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Based on PK/PD and Monte Carlo Simulation Analysis of the Dosing Regimens of Micafungin in Children with Febrile Neutropenic

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Abstract

Neutropenia with fever is a special group of patients. Due to low immune function, inflammation-related clinical symptoms and signs are often not obvious, and pathogenic bacteria and infection focus are not clear. Fever may be the only sign of infection. If appropriate antimicrobial treatment is not given in time, infection-related mortality is high. In our study, we aimed to optimize the dosage regimen of Micafungin in children with febrile neutropenic against *Candida* spp. by Mote Carlo Simulation (MCS). Pharmacokinetic parameters and microbiological data of Micafungin were collected. Then we used MCS to calculate Probability of Target Attainment (PTA) and Cumulative Fraction of Response (CFR). With dosages of 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg, and 4 mg/kg in oral group and dosages of 100 mg, and 200 mg in intravenous administration, all have different degree of antifungal effect. But when the dosage regimen was 50 mg IV, the therapeutic effect of Micafungin against *Candida* spp. was not good.

Keywords

PK/PD Model, Mote Carlo Simulation, Micafungin, Febrile Neutropenic

1. Introduction

Neutropenia is the most common cause of death and morbidity in childhood cancer patients. Invasive fungal infections have significant morbidity and mortality in pediatric patients. It is found shortly after chemotherapy-induced neu-

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tropenia or hematopoietic Stem Cell Transplantation (HSCT). Among patients, about one-third of neutropenia episodes have a febrile reaction. When the absolute neutrophil count is less than 500 cells/L, the risk of serious bacterial or fungal infection increases [1]. At present, Micafungin is one of the main drugs for the treatment of bacterial infections in children with neutropenia.

Micafungin is an echinocandin antifungal drug that selectively inhibits the synthesis of 1,3-β-D-glucan in the cell wall of fungi [2]. At present, the invasive fungal infection in patients with neutropenia is *Candida* spp. and Micafungin has good antibacterial activity against the above-mentioned bacteria and is effective against azole-resistant *Candida* [3]. In addition, Micafungin slowly degrades through the catechol-o-methyltransferase pathway, has no inhibitory effect on cytochrome P450 enzymes [4], and has become a common medicine for the treatment of patients with febrile neutropenia.

Mote Carlo Simulation (MCS) is an effective tool for dose screening in clinical treatment. It can evaluate the efficacy of antibacterial drugs, maximize the possibility of obtaining clinical efficacy, and minimize the possibility of antimicrobial resistance sex. This method has been used to analyze the suitability of the dosing regimen of Micafungin in critically ill patients with invasive fungal infection [5] and critically burned patients with abdominal cavity infection [6]. In this study, Monte Carlo simulation was used to optimize the dosing regimen of Micafungin in children with invasive *Candida* infection and febrile neutrophil deficiency, which provides a basis for clinical application.

2. Materials and Methods

2.1. Pharmacokinetic Parameters

Micafungin is a concentration-dependent antifungal drug, and its antibacterial effect is evaluated by the ratio AUC/MIC of Area under the concentration time curve (AUC) and Minimum inhibitory concentration (MIC) [7]. The calculation formula is: *f*AUC/MIC = (f × dose)/(CL × MIC), where Dose is the administered dose. In the formula, $f = 1 - PBs$ represents the free drug fraction. The plasma protein binding rate for Micafungin is 99% representative [8], so its f-value is 1%; and CL is drug clearance rate.

The pharmacokinetic parameters of Micafungin in children with febrile neutrophil deficiency are derived from the research literature of Seibel *et al.* [3], as shown in **Table 1**.

2.2. Microbial Information

MIC distributions of Micafungin against *Candida* spp. derived from EUCAST website (https://mic.eucast.org/search/, MIC distributions for Micafungin, 2021-10-20) (shown in **Table 2**).

2.3. Monte Carlo Simulations

MCSs combine pharmacokinetic parameters and MIC distribution characteristics

Table 1. Pharmacokinetic parameters of Micafungin in children with febrile neutropenia.

