required in only one patient because of side effects. Monitoring plasma levels of voriconazole was not implemented in our center. IFI-induced surgical procedure was not applied to any patient.

DISCUSSION

IFI-related mortality rates range from 45% to 90%, and treatment success for IFI is reported to be around 60% in various reports[1,5,23,24]. The advantages and disadvantages of CAT in the treatment of IFI have not been determined compared to monotherapy. However, thanks to increased drug synergy and efficacy, and decreased resistance to antifungal drugs, the expectation that CAT may improve the outcome of the patients is still a valid assumption. Due to the absence

Table 1. Demographic and clinical characteristics of the patients, and data for IFI episodes	
Total cases	28
Age (years)	
Mean ± SD	8.79±5.03
Median (range)	7 (3.5-18)
Gender, n (%)	
Male	15 (53.6%)
Female	13 (46.4%)
Underlying diseases, n (%)	
ALL	19 (67.9%)
AML	9 (32.1%)
Status of underlying disease at the time of IFI episode, n (%)	
Remission	7 (25%)
Relapse	21 (75%)
Prophylactic agent before onset of IFI episode, n (%)	
Flucanazole	26 (92.8%)
Voriconazole	2 (7.2%)
Chemotherapy phase during IFI	
Induction	33 (100%)
Consolidation	0
Duration of prophylaxis before onset of IFI episodes (days)	
Mean ± SD (range)	47±24.04 (30-84)
Duration of neutropenia at the onset of IFI (days)*	
Mean ± SD (range)	42.87±35.5 (7-140)
in ALL	42.18±40.1 (7-140)
in AML	44.75±20 (20-64)
IFI classification, episode (%)	
Possible	26 (78.8%)
Probable	5 (15.1%)
Proven	2 (6.1%)
No statistical difference was found according to the underlying disease (p=0.18)	
ALL: Acute lymphoblastic leukemia, AML: Acute myeloblastic leukemia, IFI: Invasive fungal infection, SD: Standard deviation	

Table 2. Preferred combination regimens; duration of therapy, treatment responses, and mortality rates					
Combination regimens*	**n (%)**	**Duration (day) of therapy† Median (min-max)**	**Treatment response rates (%)**		**Mortality rates (%)**
			CR	**OR**	
LAmB plus Caspofungin	4 (12.1%)	23.5 (10-67)	25	50	50
LAmB plus Voriconazole	18 (54.5%)	32 (10-300)	33.4	50	50
Voriconazole plus Caspofungin	10 (30.3%)	65 (7-450)	20	20	80
LAmB plus Posaconazole	1 (3)	20	100	100	0
Total	33 (100%)	32 (7-450)	45	55	60.7
CR: Complete response, LAmB: Liposomal amphotericin B, OR: Overall response					
*All antifungals applied during CAT were used at the recommended doses for monotherapy.					
†was not statistically significant according to the combination regimen used (p=0.571)					

of prospective and randomized controlled clinical trials with an adequate statistical power, combined antifungal use in the treatment of IFI is included in current international guidelines as having a low level of evidence and recommendation[21,22]. Although the CAT approach in IFI has weak foundations, it is frequently applied in daily practice[14], and there are even reports emphasizing that this alternative has been used in up to 90% of the cases[25]. In a multicenter point prevalence survey from Turkey, Çağlar et al.[26] revealed that CAT was preferred in 8.4% and 61.5% of pediatric hematology, and oncology patients, respectively.

In our study, IFI-related mortality rates were not significantly different from the expected IFI-related mortality rates (46.4%). In previously published studies, overall treatment response to CAT was reported at rates ranging from 35% to 60%[8]. Generally higher 12-week survival rates were reported when compared with the overall response rates[8-12,16]. Previous studies reported that CAT appears helpful especially in patients with poor prognostic features[8,16-19]. Based on our results, considering that our patient population generally consisted of children with poor prognostic factors such as prolonged neutropenia and relapsed leukemia, despite lack of any control group, the overall response to CAT can be interpreted as favourable. However, ultimately the IFI-related mortality rates were quite high. Neutropenia is an important risk factor for IFI, and the duration of neutropenia affects the treatment response and mortality rates[2]. In our patient group, the mean duration of neutropenia was found to be 42.87±35.5 days which was longer than reported in previous studies[13,23]. Although the duration of neutropenia was not statistically different in the episodes with/without fatal outcomes, we thought that it was the main determinant in the higher IFI-related mortality rates.

