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Micafungin Use in Children: A Tertiary Referral Hospital Experience in the Treatment of Invasive Fungal Infections

Çocuklarda Mikafungin Kullanımı: İnvaziv Mantar Enfeksiyonlarının Tedavisinde Üçüncü Basamak Merkez Deneyimi

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Abstract

Objective: Invasive fungal infections (IFIs) are a major cause of mortality and morbidity in hospitalized pediatric patients due to limited treatment options. Micafungin has been the most recently approved echinocandin for the treatment of IFIs in children; however, the data on efficacy and adverse events in children has been limited. This study aimed to evaluate the characteristics, treatment responses, and the incidence of adverse events of the micafungin treatment in children.

Material and Methods: This retrospective study was designed to evaluate all patients under 18 years old who received micafungin for treatment between January 2017-December 2019. A standardized form was used to collect demographic characteristics, underlying medical conditions, diagnosis of fungal infections, laboratory findings, prognosis, and mortality (14-day mortality, 30-day mortality).

Results: We evaluated 43 episodes of 39 patients who received micafungin for treatment. Median age of the patients who received micafungin for treatment was 2.3 (10 days-17 years and six months) years. Micafungin was used for definitive treatment in 18 (41.9%) patients, for empiric treatment in 15 (34.9%) patients, and for febrile neutropenia in 10 (23.3%) patients. Median duration of micafungin treatment was 14 (3-53) days. Treatment efficacy was found as 79.1% in clinical response and 81.3% in mycological response. The incidence of hepatic adverse events was 20.9% and renal adverse events 2.3% while using micafungin for treatment. In patients who received micafungin for

Öz

Giriş: İnvaziv fungal enfeksiyonlar, sınırlı tedavi seçenekleri nedeniyle hastanede yatan ve bağışıklığı baskılanmış çocuk hastalarda önemli bir mortalite ve morbidite nedenidir. Mikafungin, çocuk hastalarda invaziv fungal enfeksiyonların tedavisi için en yeni onaylanmış ekinokandin grubu bir antifungaldir; ancak, çocuklarda etkililik ve yan etkileri hakkındaki veriler sınırlıdır. Bu çalışmada, mikafungin tedavisi kullanan çocuk hastaların özelliklerinin, tedaviye yanıtlarının ve yan etki sıklığının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Tek merkezde, Ocak 2017-Aralık 2019 tarihleri arasında tedavi için mikafungin kullanan 18 yaşından küçük çocuk hastalar geriye dönük olarak değerlendirildi. Hastaların demografik özellikleri, altta yatan hastalıkları, mantar enfeksiyonlarının özellikleri, laboratuvar bulguları, prognoz ve mortalitesi (14 günlük mortalite ve 30 günlük mortalite) standart bir forma yazılarak kaydedildi.

Bulgular: Çalışmamızda tedavi için mikafungin kullanan 39 hastanın 43 epizodu değerlendirildi. Tedavi için mikafungin kullanan hastaların yaş ortanca değeri 2.3 (10 gün-17 yıl altı ay) yıldı. Mikafungin tedavisi, 18 (%41.9) hastada etkene yönelik tedavi, 15 (%34.9) hastada ampirik tedavi ve 10 (%23.3) hastada febril nötropeni için kullanıldı. Hastaların tedavi için mikafungin kullanma ortanca süresi 14 (3-53) gündü. Tedavi etkinliği değerlendirildiğinde hastaların %79.1'inde klinik yanıt, %81.3'ünde mikolojik yanıt alındı. Tedavi için mikafungin kullanan hastalarda hepatik yan etki %20.9 oranında ve renal yan etki %2.3 oranında görüldü. Tedavide

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treatment, 14-day and 30-day mortality rates were 7% and 9.3%, respectively. However, these deaths were not attributable to a fungal infection (two patients died due to heart failure, and two patients died due to respiratory failure).

Conclusion: We demonstrated that micafungin might be a safe and effective antifungal agent for empiric therapy and definitive therapy. Further and more extensive prospective studies to evaluate the efficiency and safety of micafungin in children are needed.

