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Systemic Antifungal use in a Pediatric Cancer Center - Audit Comparing Pharmacy Dispensing Data with Patient - Derived Consumption

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Keywords: Pediatric cancer patients; Invasive fungal infection; Antifungal treatment; antifungal consumption; Pharmacy dispensing data.

Abbreviations: AFS: Antifungal Stewardship; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloblastic Leukemia; BSA: Body Surface Area; FN: Febrile Neutropenia; IFI: Invasive Fungal Infection; NHL: Non Hodgkin Lymphoma; POC: Pediatric Oncology Centers; TDM: Therapeutic Drug Monitoring.

Abstract

Background: The critical analysis of systemic antifungal use in pediatric cancer patients may elucidate targets for antifungal stewardship in the prophylaxis and treatment of Invasive Fungal Infection (IFI). Hitherto, any correlation between pharmacy dispensing data (antifungals) and patient-derived consumption in g/100 inpatient days is unknown.

Methods: Retrospective audit (April 2016 - June 2018) of systemic antifungal use in a pediatric cancer center comparing pharmacy dispensing and patient derived consumption data.

Results: Out of 203 consecutive patients, 18.7% received at least one cycle of systemic antifungal treatment (in total 86 cycles). The main antifungals used were fluconazole, liposomal amphotericin B and caspofungin. Concerning the indication, 44 cycles referred to IFI prophylaxis, and 42 to therapy (28 empirical, 9 pre-emptive, 5 probable IFI). Pharmacy dispensing data for systemic antifungals (in g/100 inpatient days) showed no correlation to patient-derived consumption data and were 2.13 times higher.

Discussion & conclusion: Pharmacy dispensing data do not realistically depict the actual use of antifungals in pediatric cancer patients. Patient - and case - related analyses and the implementation of electronic patient records are essential for a more precise analysis, paving the way for an antifungal stewardship program.

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Introduction

Invasive Fungal Infections (IFIs) are rare, but serious treatment complications and represent an important cause of morbidity and mortality in immunocompromised pediatric cancer patients. Children with cancer who receive intensive chemotherapy and develop neutropenia for more than 10 days, those with relapsed leukemia, prolonged high-dose steroid treatment and children after hematopoietic stem cell transplantation, face an increased risk of IFIs caused by *Candida spp*. or molds (e.g. *Aspergillus spp*.) [7,11]. In high-risk patients, there is an indication for systemic antifungal prophylaxis and, in the case of persistent fever, empirical therapy [5]. The precise characterization of high-risk patients within the total population of pediatric oncology patients is still under research [2,16,27]. Dosing of antifungals in pediatric patients is determined in mg/kg [or in mg/m^2 body surface area (BSA)]. Accordingly, residues from the available standard ampoules are often discarded, since these ampoules are allocated as "single use only", and in most Pediatric Oncology Centers (POCs) their reconstitution is not carried out under clean room conditions in the pharmacy. Thus, the quantities of antifungals dispensed by the pharmacy may not correspond to the actual patient-related consumption (in g/100 patient days). Only a few recent publications have addressed the appropriateness of antifungal use in pediatric cancer patients, describing consumption data and Antifungal Stewardship (AFS) initiatives [13,18,19,28]. The internal audit presented here intended to identify starting points for future AFS programs by evaluating the use of antifungal agents in pediatric cancer patients. In addition, we compare actual antifungal drug use based on a retrospective analysis of patient records and pharmacy dispensing data, and critically review the indication (prophylaxis, empirical and targeted therapy), selection of antifungals, dosage and duration of therapy.Methods

Setting

This study refers to a monocentric quality improvement in health audit (QIHCA) in a specialized inpatient tertiary care facility with 15 inpatient and 4 outpatient beds with 60-80 newly diagnosed pediatric cancer patients per year [9].

Identification of all patients during the observational period and patients receiving antifungal drugs

The internal audit included all patients who were admitted to this department with an oncological or hematological disease in the period from April 1, 2016 to June 30, 2018. We assigned all patients who received a systemic antifungal drug at least once to the *antifungal group*. A case report form was prepared to document basic demographic data (sex, age at first admission), the underlying malignancy/hematological disease as well as detailed patient history. To assess the individual course of all episodes with Fever during Neutropenia (FN), patient-related data such as laboratory findings, microbiological and radiological findings, duration of neutropenia and clinical outcomes were collected retrospectively. The evaluation of patient records enabled the determination of the absolute dose (in g) and the total amount of antifungal drugs used during each treatment episode and cumulatively for all patients during the period of observation. Based on this information, the total amount of antifungals administered in the POC was calculated in g/100 patient days.

