Micafungin twice-a-week for prophylaxis of invasive Aspergillus infections in children with acute lymphoblastic leukaemia

Bury, D.; Wolfs, T. F.W.; Muilwijk, E. W.; Fiocco, M.; Pieters, R.; Brüggemann, R. J.; Tissing, W. J.E.

Published in:
International journal of antimicrobial agents

DOI:
10.1016/j.ijantimicag.2023.107058

Publication date:
2024

International Journal of Antimicrobial Agents 63 (2024) 107058

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Micafungin twice-a-week for prophylaxis of invasive *Aspergillus* infections in children with acute lymphoblastic leukaemia: A controlled cohort study

D. Bury[a,b,*], T.F.W. Wolfs[a,c], E.W. Muilwijk[a], M. Fiocco[a,d,e], R. Pieters[a], R.J. Brüggemann[a,b,f,$], W.J.E. Tissing[a,g,$]

[a] *Princess Máxima Center for pediatric oncology, Utrecht, The Netherlands*
[b] *Radboud university medical center, Radboud Institute for Health Sciences, Department of Pharmacy, Nijmegen, The Netherlands*
[c] *Wilhelmina Children's Hospital/University Medical Center Utrecht, Utrecht, The Netherlands*
[d] *Leiden University, Mathematical institute, Leiden, The Netherlands*
[e] *Department of Biomedical Data Science, Medical statistics section, Leiden University Medical Centre, The Netherlands*
[f] *Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands*
[g] *Department of paediatric oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

ARTICLE INFO

Article history:
Received 22 June 2023
Accepted 6 December 2023

Editor: D. Cluck

Keywords:
Prevention
Paediatrics
Antifungal
Echinocandin
Moulds

ABSTRACT

Objectives: Invasive *Aspergillus* infections during the early phase of childhood acute lymphoblastic leukemia (ALL) treatment come with morbidity and mortality. The interaction with vincristine hampers first-line azole prophylaxis. We describe the efficacy of an alternative twice-a-week micafungin regimen for *Aspergillus* prophylaxis.

Methods: Newly diagnosed paediatric patients with ALL treated according to the ALL-11 protocol received micafungin twice-a-week (9 mg/kg/dose [max. 300 mg]) during the induction course (first 35 days of treatment) as part of routine care. A historical control cohort without *Aspergillus* prophylaxis was used. During the first consolidation course (day 36-79), standard itraconazole prophylaxis was used in both groups.

The percentage of proven/probable *Aspergillus* infections during the induction/first consolidation course was compared between the cohorts. The cumulative incidence of proven/probable *Aspergillus* infections was estimated using a competing risk model. For safety evaluation, liver laboratory chemistry values were analysed.

Results: A total of 169 and 643 paediatric patients with ALL were treated in the micafungin cohort (median age: 4 years [range 1-17]) and historical cohort (median age: 5 years [range 1-17]). The percentage of proven/probable *Aspergillus* infections was 1·2% (2/169) in the micafungin cohort versus 5·8% (37/643) in the historical cohort (p=0.013; Fisher's exact test). The differences in estimated cumulative incidence were assessed (p=0·014; Gray's test). Although significantly higher ALT/AST values were reported in the micafungin cohort, no clinically relevant side effects were observed.

Conclusions: Twice-a-week micafungin prophylaxis during the induction course significantly reduced the occurrence of proven/probable *Aspergillus* infections in the early phase of childhood ALL treatment.

1. Introduction

The 5-year overall survival of childhood acute lymphoblastic leukemia (ALL) has increased to ~90% [1]. To further improve overall survival, reducing treatment-related mortality (TRM) remains an important focus of interest. One of the leading causes of TRM in paediatric patients with haematological malignancies is invasive fungal disease (IFD) [2], most importantly *Aspergillus* infections. Two recent guidelines for paediatric haematology patients recommend considering antifungal prophylaxis during at-risk treatment courses of ALL treatment [3,4]. The majority of IFD occur during the induction and first consolidation course, when paediatric patients with ALL are severely immunocompromised [5]. *Aspergillus* spp. are most frequently responsible for fungal in-