Keywords: Invasive fungal infections, children, micafungin

mikafungin kullanan hastalarda 14 günlük ve 30 günlük mortalite oranı sırasıyla %7 ve %9.3 idi. Ancak, mikafungin kullanan hastalarda görülen ölümler enfeksiyonu ile ilişkili değildi (iki hastada mortalite nedeni kalp yetmezliğiydi ve iki hastada mortalite nedeni solunum yetmezliğiydi).

Sonuç: Bulgularımız, mikafunginin pediyatrik hastalarda invaziv fungal enfeksiyonların tedavisi için kullanıldığında güvenli ve etkili bir antifungal ajan olabileceğini düşündürmüştür. Çocuklarda mikafungin kullanımının etkinliğini ve güvenliğini değerlendirmek için daha fazla ve daha geniş prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İnvaziv mantar enfeksiyonları, çocuk, mikafungin

Introduction

Invasive fungal infections (IFIs) are still a significant cause of mortality and morbidity in critically ill and immunocompromised pediatric patients (1). *Candida* and *Aspergillus* species are the most common causative agents for these infections (2). Treatment of IFIs is a major challenge for clinicians due to increased triazole antifungal resistance, and new treatment options are required (3). Micafungin, an echinocandin class antifungal agent, can be an alternative treatment option in IFIs due to the fungicidal activity against most C*andida* spp. and the fungistatic activity against *Aspergillus* spp. (4,5). However, micafungin is not active against *Cryptococcus neoformans* and shows little activity against *Fusarium* spp. and *Zygomycetes* spp (5). Micafungin is also effective in prophylaxis against invasive fungal infections in pediatric patients with hematological malignancies or hematopoietic stem cell transplantation (HSCT) (6,7).

Micafungin shows activity by inhibiting the synthesis of (1,3)-beta-D-glucan, a major polymeric polysaccharide of the fungal cell wall, well-tolerated and does not require a loading dose (2,4,5,8). Micafungin can be an alternative treatment option due to lower rates of renal injury than amphotericin B (4). However, the liver is the leading site of micafungin metabolism, and it can potentially cause liver test abnormalities and rarely life-threatening hepatotoxicity as a side effect (4,9). Other most common adverse reactions include diarrhea, nausea, vomiting, pyrexia, thrombocytopenia, and headache (9,10).

Micafungin has Food and Drug Administration (FDA) approval, including indications for treatment of adults and pediatric patients aged four months and older with candidemia, acute disseminated candidiasis, *Candida* peritonitis, abscesses, esophageal candidiasis, and prophylaxis of *Candida* infections in patients undergoing HSCT. It also received approval for children younger than four months in January 2020 (10). Infectious Diseases Society of America (IDSA) recommends using micafungin as initial therapy for candidemia in neutropenic and non-neutropenic patients and as a salvage therapy for aspergillosis (11,12). In Türkiye, micafungin was licensed in February 2014, and we have been using micafungin for the treatment of pediatric patients since January 2017 in our hospital.

This study aimed to evaluate the children who had received micafungin for treatment and describe their characteristics, treatment responses, and the incidence of adverse events while using micafungin.

Materials and Methods

Study Design and Study Population

A retrospective observational study was performed between January 2017-December 2019 in a 216-bed tertiary care facility. All patients under 18 years old who received micafungin for treatment were evaluated, which included 43 episodes from 39 patients. All patients were identified retrospectively through medical records. A standardized form was used to collect demographic characteristics, underlying medical conditions, diagnosis of fungal infections, laboratory findings, prognosis, and mortality (14-day mortality, 30-day mortality). Micafungin 2 mg/kg/day was used with the option to increase to 4 mg/kg/day (maximum 200 mg/g) once daily to treat IFIs. In neonates, micafungin 10 mg/kg/day once daily was used to treat IFIs.

Data on the reason for stopping micafungin, the evolution of IFIs, and adverse events were also collected during micafungin treatment. Adverse events were evaluated by monitoring alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, and creatinine on treatment days zero, three, seven, and 14.