Pharmacy consumption data of antifungals

A further part of the data basis for this retrospective internal audit was a data set from IQVIA's digital evaluation portal PREMAX AVS. Here, the data are evaluated quarterly in g/100 patient days. For the retrospective internal audit, the available IQVIA data were used to analyze the following target parameters:

- Antifungal consumption of fluconazole, liposomal amphotericin B (hereinafter L-AMB), caspofungin and micafungin per 100 patient days (in g).
- Defined Daily Doses (DDD) per 100 patient days for fluconazole, L-AMB , caspofungin, and micafungin.
- Proportion of the drug consumption in the corresponding class of antifungals.

Eventually, we compared patient-related consumption values (in g/100 inpatient days) with pharmacy dispensing data. In addition, the consumption data were correlated with the Case Mix Index (CMI) derived from diagnosis-related groups provided by the administrative control department of the hospital. The analysis focuses on inpatients. At our institution, most antifungal treatments (except Fluconazole for oropharyngeal thrush) is initiated and completed in inpatients. Patients with newly diagnosed Acute Lymphoblastic Leukemia (ALL) stay in the hospital until their first remission is documented on day 33 of induction therapy. Patients with newly diagnosed Acute Myeloblastic Leukemia (AML) are discharged from hospital for the first time after their second induction chemotherapy cycle.

Internal antifungal treatment standards

The systemic antifungals used in this POC are fluconazole, L-AMB and the echinocandins caspofungin and micafungin. Fluconazole is prescribed for pronounced thrush or clinical suspicion of candida esophagitis (6-12 mg/kg/day) [14]. Antifungal prophylaxis in high-risk patients is accomplished with L-AMB (2 x 2.5 mg/kg/week) [3,23] or micafungin (2 x 3-4 mg/kg/week) [1]. For empirical antifungal therapy in case of persistent fever (> 96h), L-AMB (1mg/kg/day) or caspofungin (70 mg/m^2 BSA on day 1, than 50mg/m^2 BSA once daily; max. daily dose 70 mg) is usually prescribed by the attending pediatric oncologists [26]. Itraconazole is the first choice for antifungal prophylaxis in children with septic granulomatosis (5 mg/kg/day orally in two divided doses) [10]. Posaconazole is prescribed in children aged ≥13 years for treatment of IFI that is presumed to be caused by Mucorales (300 mg in tablets two times a day on day one, than once daily plus TDM) [10]. IFIs were defined according to international criteria [6].

Statistic analysis

The computer program SPSS Version 25 for Windows was used for the statistic analysis (campus license of Saarland University). Simple descriptive methods like frequency, mean value, median, interquartile distance, minimum and maximum were used for analysis. To determine correlations between the corresponding variables, Pearsons`s correlations were calculated. A significance level of $\alpha < 0.05$ was chosen. For the comparative analysis, the Mann-Whitney-U-Test and the Chi-Square-Test were used.

Approval from the ethic committee

The Ethic Commission of the Medical Association of Saarland provided a waiver concerning the need for an ethic approval, and categorized the study as internal audit and health care quality improvement initiative [24] relying on clinical routine

data with strict anonymization before analysis. The study included no intervention concerning routine patient care.

Results

Out of 203 consecutive pediatric cancer patients in our POC, 38 (18.7%) received at least one cycle of systemic antifungal treatment. The most frequent underlying disease among these patients was ALL with 19 patients (50%), followed by AML (n= 6), non-Hodgkin lymphomas (n= 5) and solid tumors outside the CNS (n= 5). Rarely CNS tumors (n= 2) and myelodysplastic syndromes (n= 1) occurred in this patient population (Table 1). In total, 38 patients received systemic antifungals in 86 treatment cycles (hereinafter: Cases). In 84.9% (n= 73) of the cases the patients had fever at onset of the antifungal treatment. The indication was prophylaxis in 44 cases and therapy in 42 cases.

