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ORIGINAL PAPER

Improving quality of antifungal use through antifungal stewardship interventions

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Abstract

Purpose In recent years antifungal stewardship (AFS) programmes have been increasingly recommended to provide optimal antifungal treatment. In a previous study (study I) in the department of haematology and oncology of a German tertiary care hospital we found areas for improvement concerning antifungal prescription. Subsequently, AFS measures were implemented and their impact on quality of antifungal use was assessed in this study.

Methods AFS measures included medical training (two sessions), a pocket card summarising main recommendations for antifungal use, and daily pharmaceutical counselling on the ward. In a 6-month observational study, antifungal prescriptions were analysed and compared to the previously collected data (study I) concerning indication, choice of drug, dosing, duration and drug–drug interactions. The study was approved by the university hospital ethical review board.

Results Antifungal agents were prescribed for 103/1169 inpatients. Compared to study I, a significant increase in dosage accuracy (+ 19.3%; $p < 0.05$) and correct choice of drug (+ 15.9%; $p < 0.05$) was noted, as well as a decrease in potential clinically relevant drug–drug interactions with concomitant medication (− 13.9%; $p < 0.05$). However, no significant improvement in indication and duration of antifungal treatment was identified. 56 recommendations were given to the prescribing physicians (acceptance rate: 66.1%).

Conclusions The implementation of AFS interventions based on pharmaceutical presence on the ward was associated with an improvement in antifungal use; however, indication and duration of therapy need to be communicated by infectious disease specialists. Considering the proportionally short observation period, the long-term effects of our AFS interventions need to be further investigated.

Keywords Haematology/oncology · Invasive fungal infection · Use of antifungals · Quality assessment · Antifungal stewardship · Drug safety

Introduction

Invasive fungal infections often occur in patients with haematological and oncological malignancies due to severe immunosuppression [1–3]. Despite improvement in diagnostics and management in recent years, invasive fungal infections remain associated with a high morbidity and mortality in these high-risk patients [4, 5]. As the mortality rate of invasive fungal infections amounts to 39% among patients suffering from haematological malignancies, antifungal agents are widely used in this population [6]. Physicians are often in a conflict between not-treating an undiagnosed invasive fungal infection and over-treatment. Negative effects of broad antifungal usage result in increasing resistance against antifungals, involve unnecessary toxicity and produce high

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treatment costs [7–11]. In a previous study in a cohort of haematological and oncological patients at our centre (study I), we found areas for improvement regarding antifungal prescriptions. Indication of antifungal prescription was classified as not appropriate in 25.7% of cases and choice of drug in 22.8% of cases. Incorrect dosing of antifungals was found in 23.4% of prescriptions, and 19.9% of antifungals were co-administrated with interacting drugs [12]. Choosing the appropriate drug and the correct dose, reducing the risk of potential drug–drug interactions as well as avoiding unnecessary treatment, are important strategies to achieve rational antifungal use and are increasingly implemented in the form of antifungal stewardship programmes. Antifungal stewardship programmes have demonstrated positive effects concerning antifungal treatment in many countries [13–18]. For Germany, there are currently sparse data regarding antifungal stewardship programmes, specifically in the field of haematology/oncology, despite patients in this field receiving a high proportion of antifungals. On the basis of our previous study (study I), we decided to implement specific measures to optimise antifungal treatment and to pilot these measures on two wards in the department of haematology/oncology. The overall objective of this study was to assess the impact of antifungal stewardship interventions on quality of antifungal use on general wards in the department of haematology and oncology in a German tertiary care centre.

Methods

Setting and study design

This observational single-centre study was conducted at the department of Haematology and Oncology at the University Hospital of Munich, Germany. The study took place on the same two wards as our previous study on antifungal use (study I) [12]. Antifungal stewardship interventions (see below) were implemented and afterwards antifungal usage over a 6-month period (01–06/2017) was compared to study I (data collection 01–06/2016). We retrospectively analysed antifungal prescriptions for therapy and prophylaxis in hospitalised adult patients (≥ 18 years) with a diagnosis of a haematological or oncological malignancy. Patients receiving systemic antifungal agents for topical fungal infection or patients treated for oral thrush were excluded from the study. All antifungal agents, apart from fluconazole and itraconazole, are ordered through a computerized physician order entry system (Zenzy® 2.40, Dr. Heni Software, Kirchzarten, Germany). During our study period and in study I, therapeutic drug monitoring (TDM) of antifungal agents was available for posaconazole and voriconazole; however, was not recommended as standard procedure in the internal guidelines.