Microbiologic Methods

Fungi were isolated from blood cultures using the BacktAlert system (bioMérieux, France). They were identified with conventional mycological methods, and their assimilation profiles were determined with ID 32 C (bioMérieux, France) between 2008-2014; and identified by MALDI TOFF MS (bioMérieux, France) between 2014-2019.

Definitions

European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) definitions were used to define IFIs as proven, probable, or possible (13). A breakthrough IFI was defined after ≥3 days of receiv-

ing micafungin, even if IFI was due to an organism outside the usual spectrum of activity of the antifungal drug the patient was exposed to (14,15). The second episode of IFI occurring in the same patient within two weeks of the first negative culture was defined as a new episode.

In neonates, fluconazole was primarily preferred for the treatment of fungal infections. Liposomal amphotericin B was administered in neonates if they had received fluconazole prophylaxis or if the fungus was resistant to fluconazole. Micafungin treatment was preferred in neonates with elevated renal function tests, or the fungus was resistant to other antifungals.

Monotherapy was defined as administering a single antifungal agent on a given day. Combination therapy was described in patients who received at least two antifungal agents. De-escalation was defined as switching micafungin to another antifungal for maintenance therapy once a therapeutic response was achieved (3). Complete clinical response was defined as the resolution of all attributable signs, symptoms, and radiographic abnormalities related to fungal infection. Partial clinical response was defined as improvement in attributable signs, symptoms, and radiographic abnormalities associated with the fungal infection. Stabilization or progression of disease was considered a failure of therapy. The mycological response was defined as clearance of microbiological culture. Persistence was defined as continued isolation or historical documentation from the primary site after 14 days of micafungin treatment. Prolonged neutropenic fever was defined as persistent fever after 96 hours of intravenous antibiotic therapy.

Thrombocytopenia was defined as platelet count below 150 x 10^9/L, and neutropenia was described as absolute neutrophil count below 1.5 x 10^9/L. Renal function test abnormality was defined as >50% increase from the baseline serum creatinine (16). Liver function test abnormality was described as a three-fold increase in AST or ALT or a two-fold increase in bilirubin from the upper limit of normal (ULN) (3).

Statistical Analysis

Statistical analysis was performed using SPSS statistical package (version 25 for Windows). Data were expressed as mean ± standard deviation (SD) or median (interquartile range) for continuous variables or percentages for categorical variables. Repeated measures ANOVA test was used to compare biochemical parameters on days zero, three, seven, and 14. Paired sample t-test was performed for the values of $p< 0.05$ to determine the significant difference between repeated measures. Differences and correlations were considered significant at $p< 0.05$.

Ethics

Necessitated approval was obtained from the Ege University Faculty of Medicine Medical Research Ethics Committee (ethical decision No: 20-3T/2).

Results

Patient Characteristics

We identified 43 episodes from 39 patients who received micafungin for treatment at a tertiary-level hospital, having subdivisions including intensive care, bone marrow/solid (renal/cardiac/liver) organ transplantation, intestinal failure, and rehabilitation and immunology subunits. In our study group, 39 patients had one episode, three patients had two episodes, and one patient had three episodes for micafungin treatment.

Median age of the patients who received micafungin for treatment was 2.3 years (range= 10 days-17.5 years), and 48.8% were males. The most common underlying disease was hematologic malignancy (34.9%), followed by gastrointestinal system disorders (32.6%) and solid organ-bone marrow transplantation (14%). Micafungin was used for treatment most commonly in the hematology-oncology unit (37.2%), followed by the pediatric surgery unit (23.3%) and gastroenterology unit (18.6%). Neutropenia was present in 18 patients (41.9%) for a median duration of eight (range= 1-34) days. Table 1 summarizes the demographic and clinical characteristics of the patients who received micafungin for treatment.

In our study group, there were five neonatal patients, three of whom were premature and two of whom were mature. Three (60%) of them were diagnosed with congenital heart disease, and the other two (40%) patients were diagnosed with gastrointestinal system disorders. Median gestational age was 37 weeks (range 34-38 weeks), and four (80%) of them were males.