Comparison of the total population with the antifungal group

When comparing the total patient population with patients receiving systemic antifungals, the difference in the distribution of underlying diseases within the two groups was statistically significant (P<.001). The proportion of leukemia patients in the antifungal group was higher than in the total population (Table 1). There were no significant differences in age, sex, and the proportions of first or relapsed malignancy (Table 1).

Antifungal prophylaxis and therapy

A total of 25 patients received systemic antifungal prophylaxis. Within the prophylactically treated patients, the underlying cancer diagnoses occurred with the following frequency: ALL (n= 14; 56%), AML (n= 5; 20%), non-Hodgkin lymphomas (n= 4; 16%), myelodysplastic syndrome (n= 1; 4%) and CNS tumors (n= 1; 4%). Among the 44 prophylaxis cases, L-AMB (n= 33; 75%) was the most frequently used drug, followed by caspofungin (n= 5; 11%), fluconazole (n= 3; 7%) and micafungin (n= 3; 7%). The median duration of prophylaxis was 5 days (min= 1 day; max= 28 days). No patient in the prophylaxis group died from IFI. One patient experienced a failure of antifungal prophylaxis under micafungin, diagnosed shortly after the observation period of this internal audit.

26 patients received systemic antifungal therapy (the cases with confirmed fungal IFI are described in the online supplementary material). In this group, ALL (n= 13; 50%) was also the most common underlying disease. A solid tumor outside the CNS was the diagnosis in 5 patients (19%). In 5 patients (19%) from the therapy group, NHL was the underlying diagnosis, in 2 patients (8%) AML, and one patient (4%) had a medulloblastoma. In total, there were 42 antifungal treatment cases. Of these, 28 cases were treated empirically, 9 cases were treated preemptively, and 5 cases were treated specifically on the basis of a confirmed IFI. In 36 (86%) cases, the patients had fever at onset of antifungal therapy. Neutropenia was present in 32 cases (76%), while in 10 cases (24%), the peripheral neutrophil count was above 0.5 x 10^9/L at baseline. The duration of granulocytopenia was ≤ 10 days in 16 cases and > 10 days in 16 cases, respectively. Fluconazole (n=15; 36%) was the most commonly used therapy. L-AMB was used in 14 cases (33%) and caspofungin in 13 (31%). The median duration of antifungal treatment in the therapy group was 7 days (min. = 1 day, max. = 41 days, IQR=4). Within the therapy group, the IFI cured in 35 cases (83%) and in 4 children the underlying disease progressed and led to death without a causal link to an IFI.

Comparison of antifungal consumption between pharmacy and patient data

The results of the individual antifungal consumption data from pharmacy dispensing and patient data and the Pearson`s correlation as well as the correlation with the Case Mix Index are shown in Table 2. The course of L-AMB and caspofungin consumption is shown in Figures 2 & 3.

Total consumption and relative proportion of each antifungal

The total amount of all antifungals derived from pharmacy dispensing data was 13.6 g/100 patient days. In comparison, the total consumption of all antifungals derived from patient-related data was 6.4 g/100 patient days.

Concerning pharmacy-dispensing data, fluconazole was most commonly supplied with a proportion of 55%. followed by L-AMB (19%), itraconazole (9%), caspofungin (7%), posaconazole (5%), nystatin (2%) and micafungin (2%).

In terms of patient-derived data, fluconazole also accounted for the largest proportion (49%) followed by L-AMB (34%), caspofungin (16%), and micafungin (2%). Posaconazole and itraconazole were not used in any patient during the observation period.

A Pearson's correlation analysis of total antifungal consumption and CMI did not yield a significant result (data not shown) (P= 0.89).

Discussion

This internal audit on antifungal use in a German university clinic affiliated POC shows that the pharmacy dispensing data and patient derived consumption differ substantially but the difference was only statistically significant for caspofungin (Figure 1 & Table 2). Pharmacy dispensing data do not correlate to the actual consumption in the respective quarter. If the analysis of antifungal consumption only refers to pharmacy dispensing data, the corresponding approach will only provide preliminary and indicative information.