* Corresponding author: Didi Bury, PharmD, Princess Máxima Center for paediatric oncology, PO BOX 113, 3720 AC Bilthoven, Utrecht, The Netherlands.
E-mail address: d.bury-3@prinsesmaximacentrum.nl (D. Bury).
$ Equally contributed to this work.

https://doi.org/10.1016/j.ijantimicag.2023.107058
0924-8579/

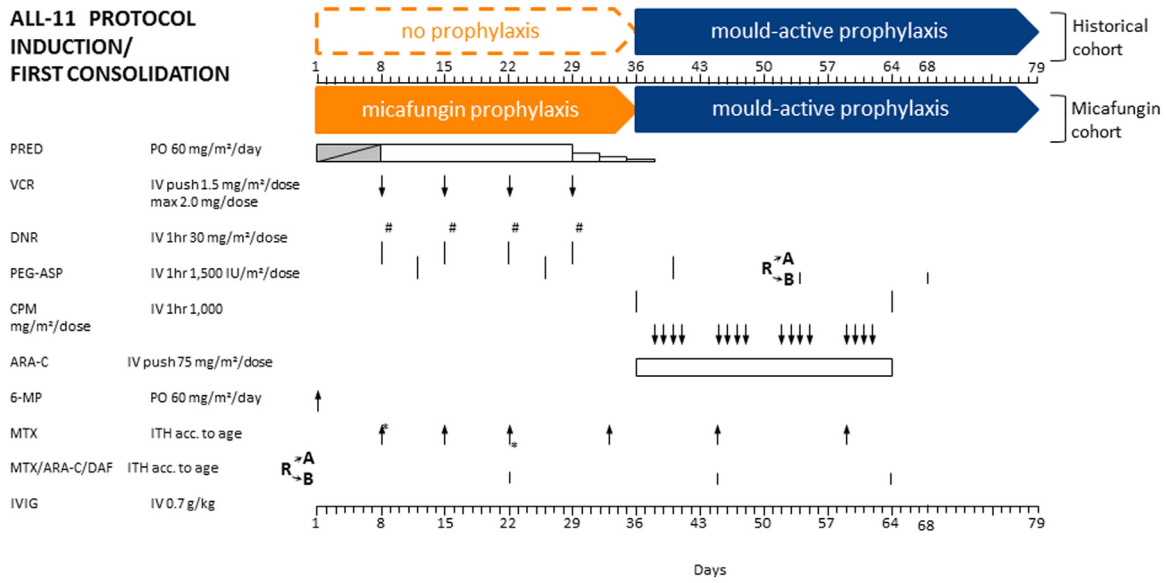

Figure 1. An overview of the induction and first consolidation course of ALL treatment with a different antifungal prophylaxis strategy in the micafungin and historical cohort.
Abbreviations: PRED=prednisolone; VCR=vincristine; DNR=daunorubicine; PEG-ASP=PEG-asparaginase; CPM=cyclophosphamide; ARA-C= Cytosine Arabinoside; 6-MP=6-mercaptopurine; MTX= methotrexate; DAF= Diadreson F aquosum; IVIG= intravenous immunoglobulines. #Not in children with Down Syndrome. *Only in children with central nervous system involvement or traumatic puncture with leukemic cells at diagnosis.

fections in this phase, with an incidence of ~6% [data on file, Dutch Childhood Oncology Group (DCOG)] for invasive *Aspergillus* infections. This high incidence has prompted the use of *Aspergillus* prophylaxis during the early treatment phase of childhood ALL.

Finding a suitable antifungal agent for *Aspergillus* prophylaxis remains challenging during the induction course (first 35 days of treatment) of ALL treatment. The required antifungal agent needs to be compatible with the chemotherapeutic agents given, and must fit a patient-friendly dosing schedule during this mostly outpatient treatment phase. Triazoles are the preferred agents for primary prophylaxis in patients with a high risk to develop IFD [4]. Considering the clinically relevant drug-drug interaction of triazoles with vincristine [6], these agents do not meet the specific profile for a prophylactic agent outlined above. In the past years, echinocandin prophylaxis in a daily regimen has been demonstrated to be of value in paediatric patients with acute myeloid leukemia (AML) in a large controlled trial but with varying outcomes in other smaller studies for *Aspergillus* prophylaxis in paediatric haematology populations [7]. The proven efficacy of echinocandins for prophylaxis of invasive *Aspergillus* infections in patients with AML [7], offers an alternative perspective for *Aspergillus* prophylaxis in the early setting of ALL treatment. Echinocandins are generally well tolerated due to their fungi-specific target and no clinically relevant drug-drug interactions are expected [8]. The difficulty is their invasive daily intravenous dosing regimen.