Based on our results, LAmB was found to be the mostly preferred first-line agent to be used in monotherapy due to the inability to distinguish invasive aspergillosis from mucormycosis on the day of diagnosis. Monotherapy was switched to CAT within approximately two weeks in all IFI episodes and voriconazole-based combination regimen was applied most frequently. Although in vitro studies have reported that caspofungin and voriconazole have a synergistic effect against *Aspergillus* spp.[27,28] and this combination reduces fungal burden in animal tissues compared to single echinocandin or triazole administration[11], the combination regimen preferences may vary in practice[8,14,15]. In the literature, it is stated that LampB is often preferred as the first-line agent and voriconazole is included as a second agent in CAT regimens[16,18,19]. In our experience, the choice of antifungal combination was found to vary according to the first antifungal chosen in monotherapy, and LAmB plus voriconazole was the most common preference. The total mortality rate in combination regimens was around 60% in our patients, and the highest mortality rate was seen in the voriconazole plus caspofungin combination at a rate of 80%. When evaluating this result, it should be kept in mind that our study did not contain a control group, and a patient group that received monotherapy for the purpose of comparison. In response to the expectation of improvement in the outcomes of the patients, some authors have claimed that CAT is ineffective in improving patient outcomes in general[6,13,14,29], despite clinical trials with favourable results[6,12]. In our study, CAT could not be compared with monotherapy due to the absence of a control group, but the type of combination regimen used had not any impact on mortality. This study has demonstrated once again that the uncontrolled underlying disease was one of the most important factors affecting the mortality rates[1,2].

When the previously performed relevant studies are evaluated, it is seen that both the transition time from monotherapy to CAT and the duration of CAT have not been standardized, and varies widely[6,8,10,12-15]. In this study, the mean duration of therapy was 42.36±36.4 days, and remained unchanged according to the type of combination treatment regimen. The main determinant of the duration of CAT apparently is specified in consideration of the combined clinical, radiological and microbiological response of the patient. Due to individual differences in determining the treatment alternative, duration of CAT can be very short or very long[6,12-15,17].

CAT has been generally reported in association with an increased risk of adverse events[13,14]. Although adverse effects vary with the type of antifungal drug used, the most common side effects of CAT were reported as hepatic, renal, and neurologic toxicity[12,13]. Despite reports indicating increased risk of side effects, there are also studies reporting that CAT with proven efficacy does not cause significant side effects other than mild or moderate adverse events[6,16,17,30]. Based on our experience, treatment results of CAT are generally well tolerated. In other words, CAT has been found to have a favourable safety profile for use in the treatment of IFI episodes of pediatric leukemia.

Study Limitations

Our retrospective study has reported data coming from only one institute. Due to the small number of patients, the power of statistical comparisons decreased. Furthermore, due to quite limited number of cases with proven IFI, it is not clear which combined antifungal regimen was administered for IFI, which fungal agent was the causative pathogen. Despite the limitations, we think that the data of this study may contribute to the analysis of combined antifungal use in daily clinical practice, tolerability and treatment outcomes of CAT in IFI patients with hematologic malignancies.

CONCLUSIONS

Optimal therapy for IFI in patients with pediatric hematologic malignancies is unknown, while some clinicians use the CAT approach as an alternative to improve the outcome of these critically ill patients. However, though various preclinical studies suggest the possibility of using this preference, there is no definite accepted recommendation yet. Well-designed and randomized trials are required to define the role of combined antifungal use in pediatric patients with hematologic malignancies.

Ethics

Ethics Committee Approval: Research ethics committee approval was obtained for the study from the Ankara Child Health and Diseases Hematology-Oncology Training and Research Hospital Clinical Research Ethics Committee of the institution (decision number: 2013-057, date: 19.11.2013).

Informed Consent: Retrospective study.

Peer-review: Internally peer reviewed.

Author Contributions

Surgical and Medical Practices: S.K.Y., Concept: S.K.Y., Design: A.Ö.P., Data Collection and/or Processing: B.G., Analysis and/or Interpretation: N.Y., N.Y.Ö., H.T., Literature Search: S.K.Y., B.G., Writing: S.K.Y.

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