As the dosage in children is very individually based on body weight or BSA, there are no "standard ampoules" available as in adults. The range of patients in pediatrics extends from newborns to young adults. Consequently, there are large differences in the required quantity of the antifungals used in each individual case. Since reconstitution does not take place under clean room conditions in the pharmacy, residues from the ampoules often have to be discarded [12]. To our knowledge, only a minority of all POCs in Germany is capable to document exact patient-related dosing and administration schedules in an electronic data management tool in clinical practice [4]. Therefore, the detailed evaluation of the real (patient-related) antifungal consumption still requires a manual excerpt of the (paper) patient records, which is associated with a considerable additional expenditure of time and personnel. The introduction of electronic patient records is therefore indispensable in order to be able to map and examine the real antifungal consumption in clinical practice.

In this retrospective internal audit, the type of underlying disease had a significant influence on the probability of any systemic antifungal treatment. This was particularly true for Acute Lymphoblastic (ALL) and Acute Myeloid Leukemia (AML), and for certain childhood brain tumors with intensive chemothera-

py (medulloblastoma), too. The high proportion of leukemia patients in the antifungal-treated patient group corresponds with the increased risk of IFI in pediatric leukemia patients [2,7,18]. Particular challenges with regard to the timely diagnosis of an IFI [15,17], the high mortality of IFIs in patients with persistent neutropenia and the negative impact of such a complication on the treatment intensity of the underlying disease, support the need for antifungal prophylaxis in high-risk pediatric cancer patients. In their retrospective audit, Yunus et al. examined the appropriateness of an azole-based antifungal prophylaxis approach for the prevention of IFIs in pediatric cancer patients and found that it was indicated, well tolerated and effective in AML patients and patients with recurrent leukemia [28]. Although antifungal prophylaxis is an essential part of supportive therapy for all children with AML or relapsed leukemia [27], its details remain a controversial topic without a clear consensus between different centers and study groups [25]. Therefore, the decision for or against antifungal prophylaxis - regardless of the patient's allocation to a high-risk group - requires a medical risk assessment adapted to the individual treatment situation [10].

Micafungin led to prophylactic failure in a patient with AML after the observation period. In this case of prophylactic failure, it is important to note that the granulocyte count had already recovered at the time of the prophylaxis interruption (1.5 x 10^9/L with 43% neutrophils). Primary prophylaxis beyond the duration of granulocytopenia is not recommended in the current guidelines [10]. Breakthrough infections despite prophylactic treatment with micafungin have been reported in other studies in both adults [20] and children [8].

Within the observation period of this audit, no patient died related to an IFI. In general, the difficult question arises when dealing with antifungals, which patients require treatment and which do not, without compromising patient safety. Both the ECIL (European Conference on Infections in Leukaemia) and AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) guidelines recommend empirical antifungal therapy for high-risk patients after 4 days (96 hours) of fever of unknown origin that does not respond to appropriate antibiotic therapy. Empirical antifungal therapy should be continued until the neutrophil count has recovered [5,10]. Due to the difficulties in diagnosis and the serious complications that can result from delayed IFI treatment [2,27], most POCs follow an empirical treatment strategy for persistent fever [22]. This may result in an over use of systemic antifungals in patients without an IFI. With their prospective multicenter study on incidence and outcome of IFIs at three European pediatric cancer centers and their respective management of IFIs, Lehrnbecher et al. suggested the inclusion of certain leukemia patients (adolescents during induction treatment) into the concept of routine antifungal prophylaxis [18].

This internal audit will provide starting points for the establishment of an AFS initiative. The establishment of a multidisciplinary protocol and training in the use of antifungal drugs can improve the quality of antifungal prescriptions and the knowledge of physicians regarding the use of particular antifungal drugs. These methods therefore play an important role in the introduction of AFS programs in pediatrics [21]. Since this analysis focuses on inpatients, it may be interesting to add data on outpatient antifungal treatment in future studies involving pediatric cancer patients.

Figure 1: Longitudinal (quarterly) observation of antifungal drug use in pediatric cancer inpatients, comparing pharmacy dispensing and patient derived (ward) date in g/100,0 inpatient days.