An intermittent twice-a-week echinocandin dosing regimen may be a more patient-friendly approach for this outpatient treatment phase. The pharmacokinetic background of such intermittent regimens has been reported in adult patients for both anidulafungin and micafungin [9,10]. We recently showed that a twice-a-week micafungin regimen in paediatric patients was pharmacokinetically equivalent to a daily micafungin regimen in adult patients [11]. This paper describes the efficacy of this twice-a-week micafungin regimen for prophylaxis of invasive *Aspergillus* infections in the early phase of childhood ALL treatment.

2. Methods

2.1. Study design and patients

The set-up of this investigation was a prospective, observational treatment protocol with a historical control group.

All newly diagnosed paediatric patients with ALL between 2018 and 2020 in the Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands, aged between ≥1 and <18 years and treated according to the DCOG ALL-11 protocol were included in the prospective cohort. They received micafungin in a twice-a-week regimen during the induction course (first 35 days of treatment) as part of standard care.

The historical control cohort consisted of newly diagnosed paediatric patients with ALL between 2012 and 2018, aged between ≥1 and <18 years and treated according to the same DCOG ALL-11 protocol. These patients did not receive antifungal prophylaxis during the induction course, as this was not part of standard practice during this time period.

Both the micafungin and the historical cohort received standard itraconazole prophylaxis during the first consolidation course (days 36-79 of treatment). An overview of the induction and first consolidation course (first 79 days of treatment) of the DCOG ALL-11 protocol and prophylactic antifungal strategy is given in Figure 1.

2.2. Ethics

All patients provided written informed consent for the DCOG ALL-11 protocol. The study protocol was approved by the Medical Ethics Committee Erasmus MC of Rotterdam (MEC-2018-1684).

2.3. Procedures

As of 2018, paediatric patients with ALL received off-label micafungin in a twice-a-week regimen during the induction course as mould-active prophylaxis. Micafungin was given twice-a-week in a dose of 9 mg/kg/administration (max. 300 mg) over a central venous line, with an infusion time of 2 hours per dose. The dose

was chosen based on a bio-equivalence approach, where the cumulative licensed weekly dose of 2-4 mg/kg/day was given in two administrations. Details on this dosing strategy have recently been published [11].

During the first consolidation course both the micafungin and historical cohort received itraconazole prophylaxis according to the standard DCOG ALL-11 protocol. In case of intolerance for itraconazole, switching *Aspergillus* prophylaxis was decided by the treating physician.

The toxicity adverse events (AEs) were documented and evaluated by data managers of the DCOG according to the standard ALL-11 protocol procedures. During the induction course laboratory values of blood bilirubin, alanine transaminase (ALT) and aspartate transaminase (AST) were routinely monitored before every PEG-asparaginase infusion every two weeks. The highest measured laboratory value during the induction course was used for categorizing toxicity AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) grading scale (Version 4.03 [12]). The categorization of the toxicity AEs was as follows: for blood bilirubin; no or low grade, >3.0 - 10.0 times upper limit of normal (ULN), >10.0 times ULN or unknown, and for both AST and ALT; no or low grade, >5.0 - 20.0 times ULN, >20.0 times ULN or unknown. In addition, the electronic health care system was checked for spontaneous reported micafungin infusion-related AEs documented by nurses.

2.4. Definitions

Proven and probable *Aspergillus* infections were defined according to the European Organization for Research and Treatment in Cancer/Mycoses Study Group 2008 (EORTC/MSG) criteria [13]. Categorizing fungal infections according to the EORTC/MSG criteria was performed independently by two researchers of our group (DB and TW).

2.5. Outcomes

The primary outcome of interest was the percentage of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course (i.e. the first 79 days of treatment) of the DCOG ALL-11 protocol in the micafungin and the historical control cohort.