The study has been approved by the university hospital ethical review board (369-16).

Antifungal stewardship interventions

The antifungal stewardship interventions were implemented in November 2016 on the two study wards. Core members of the antifungal stewardship team were two infectious diseases specialists and one clinical pharmacist who represented the team on the wards.

Based on current guidelines for antimicrobial stewardship, the stewardship programme combined three measures [13]. The specific measures were:

- Medical training regarding therapy and prophylaxis of invasive fungal infections for the physicians of the department of haematology and oncology in two short sessions and additionally regular training on the wards in the form of pharmaceutical counselling (see below). The short sessions included information about indication, choice of drug, dose adjustments and drug–drug interactions of antifungal agents, with a special focus on frequent non-optimal prescriptions that occurred in study I.
- Preparation and distribution of a pocket card summarising main recommendations for antifungal use following local guidelines (see 'Analysis of quality of antifungal treatment'), including precise dosage recommendations (e.g. dose adjustment for body weight, hepatic and renal impairment) and information about potential drug–drug interactions.
- Pharmaceutical counselling on the wards: every antifungal prescription was evaluated by a clinical pharmacist on a daily basis (Mon–Fri) followed by feedback to the prescribing physicians. Special cases not illustrated in the guidelines were discussed in the antifungal stewardship team to give an appropriate recommendation. The definitive therapy decision was made by the attending physician.

All recommendations given to the physicians were retrospectively analysed concerning kind of recommendation and compliance rate.

To assess physicians' satisfaction regarding the antifungal stewardship interventions, an anonymized questionnaire was designed and distributed electronically after the 6 month study period. The physicians were questioned about the usefulness of the antifungal stewardship interventions and about the cooperation between physicians and pharmacist.

Data acquisition

Data were obtained retrospectively from the electronic prescribing software Zenzy® and medical records. An anonymized data set from all patients receiving antifungal agents was established using standardized software (Microsoft® Excel 2010, Seattle, WA, USA). This data set included demographic parameters (age, sex, weight, height, underlying diseases), antifungal agents (single dose per administration, number of doses per day, route of administration, duration of antifungal therapy), indication for antifungal treatment, concomitant medication, laboratory parameters (leukocyte count, neutrophil count, kidney and liver function tests), and microbiological results as well as radiographic findings.

Analysis of quality of antifungal treatment

Quality of antifungal treatment was assessed using established local guidelines, referring to national (German Society of Haematology and Oncology, DGHO) and international guidelines (Infectious Diseases Society of America, IDSA; European Conference on Infections in Leukemia, ECIL), as well as German drug labelling and current literature (randomized controlled trials)—in special cases not covered by guidelines. Antifungal prescriptions were evaluated regarding indication, choice of drug, dosing, drug–drug interactions and contraindications, and were compared to the results of the previous published data (study I) [12]. Furthermore, prescriptions of posaconazole for prophylaxis of invasive fungal infection in patients diagnosed with acute myeloid leukaemia receiving high-dose chemotherapy, were analysed concerning duration. Local guidelines of our centre state that posaconazole should be started when the neutrophil count is < 500/µL and stopped after neutrophil recovery (> 500/µL).

For identification of potential clinically relevant drug–drug interactions we used the databases Lexicomp® Drug Interactions (Wolters Kluver, Alphen aan den Rijn, the Netherlands) and Stockley's Drug Interactions (Pharmaceutical Press, London, GB) in addition to German drug labelling recommendations.

Furthermore, we compared antifungal consumption of the stewardship period to the previous study period (study I) using the number of defined daily doses (DDD) and DDD per 100 patient days.