Daily dose (mg/kg)	No. of patients	Mean wt (kg) ± SD	$AUC_{0-\infty}$ (h·μg/ml)	$t_{1/2}$ (h)	CL (ml/h/kg)
0.5	15	38.6 ± 19.59	25.9 ± 2.8	12.6 ± 0.7	22.7 ± 2.6
1.0	16	45.9 ± 32.91	52.4 ± 4.7	12.5 ± 1.1	21.8 ± 2.4
1.5	13	36.7 ± 18.33	106.8 ± 16.7	12.8 ± 1.1	17.4 ± 3.2
2.0	11	29.5 ± 11.98	113.8 ± 16.0	13.2 ± 2.0	20.8 ± 2.9
3.0	9	30.9 ± 13.18	206.6 ± 23.0	11.7 ± 0.6	15.9 ± 1.6
4.0	7	28.0 ± 11.61	247.1 ± 23.8	11.6 ± 1.0	17.4 ± 2.5

Table 2. MIC distributions of Micafungin against *Candida* spp.

Species	Observations	0.002	0.004	0.008	0.016	0.032	0.06	0.125	0.25	0.5	1	2	4
C. albicans	940	0	290	360	243	39	5	1	0	0	2	0	0
C. glabrata	418	0	90	182	100	35	3	4	0	1	1	2	0
C. guilliermondii	22	0	0	0	0	0	0	1	5	7	8	1	0
C. krusei	481	0	1	0	4	26	185	215	37	9	0	4	0
C. parapsilosis	743	0	0	0	3	1	0	1	35	113	332	244	14
C. tropicalis	623	0	48	51	247	200	59	14	2	0	2	0	0

to evaluate the probability of AUC/MIC pharmacodynamic target values in plasma [9] [10]. Use to obtain PK/PD parameters, conduct MCSs analysis on 10,000 simulated patients to obtain the PTA value of Probability of target attainment (PTA). The percentage of subjects which PTA reaches the target PK/PD value, PTA ≥ 90% is the best. The target *Candida* target value *f* AUC/MIC ≥ 10 is the best antifungal effect [11]. According to the MIC value distribution of Micafungin against *Candida* spp. published by EUCAST, calculate the expected probability of the corresponding strain to the target value, that is, the Cumulative fraction of response (CFR) value, and CFR ≥ 90% is considered to be the most effective treatment for empirical treatment which is the best choice [10], its calculation formula is as follows:

$$CFR = \sum_{i=1}^{n} PTA\left(MIC_i\right) \cdot i\left(MIC\right)_i$$

2.4. Calculation Software

Crystal Ball (Version 11.1.2.4.600, Oracle) was used for Monte Carlo simulation of drug administration schemes.

3. Results

3.1. PTA

PTA values of Micafungin under MIC distribution of the different *Candida* spp. infection in Febrile Neutropenic Pediatric Patients were shown in **Figure 1**. In