The secondary outcomes included I) the cumulative incidence of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course, and II) toxicity AEs of the twice-a-week micafungin regimen during the induction course.

2.6. Statistical analyses

For the sample size computations information about the percentage of invasive *Aspergillus* infections in the historical and micafungin cohorts was used. The percentage during the induction and first consolidation course was equal to 6% in the historical cohort and was assumed to be 1% in the micafungin cohort. A group sample size of 178 micafungin-treated patients and 600 patients in the historical cohort achieved 80% power to detect a difference between the two groups of 5%. The test statistics used is the two-sided Z-test with continuity correction and pooled variance. The significance level was 5%.

The efficacy of micafungin was evaluated on an intention-to-treat basis. The difference between the percentage of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course in the micafungin and historical cohort was assessed by using the same test as discussed in the sample size computations.

A competing risk model [14] from start of treatment was used to estimate the cumulative incidence (i.e. the cumulative failure rates over time due to a particular cause) of proven or probable invasive *Aspergillus* infection during the induction and first consolidation course. Patients alive without having experienced any event at the end of the study period were censored.

Four competing events were included in the model: I) proven or probable *Aspergillus* infection during the induction and first consolidation course, II) use of any mould-active agent for treatment of an IFD other than a proven or probable *Aspergillus* infection during the induction course, III) major violation of the DCOG ALL-11 protocol during both the induction and first consolidation course, and IV) all-cause mortality during both the induction and first consolidation course. The Gray's test was used to assess the difference between the cumulative incidence of proven and probable invasive *Aspergillus* infections in the two cohorts [14].

Fisher's exact test was used to assess the difference between different degrees of toxicity in the two cohorts.

Statistical analyses were mainly performed in R software environment with the library mstate and cmprsk [15–17], the toxicity analysis was performed using SPSS software (version 26.0.0.1.).

3. Results

3.1. Patient characteristics

A total of 169 and 643 paediatric patients were included in the micafungin and historical cohort, respectively. The patient characteristics of both cohorts are depicted in Table 1. The cohorts were comparable concerning age, gender, immunophenotype of ALL, genetic variation of ALL, ALL treatment response and duration of the induction course. During the induction course, the mean number of micafungin doses applied was 9 (range 5-14).

3.2. Outcomes

In the micafungin cohort 2/169 (1·2%) patients were diagnosed with a probable *Aspergillus* infection compared to 37/643 (5·8%)

Table 1
Patient characteristics.

	Historical cohort	Micafungin cohort
Total number of patients *N*	643	169
Age; median (range) in years	5·0 (1-17)	4·0 (1-17)
Gender *N(%)*		
Female	260 (40·4%)	73 (43·2%)
Male	383 (59·6%)	96 (56·8%)
Immunophenotype *N(%)*		
Pro-B ALL	12 (1·9%)	3 (1·8%)
c-ALL	373 (58·0%)	102 (60·4%)
Pre-B ALL	166 (25·8%)	43 (25·4%)
T-ALL	92 (14·3%)	21 (12·4%)
Genetic variation *N(%)*		
t(11;v) or MLL-rearrangement	12 (1·9%)	5 (3·0%)
t(4;11) or MLL-AF4	6 (0·9%)	2 (1·2%)
t(12;21) or TEL-AML1	142 (22·1%)	41 (24·3%)
t(1;19) or E2A-PBX1	16 (2·5%)	7 (4·1%)
del(IKZF1)	74 (11·5%)	19 (11·2%)
Down's syndrome	17 (2·6%)	5 (3·0%)
Treatment response		
Good prednisolone response (day 8)	581 (90·4%)	150 (88·8%)
Complete remission (day 33)	614 (95·5%)	158 (93·5%)
Duration treatment course		
Induction course; mean duration (range) in weeks	5·0 (2-33)	5.0 (4-11)

Abbreviations: ALL = acute lymphoblastic leukaemia; pro-B ALL = precursor B acute lymphoblastic leukaemia with no expression of CD10; c-ALL = common acute lymphoblastic leukaemia; Pre-B ALL = precursor B-lineage acute lymphoblastic leukaemia; T-ALL= T-lineage acute lymphoblastic leukaemia.