Clinical Data and Outcomes of Micafungin Treatment

Micafungin was used for definitive treatment in 18 (41.9%) patients, empiric therapy in 15 (34.9%) patients, and febrile neutropenia in 10 (23.3%) patients. Median duration of micafungin treatment was 14 (range= 3-53) days. Sixteen (37.2%) patients had proven IFI, one (2.3%) patient had probable IFI, and one (2.3%) patient had possible IFI. The most commonly isolated species in proven IFIs were *Candida parapsilosis* (n= 9, 20.9%), followed by *Candida albicans* (n= 3, 7%) and *Candida glabrata* (n= 3, 7%). Majority of the patients (95.3%) had central venous access. Before micafungin treatment, 26 (60.5%) patients were using an azole antifungal agent for prophylaxis. Nine (21%) patients received systemic antifungal therapy before starting micafungin treatment. The most common reason for micafungin therapy was clinician recommendation in 33 (76.7%) patients, followed by intolerance (hypopotassemia

Table 1. Demographic and clinical characteristics of the patients who received micafungin for treatment

Characteristics	Micafungin treatment (n= 43)
Age, year, median, (min-max)	2.3 (10 days-17.5 years)
Sex, male, n (%)	21 (48.8)
Underlying conditions, n (%)	
Hematologic malignancy	15 (34.9)
Gastrointestinal system disorders	14 (32.6)
Bone marrow/solid organ transplantation	6 (14.0)
Congenital heart disease	5 (11.5)
Chronic neurological/neuromuscular disorder	3 (7)
Neutropenia, n (%), (<1500/mm^3)	18 (41.9)
Neutropenia duration, days, median, (min-max)	8 (1-34)
Thrombocytopenia, n (%), (<150.000/mm^3)	30 (69.8)
Liver function test abnormality during micafungin administration, n (%)	9 (20.9)
Renal function test abnormality during micafungin administration, n (%)	1 (2.3)

or an allergic reaction) to liposomal amphotericin B (L-AmB) in five (11.7%) patients. Thirty-three (76.7%) patients received micafungin as a monotherapy. Combination therapy was used for 10 patients (23.3%). Seven patients received micafungin concomitant with voriconazole, and three patients received micafungin with L-AmB. Thirty-four (79.1%) patients had complete clinical response, four (5.9%) patients had partial clinical response, and five (11.7%) had stabilization or progression of the disease. Mycological response was achieved in 13 (81.3%) patients. The most common reason to stop micafungin was complete response (27, 62.8%), followed by de-escalation (7, 16.3%), mortality (4, 9.3%), and a three-fold increase in AST and ALT from ULN (1, 2.3%). four-day mortality and 30-day mortality rates were 7% and 9.3%, respectively. However, these deaths were not attributable to a fungal infection (two patients died due to heart failure, and two patients died due to respiratory failure). Table 2 summarizes the clinical characteristics and outcomes of the patients who received micafungin for treatment.

Micafungin was preferred in all five neonatal patients due to previous elevated renal function tests. Four neonates (80%) had complete clinical response, and one (20%) patient died on the 7th day of micafungin treatment. However, this patient died due to heart failure, and her death was not attributable to a fungal infection.

Adverse Events of Micafungin Treatment

The evaluation of hepatotoxicity due to micafungin showed liver function test abnormality in nine (20.9%) patients who received micafungin for treatment. Renal function test abnormality was observed in one (2.3%) patient who received micafungin for treatment. There were no significant differences in serum AST, ALT, ALP, GGT, or creatinine levels during the first two weeks of the micafungin treatment period (all p> 0.05). Changes in serum biochemistry parameters during the first two weeks of micafungin treatment from baseline are shown in Table 3. No adverse events were observed in five neonatal patients.

Discussion

Despite high morbidity and mortality of IFIs, treatment options are still limited to three classes of antifungal agents, including polyenes, echinocandins, and azoles (1). Micafungin is the most recently approved echinocandin for treating IFIs in children and has been approved in Türkiye since 2014 (10). Micafungin has fewer adverse events when compared to azoles and polyenes (3,4). However, the data on efficacy and adverse events in children has been limited. Therefore, we aimed to evaluate the children who had received micafungin treatment. We found treatment efficacy as 79.1% in clinical response, as 81.3% in mycological response and the incidence of hepatic adverse events as 20.9%, and renal adverse events as 2.3%.