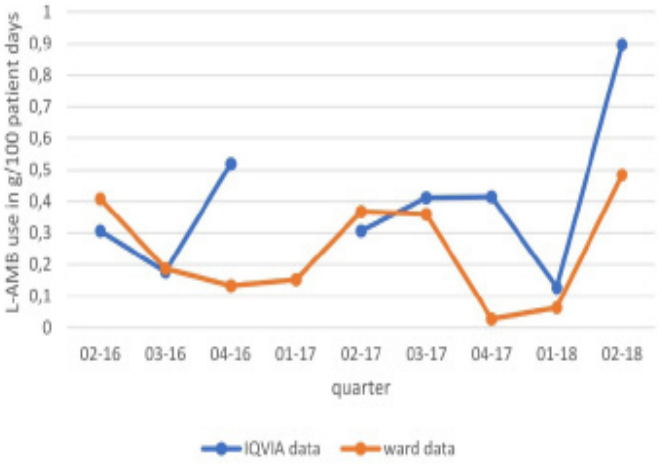

Figure 2: Longitudinal (quarterly) documentation of Liposomal amphotericin B use in pediatric cancer inpatients, comparing pharmacy dispensing and patient derived (ward) date in g/100 inpatient days (no L-AMB delivered to the ward in the first quarter of 2017).

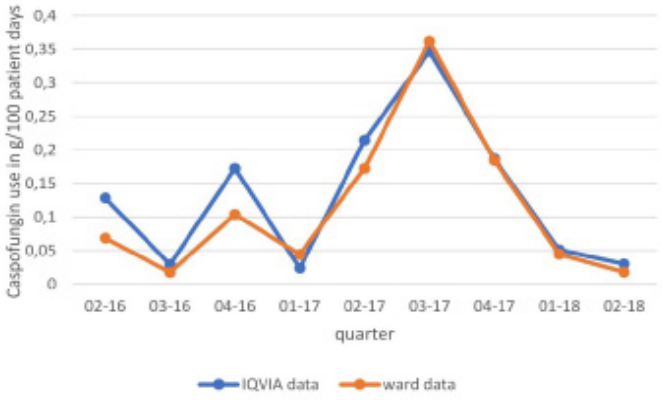

Figure 3: Longitudinal (quarterly) observation of caspofungin use in pediatric cancer inpatients, comparing pharmacy dispensing and patient derived (ward) date in g/100 inpatient days.

Table 1: Comparison of different basic items between pediatric cancer patients with and without at least one inpatient day of systemic antifungal treatment.

		Anti-fungal drug						
		No			Yes			
		Median [Min-Max] IQR	n	Percentage	Median [Min-Max] IQR	n	Percentage	p-value
Age at first admission (years)		5 [0-22] 11			5 [0-17] 10			0.345
Sex	Female		73	44.2%		15	39.5%	0.717
	Male		92	55.8%		23	60.5%	
Malignancy	Acute lymphoblastic Leukemia		18	10.9%		19	50.0%	<0.001*
	Acute myeloblastic Leukemia		2	1.2%		6	15.8%	
	Non-Hodgkin Lymphoma		3	1.8%		5	13.2%	
	Hodgkin Lymphoma		14	8.5%		0	0.0%	
	Solid Tumor outside the Central nervous System (CNS)		47	28.5%		5	13.2%	
	CNS Tumor		53	32.1%		2	5.3%	
	Neuroblastoma		15	9.1%		0	0.0%	
	Acquired immunodeficiency		1	0.6%		0	0.0%	
	MDS/SAA/FA		5	3.0%		1	2.6%	
	Others		7	4.2%		0	0.0%	
Kind of underlying disease	Primary diagnosis		164	86.8%		36	78.3%	0.166
	Relapsed malignancy		25	13.2%		10	21.7%	

*exact p-value

Table 2: Comparison between pharmacy dispensing and Patient-related antifungal consumption data and their correlation with the case mix index.

	Pharmacy dispensing data (g/100 patient days)	Patient-related data (g/100 patient days)	Pearson's correlation	P-value	Correlation with Case Mix Index	P-value
L-AMB	3.16	2.18	0.48	0.226	0.47	0.200
Caspofungin	1.18	1.02	0.96	<0.01	0.27	0.482
Fluconazole	8.98	3.13	0.28	0.507	-0.21	0.614
Micafungin	0.30	0.11	no result (only two consecutive values)			

Conclusion

This audit shows that pharmacy-dispensing data do not accurately depict the actual (patient-derived) use of antifungal drugs in pediatric oncology. Patient- and case-related analyses are essential for a more precise analysis, paving the way for an antifungal stewardship. The implementation of electronic patient records is strongly recommended for this purpose.

Conflict of Interest statement: no author declared a conflict of interest related to the topic of this article.

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