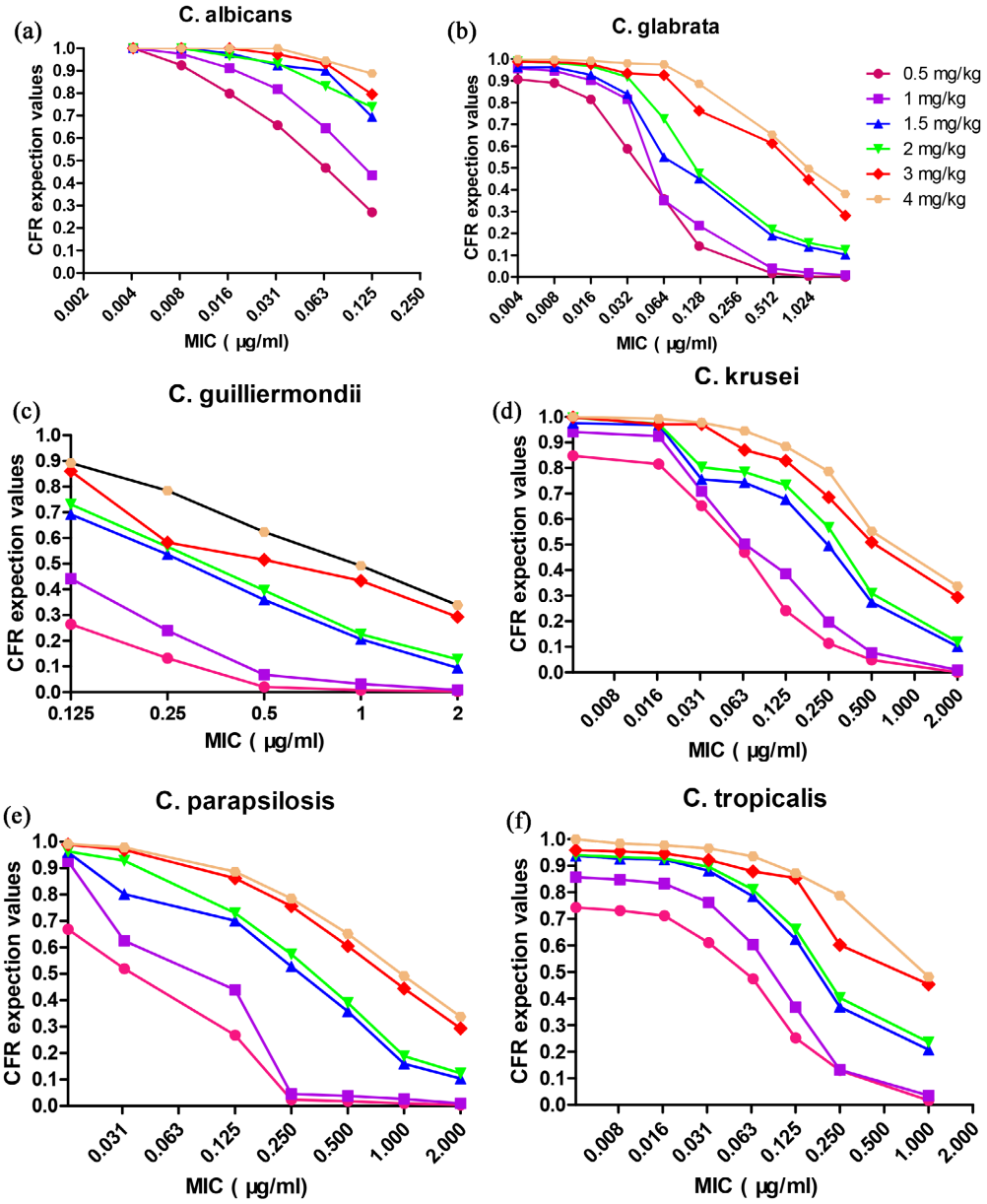

Figure 1. PTA of Micafungin estimated at different MIC values in patients with *Candida* infections.

Candida albicans, PTA was up to the standard for MIC ≤ 0.008 μg/mL, ≤0.016 μg/mL, ≤0.064 μg/ml, ≤0.032 μg/mL, ≤0.125 μg/mL and ≤0.125 μg/mL of dosage regimen included 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg and 4 mg/kg respectively. In *Candida glabrata*, PTA was reached the standard for MIC ≤ 0.004 μg/ml, ≤0.016 μg/ml, ≤0.016 μg/ml, ≤0.032 μg/ml, ≤0.064 μg/ml and ≤0.125 μg/ml of dosage regimen included 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg and 4 mg/kg respectively. In *Candida guilliermondii*, PTA of all MIC values did not meet the standards. When the administration scheme of *C. krusei* was 0.5 mg/kg, PTA of all MIC values did not meet the standards, and the rest reached the standards: 1 mg/kg, 1.5 mg/kg, 2 mg/kg with MIC ≤ 0.016 μg/ml; 3 mg/kg, 4 mg/kg with MIC ≤ 0.032 μg/ml, ≤0.064 μg/ml respectively. In *C. parapsilosis*, the

PTA < 90% of all MIC values was dosage regimen of 0.5 mg/kg. And the rest reached the standards: 1 mg/kg, 1.5 mg/kg with MIC ≤ 0.016 μg/ml; 2 mg/kg, 3 mg/kg, 4 mg/kg with MIC ≤ 0.032 μg/ml, ≤ 0.064 μg/ml respectively. In *C. tropicalis*, the PTA < 90% of all MIC values was dosage regimen of 0.5 mg/kg and 1 mg/kg. And the rest reached the standards: 1.5 mg/kg, 2 mg/kg with MIC ≤ 0.016 μg/ml; 3 mg/kg, 4 mg/kg with MIC ≤ 0.032 μg/ml, ≤0.064 μg/ml respectively.