Leverger et al. (3) have evaluated 110 pediatric patients who received micafungin for treatment or prophylaxis and reported that the therapeutic objective was achieved in 76.6% of hemato-oncology patients, in 96.6% of neonatal patients and in 85.7% of pediatric intensive care unit (PICU) patients. Styczynski et al. (17) have reported that micafungin treatment success was 85% and 60% in children with IFI in pediatric hemato-oncology and HSCT patients, respectively. Kobayashi et al. (2) have evaluated 201 pediatric patients who received micafungin for treatment. The overall clinical response rate for efficacy was 86.8% in children and 90.0% in neonates. In our study, 79.1% of the patients had complete clinical response, and mycological response was observed in 81.3% of the patients. Schüller et al. (18) have evaluated 19 extremely low birth weight infants, and micafungin treatment success was reported as 84%. Similar to previous reports, 80% of the neonates had complete clinical response in our study.

Table 2. Clinical characteristics and outcomes of the patients who received micafungin for treatment

Patients (n= 43)	
Micafungin therapy, n (%)	
Definitive treatment	18 (41.9)
Proven IFI	16 (37.2)
Candidemia	15 (34.9)
Candida parapsilosis	9 (20.9)
Candida albicans	3 (7)
Candida glabrata	3 (7)
Invasive pulmonary aspergillosis	1 (2.3)
Aspergillus flavus	1 (2.3)
Probable IFI	1 (2.3)
Possible IFI	1 (2.3)
Empiric treatment	15 (34.9)
Febrile neutropenia	10 (23.3)
Use of antifungal prophylaxis, n (%)	26 (60.5)
Voriconazole	14 (32.6)
Fluconazole	11 (25.6)
Posaconazole	1 (2.3)
Prior antifungal treatment, n (%)	9 (21)
Voriconazole	4 (9.3)
L-AmB	3 (7)
Fluconazole	2 (4.7)
Indications for micafungin treatment, n (%)	
Hypopotasemia due to L-AmB	3 (7)
Renal function test abnormality	2 (4.7)
Allergic reaction due to L-AmB	2 (4.7)
Systemic and antifungal lock therapy	2 (4.7)
Prior antifungal resistance	1 (2.3)
Clinician recommendation	33 (76.7)
Monotherapy, n (%)	33 (76.7)
Combination antifungal therapy, n (%)	10 (23.3)
Micafungin + voriconazole	7 (16.3)
Micafungin + L-AmB	3 (7)
Duration of micafungin treatment, days, median, (range)	14 (3-53)
Reasons for stopping micafungin, n (%)	
Complete clinical response	27(62.8)
Treatment de-escalation due to complete clinical response	7 (16.3)
Treatment not effective	4 (9.3)
Mortality during treatment	4 (9.3)
Adverse events	1 (2.3)
Central venous catheter, n (%)	41 (95.3)
Central venous catheter removal, n (%)	16 (39)
Negative culture time, days, median (range)	16 (1-26)

Table 2. Clinical characteristics and outcomes of the patients who received micafungin for treatment (continue)

Patients (n= 43)	
Clinical response to micafungin treatment, n (%)	
Complete clinical response	34 (79.1)
Partial clinical response	4 (9.3)
Stabilisation or progression	5 (11.7)
Mycological response to micafungin treatment, n (%)	
Yes	13 (81.3)
No	3 (7)
Outcomes, n (%)	
14-day mortality	3 (7)
30-day mortality	4 (9.3)

IFI: Invasive fungal infection, L-AmB: Liposomal amphotericin B.