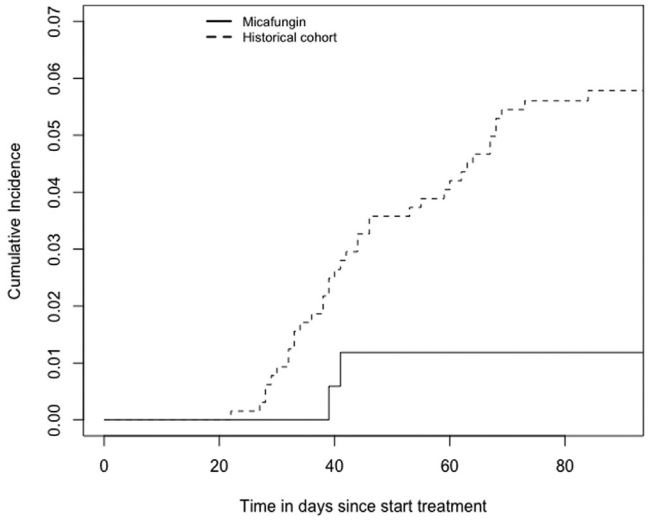

Figure 2. Cumulative incidence of invasive *Aspergillus* infections. The cumulative incidence function of invasive *Aspergillus* infections in the micafungin and historical cohort during the induction and first consolidation course of ALL treatment.

patients with proven and probable *Aspergillus* infections in the historical cohort (p=0.013; test for two proportions with continuity correction). With the number of patients present in our study, we were able to detect a 5% difference with a power equal to 78.34%. The two probable *Aspergillus* infections in the micafungin cohort occurred during the consolidation course. In the historical cohort, 13 proven and 24 probable *Aspergillus* infections were identified, of which 19 occurred during the induction course and 18 during the consolidation course.

The cumulative incidence of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course is depicted in Figure 2; (p=0·014 based on the Gray's test).

An overview of the toxicity AEs, including blood bilirubin, ALT and AST during the induction course for both cohorts is given in Table S1 (Supplementary file). Both ALT and AST values were significantly increased in the micafungin cohort compared to the historical cohort during the induction course, but bilirubin levels were not significantly different. In 9/169 (5.3%) patients micafungin prophylaxis was temporarily stopped (n=4; all of whom reinitiated micafungin prophylaxis successfully) or early terminated (n=5) due to elevated liver values. In one of these patients chemotherapy was delayed for four days due to elevated liver values including AST, ALT, and bilirubin.

In 2/169 (1.1%) paediatric patients an infusion-related AE was reported in the electronic health care system. These infusion-related AEs included I) red cheeks during infusion, and II) red hand palms and blue fingertips during infusion. In both patients these were transient infusion-related AEs. The infusion-related AEs were managed by I) pausing micafungin infusion for half an hour and restarting the infusion without signs of infusion-related problems, and II) terminating micafungin infusion during the induction protocol. In the last patient, micafungin infusion was restarted during the first consolidation course due to difficulties with itraconazole intake and infusion-related problems were no longer observed.

4. Discussion

In this report we showed that a twice-a-week prophylactic micafungin regimen resulted in a significantly lower occurrence of invasive *Aspergillus* infections during the induction course of ALL treatment in paediatric patients without clinically relevant side effects.

This accords with the previously demonstrated efficacy of a daily caspofungin regimen for prophylaxis of invasive *Aspergillus* infections in paediatric patients with acute myeloid leukaemia showing a decreased cumulative incidence of proven and probable *Aspergillus* infections as compared to a daily fluconazole regimen [7]. Although they studied a different patient population with another risk-profile, antifungal agent and follow-up period, they also demonstrated the efficacy of an echinocandin regimen for prophylaxis of invasive *Aspergillus* infections. Furthermore, our results are in line with two other, small (n=9 and n=21) studies on alternative micafungin dosing regimens of twice-a-week 5 mg/kg with a simulated target attainment, and a twice-a-week 3-4 mg/kg with clinical observations in both *Candida* and *Aspergillus* prophylaxis [18,19]. Our clinical study showed that a less invasive twice-a-week regimen is possible without compromising its efficacy. This patient-friendly regimen is of importance, as ALL treatment is mostly outpatient.