3.2. Cumulative Fraction of Response (CFR)

According to MCS analysis results, the CFR values of children who were neutropenia with fever treated with Micafungin under different administration regimens were obtained (shown in Table 3). The results showed that Micafungin had poor antibacterial effect on *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, and CFR of *C. guilliermondii, C. krusei, C. parapsilosis* 4 mg/kg of Micafungin less than 90%. CFR of *C. albicans* and *C. glabrata* excluding with the dosage of Micafungin 1 mg/kg more than 90%. CFR of *C. tropicalis* at 3 to 4 mg/kg administration of Micafungin more than 90%.

4. Discussion

Invasive fungal infections are the leading cause of death in children with neutropenia, with a high mortality rate for severe infections despite the introduction of antifungal agents in treatment [1]. Micafennet is currently the preferred drug for the treatment of *Candida* infection. ANDES *et al.* [12] showed that micafennet had good antibacterial effect when *f* AUC/MIC approached 10. Lepak *et al.* [11] showed that micafennet had good antifungal effect on *Candida* when *f* AUC/MIC was ≥10. Therefore, our study set as that the target *Candida* spp. target value *f* AUC/MIC ≥ 10 is the best antifungal effect. According to PK/PD parameters of micafennet in children with neutropenia, MCS was used to analyze whether different administration regimens of micafennet could reach the target value, so as to make the antifungal treatment of patients more reasonable.

Micafengin was initially administered at different doses for different *Candida* species, with a recommended dose of 0.5 - 4 mg/kg for children with neutropenia.

Table 3. CFR expectation values (%) against six species of *Candida* spp. for Micafungin.

Species	dosage regimen (mg/kg)					
	0.5	1	1.5	2	3	4
C. albicans	89.91	95.56	98.82	98.51	99.71	99.85
C. glabrata	83.10	90.74	92.91	96.08	97.19	98.88
C. guilliermondii	5.17	10.83	34.71	37.59	50.67	62.12
C. krusei	34.24	43.07	68.34	73.30	83.25	89.57
C. parapsilosis	1.28	2.79	19.05	21.77	42.95	47.35
C. tropicalis	64.64	77.63	88.73	89.80	92.88	96.73

Our study showed that when micafengin administration regimen was 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, The infection caused by *C. guilliermondii*, *C. krusei*, *C. Parapsilosis* is not effective, The optimal dosing regimen for *C. albicans* and *C. glabrata* and *C. tropicalis* is 1 mg/kg, 1 mg/kg, and 3 mg/kg, respectively, and the results were similar to the recommended dosing regimen for micafennet for invasive *Candida* infection in children that has been reported [13].

Considering the imperfection of immune function in children and the immature development of liver and kidney organs, the drug should not be used empirically according to the adult dose. MCSs is a random sampling analysis method, which simulates tens of thousands of times according to the pharmacological process of drugs in different patients and fully considers the difference in drug sensitivity of different strains of the same pathogen, so as to calculate PTA and CFR values and evaluate the rationality of drug administration plan. However, this study still has some limitations. Due to the lack of grouping studies of children in different age groups, relevant PK data cannot be obtained, so patients cannot be evaluated according to specific age. In summary, micafennet has been recognized for the prevention and treatment of invasive *Candida* infections in infants and children. In the treatment of invasive fungal infection in children with neutropenia, micafennet should be fully considered to adjust the administration regimen. The results of this study showed that, for infection caused by *C. albicans*, *C. glabrata* and *C. tropicalis*, the optimal administration regimen was 1 mg/kg, 1 mg/kg, and 3 mg/kg, respectively. For *C. guilliermondii, C. krusei, C. parapsilosis* infection when the antifungal effect is not good, it is recommended to adjust other drugs or combined drugs.

5. Conclusion

In conclusion, the results of PK/PD modelling and Monte Carlo simulations suggest that Micafungin has significant effects on *C. albicans* and *C. glabrata*, *C. tropicalis* in children with febrile neutropenic. The optimal administration regimen was 1 mg/kg, 1mg/kg and 3 mg/kg. In the case of infection caused by *C. guilliermondii*, *C. krusei* and *C. parapsilosis*, Micafungin has a poor antifungal effect, and then it is suggested to adjust other drugs or combine with other antifungal drugs.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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