Table 3. Changes in serum biochemistry parameters during the first two weeks of micafungin treatment in the study patients

	Day 0	Day 3	Day 7	Day 14	p
Micafungin treatment[c]	(n= 43)	(n= 39)	(n= 33)	(n= 29)	
AST (U/L)*	27 (22)	32 (41)	39.5 (30.5)	37 (39)	>0.05
ALT (U/L)*	31 (39)	34.5 (54)	31.5 (37.5)	35 (46)	>0.05
ALP (U/L)*	168.5 (189.2)	178.5 (228.2)	192 (230)	194 (248)	>0.05
GGT (U/L)*	79 (149)	87 (122)	96 (198.5)	87 (114)	>0.05
Total bilirubin (mg/dL)*	0.52 (0.53)	0.54 (0.55)	0.43 (1.27)	0.5 (0.6)	>0.05
Creatinine (mg/dL)*	0.29 (0.22)	0.27 (0.33)	0.29 (0.28)	0.28 (0.22)	>0.05

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase.
Note: Continuous variables presented as the mean ± SDS.
[c]Comparison of the serum levels of total bilirubin, ALT, AST, ALP, GGT, and creatinine on the 3rd day, 7th day, and 14th day, respectively, with the day on starting micafungin.
*median (IQR).

It is difficult for clinicians to decide the optimal antifungal agent because many antifungal agents are expensive and have significant side effects. Neoh et al. (19) have reported that micafungin has been more cost-effective than liposomal amphotericin B to treat invasive candidiasis in adults. Micafungin is well tolerated and has a low potential for drug interactions (20,21). The most severe adverse reaction of micafungin is hepatotoxicity. Other common adverse reactions include diarrhea, nausea, vomiting, pyrexia, thrombocytopenia, and headache (9,10). Kobayashi et al. (2) have reported the rate of adverse drug reactions in 22.1% of the pediatric patients, and hepatobiliary disorders were the most common adverse drug reaction (13.7%). No adverse drug reactions have been reported in neonates. Yesil et al. (22) have evaluated 125 pediatric patients and reported that no micafungin treatment-related significant side effects were observed in any of the patients. Park et al. (23) have reported the rate of liver abnormalities at 45%, and Bui et al. (20) have reported liver abnormalities at 81.3% and renal abnormalities at 62.5% in pediatric patients receiving micafungin prophylaxis. Leverger et al. (3) have reported an adverse drug reaction rate in 21.8% of the children in their study group. We determined liver function test abnormality in 20.9% of the patients in during micafungin treatment, similar to previous studies. Only one patient discontinued micafungin treatment due to a three-fold increase in AST and ALT from ULN. In addition, 2.3% of the patients developed renal function abnormality during treatment. Cakır et al. (24) have evaluated 15 neonates and no abnormal kidney or liver function tests due to micafungin use were reported. Moreover, no adverse events were observed in five neonate patients in our study.

Viscoli et al. (25) have reported survival at the end of micafungin treatment at 97% in 36 pediatric patients. Hashii et al. (26) have evaluated nine immunocompromised pediatric patients, and Kobayashi et al. (27) have evaluated 30 pediatric patients with febrile neutropenia who received micafungin treatment, and no deaths were reported. Telles et al. (28) have reported a mortality rate of 1.9% in 48 pediatric patients during micafunin treatment. In other previous studies, mortality rates have been reported as high as 16% (19-20). In our study, 14-day mortality rate was 7%; however, these deaths were not attributable to a fungal infection. The higher comorbidity of the patients can explain the higher mortality rate in our study.

There are several limitations to this study. The first limitation of our study is its retrospective design; therefore, some clinical information might be missed. Second, it was a single-center study. The efficiency and adverse event rates may differ between centers. The other limitation of our study includes its small sample size, and there was no control group to compare the results in a similar group of patients not receiving micafungin. Additional limitations include difficulties in the assessment of true incidence of nephrotoxicity and hepatotoxicity due to the comorbidities in the patients, and the concomitant administration of nephrotoxic agents and hepatotoxic agents. Additionally, our study group included heterogeneous patient populations, including neutropenic patients, neonates, and patients with chronic comorbidities. Despite these limitations, our study gives information about the data on efficacy and adverse events of micafungin in children.

Conclusion

In conclusion, micafungin might be a safe and effective antifungal agent for empiric therapy. Further and more extensive prospective studies to evaluate the efficiency and safety of micafungin in children are needed.

Ethics Committe Approval: This study approval was obtained from Ege University Medical Research Ethics Committee (Decision no: 20-3T/2, Date: 04.03.2020).

Informed Consent: Patient consent was obtained.

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