The main limitation of this study is its design. A randomized controlled trial would have been optimal. First of all, we felt the clinical urge to start a prophylactic regimen given the high incidence in the historical cohort (~6%). Secondly, given the benefits of this historical cohort, such as the large number of paediatric patients and the exact similar ALL treatment protocol in both cohorts, this seemed a suitable control group. Lastly, this study was part of the DCOG ALL-11 study, a prospective study for the treatment of childhood ALL, with an already existing database on treatment effect and toxicity. A note of caution is required in the interpretation of the results as the study technically did not meet the power (78.34% versus 80%) due to the opening of the ALLTogether protocol in July 2020.

To minimize the risk of bias in the reported *Aspergillus* infections, the fungal infections documented by the DCOG were checked and categorized for both cohorts according to the EORTC/MSG independently by two researchers [13]. In the unlikely event that the documentation of *Aspergillus* infections was incomplete in the historical cohort, the decrease in the occurrence of these infections using the twice-a-week micafungin strategy would be even more pronounced. Compared to the historical cohort, the occurrence of *Aspergillus* infections during the first consolidation course, when all patients received *Aspergillus* prophylaxis, was also lower. We could hypothesize that given the onset of *Aspergillus* infections over time, most infections were prevented during the first consolidation course due to micafungin prophylaxis in the induction course.

For the safety of micafungin, it was decided to focus on laboratory chemistry values as these were routinely reported and structured nurse- or physician-directed reporting of AEs was not part of clinical practice. It is not expected that clinically relevant toxicity of micafungin was overseen, given the close monitoring of these patients in clinical care. We demonstrated that this twice-a-week micafungin dose was generally well tolerated. Although increased AST and ALT values were reported during the induction course in the micafungin cohort, these elevated values were not considered clinically relevant in the vast majority of the patients. The comparable bilirubin values and duration of the induction course between the micafungin and historical cohort strengthens the assumption that micafungin did not lead to clinically relevant toxicity.

A dose reduction was advised in 19 out of 47 patients. This was included in our strategy in the initial phase of the study as a precautionary measure to prevent toxicity despite the higher tolerable dose known from literature. The trigger for dose reduction was based on an empirically chosen measure of exposure of micafungin together with a clinical judgment of both the pharma-

cist and treating physician to prevent unknown side effects. As no clinically relevant micafungin toxicity occurred during this initial phase, the decision was made to continue with a 9 mg/kg (max. 300 mg) micafungin dose to all patients in the clinical evaluation part. Nevertheless, it would be interesting to address whether lower dosage micafungin regimens would result in comparable efficacy for *Aspergillus* prophylaxis, specifically if they would come at the benefit of lower liver enzymes. As toxicity in our case was very mild, the need to study this matter promptly is less urgent.

To conclude, a twice-a-week micafungin regimen during the induction course of childhood ALL treatment resulted in a significantly lower percentage of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course compared to the historical cohort without antifungal prophylaxis during the induction course. When a high incidence in local epidemiology drives the need for *Aspergillus* prophylaxis, a patient-friendly twice-a-week micafungin regimen could be used for prophylaxis of invasive *Aspergillus* infections during the early phase of childhood ALL treatment.

Declarations

Funding: This work was supported by the Paediatric Oncology Foundation Groningen (SKOG)

Competing interests: No conflicts of interest/competing interests are applicable for this work.

Disclosures outside of this work: R.J.B. has served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Scynexis, Gilead Sciences, Mundipharma, and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. None of the other authors have a conflict to declare.

Ethical Approval: The study protocol was approved by the Medical Ethics Committee Erasmus MC of Rotterdam (MEC-2018-1684).

Sequence Information: Not applicable

Author Contributions: Design of the protocol: DB, WT, TW, RP and RB. Data collection: DB. Interpretation of the data: DB, WT, TW, and RB. Formal statistical analysis: DB, MF. Writing original draft: DB, WT, TW, MF and RB. Critical revision draft: EM, RP. Editing draft: DB, WT, TW, MF and RB. All authors provided approval of the final version.

Acknowledgement: A special thanks to H.A. de Groot-Kruseman for providing the data of the Dutch Childhood Oncology group.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.107058.

References

[1] Pieters R, de Groot-Kruseman H, Van der Velden V, Fiocco M, van den Berg H, de Bont E, et al. Successful Therapy Reduction and Intensification for Childhood Acute Lymphoblastic Leukemia Based on Minimal Residual Disease Monitoring: Study ALL10 From the Dutch Childhood Oncology Group. Journal of Clinical Oncology 2016;34:2591–601.

[2] Loeffen EAH, Knops RRG, Boerhof J, Feijen E, Merks JHM, Reedijk AMJ, et al. Treatment-related mortality in children with cancer: Prevalence and risk factors. Eur J Cancer 2019;121:113–22.

[3] Lehrnbecher T, Fisher BT, Phillips B, Beauchemin M, Carlesse F, Castagnola E, et al. Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients. Journal of Clinical Oncology 2020;38:3205–16.

[4] Warris A, Lehrnbecher T, Roilides E, Castagnola E, Brüggemann RJM, Groll AH. ESCMID-ECMM guideline: diagnosis and management of invasive aspergillosis in neonates and children. Clinical Microbiology and Infection 2019;25:1096–113.

[5] Wang SS, Kotecha RS, Bernard A, Blyth CC, McMullan BJ, Cann MP, et al. Invasive fungal infections in children with acute lymphoblastic leukaemia: Results from four Australian centres, 2003-2013. Pediatric Blood & Cancer 2019;66:e27915.

[6] van Schie RM, Brüggemann RJ, Hoogerbrugge PM, te Loo DM. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J Antimicrob Chemother 2011;66:1853–6.

[7] Fisher BT, Zaoutis T, Dvorak CC, Nieder M, Zerr D, Wingard JR, et al. Effect of Caspofungin vs Fluconazole Prophylaxis on Invasive Fungal Disease Among Children and Young Adults With Acute Myeloid Leukemia: A Randomized Clinical Trial. JAMA 2019;322:1673–81.

[8] EMA. Assessment report for mycamine.[Available from: https://www.ema.europa.eu/en/documents/assessment-report/mycamine-epar-public-assessment-report_en.pdf.]

[9] Brüggemann RJ, Van Der Velden WJ, Knibbe CA, Colbers A, Hol S, Burger DM, et al. A rationale for reduced-frequency dosing of anidulafungin for antifungal prophylaxis in immunocompromised patients. J Antimicrob Chemother 2015;70:1166–74.

[10] Muilwijk EW, Maertens JA, van der Velden W, Ter Heine R, Colbers A, Burger DM, et al. Pharmacokinetics of extended dose intervals of micafungin in haematology patients: optimizing antifungal prophylaxis. J Antimicrob Chemother 2018;73:3095–101.

[11] Bury D, Wolfs TFW, ter Heine R, Muilwijk EW, Tissing WJE, Brüggemann RJ. Pharmacokinetic evaluation of twice-a-week micafungin for prophylaxis of invasive fungal disease in children with acute lymphoblastic leukaemia: a prospective observational cohort study. Journal of Antimicrobial Chemotherapy 2021.

[12] CTCAE. Common Terminology Criteria for Adverse Events (CTCAE) v4.03. [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40.]

[13] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clinical Infectious Diseases 2008;46:1813–21.

[14] Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics 1988;16:1141–54.

[15] Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.

[16] de Wreede LC, Fiocco M, Putter H. mstate: An R Package for the Analysis of Competing Risks and Multi-State Models. Journal of Statistical Software 2011;38:1–30.

[17] Gray B. Package 'cmprsk'. 2021. [Available from: https://cran.r-project.org/web/packages/cmprsk/cmprsk.pdf.]

[18] Chandra S, Fukuda T, Mizuno K, Davies SM, Teusink-Cross A, Tarin R, et al. Micafungin antifungal prophylaxis in children undergoing HSCT: can we give higher doses, less frequently? A pharmacokinetic study. J Antimicrob Chemother 2018;73:1651–8.

[19] Bochennek K, Balan A, Müller-Scholden L, Becker M, Farowski F, Müller C, et al. Micafungin twice weekly as antifungal prophylaxis in paediatric patients at high risk for invasive fungal disease. J Antimicrob Chemother 2015;70:1527–30.