Statistical analysis

Qualitative variables are presented with their frequency distribution. Quantitative variables are expressed as the median and range. For comparison of patients' characteristics and quality of antifungal prescriptions during the two study periods, Chi square test was used for categorical variables and Mann–Whitney *U* test for continuous variables. Statistical significance was established at $p < 0.05$. Analyses were performed using Microsoft Excel® 2010 (Seattle, WA, USA) and IBM SPSS Statistics® version 23.0 software (IBM, Armonk, NY, USA). Figures were created with Adobe Illustrator®CC (Adobe Systems Software, Dublin, Ireland).

Results

Study population and descriptive data

During our study period we identified 103 out of 1169 inpatients (8.8%) receiving systemic antifungal agents—which is comparable to study I (104/1278; 8.1%) ($p = 0.550$). For detailed patient characteristics see Table 1 [12].

Overall, 145 antifungal agents were prescribed for the 103 patients (on average 1.4 antifungals during inpatient stay), compared to 171 antifungal agents for 104 patients in study I (on average 1.6 antifungals during inpatient stay) [12]. As in study I, no patient received two or more antifungal agents simultaneously in the stewardship period [12]. In the stewardship period, the number of total DDD used in the 103 patients was 1,645, which led to 18 DDD/100 patient days. When compared to study I with 104 patients, no difference was observed (total DDD 1,576; 16 DDD/100 patient days).

Interventions

The clinical pharmacist as representative of the antifungal stewardship team gave 56 recommendations during the 6-month stewardship period (see Table 2), hence advice concerning antifungal treatment was given for every second patient. Recommendations regarding dose adjustments (13/56; 23.2%) and modifications of antifungal choice (12/56; 21.4%) were the most common interventions, followed by advice concerning discontinuation of antifungal prophylaxis or therapy (9/56; 16.1%), as well as questioning of indication (9/56; 16.1%). Among the recommendations concerning dose adjustments, adaptions to body weight represented the majority (7/13), followed by dose adjustments due to underdosage ≥ 25% (3/13; excluding cases with lacking dose adjustments to body weight).

The interventions were accepted by the treating physicians with a compliance rate of 66.1%. The highest compliance rate was achieved for recommendations related to initiation of antifungal prophylaxis (100.0%), dosage recommendations (84.6%) and modifications due to potential drug–drug interactions (75.0%). In contrast, recommendations concerning indication were accepted with a compliance rate of 33.3%.

Table 1 Comparison of patient cohorts of the stewardship period and study I

Characteristics	Stewardship period, $n=103$	Study I, $n=104$	p value
Age—years, median (range)	59 (19–83)	62 (23–82)[b]	0.385
Gender, male—no. (%)	68 (66%)	53 (51%)[b]	0.005
BMI—kg/m^2, median (range)	24.7 (15.8–45.3)	23.2 (15.8–39.8)	0.015
Mean duration of admission—days, median (range)	23 (2–103)	24 (2–77)[b]	0.397
Underlying malignancy—no. (%)			
Acute myeloid leukaemia	65 (63%)	61 (59%)[b]	0.512
Lymphoma	14 (14%)	18 (17%)[b]	0.460
Acute lymphoblastic leukaemia	10 (10%)	5 (5%)[b]	0.174
Multiple myeloma	1 (1%)	5 (5%)[b]	0.100
Myelodysplastic syndrome	2 (2%)	3 (3%)[b]	0.659
Solid tumor	6 (6%)	5 (5%)[b]	0.744
Other malignant diseases	5 (5%)	7 (7%)[b]	0.564
Charlson comorbidity index—median (range)	3.0 (2.0–11.0)	3.0 (2.0–13.0)	0.777
Neutropenic for ≥10 days (ANC[a] < 500 cells/µl)—no. (%)	56 (54%)	48 (46%)[b]	0.237
Certainty of invasive fungal infection according to EORTC/MSG criteria [19]—no. (%)			
Proven	3 (3%)	2 (2%)[b]	0.643
Probable	12 (12%)	8 (8%)[b]	0.335
Possible	24 (24%)	18 (17%)[b]	0.284
None	29 (28%)	52 (50%)[b]	0.001
Only prophylaxis	35 (34%)	24 (23%)[b]	0.082

[a]*ANC* absolute neutrophil count

[b]Published data: Lachenmayr et al. [12]

Table 2 Pharmacist's recommendations and implementation rate in the stewardship period

Kind of recommendation	n (%)	Implementation rate, n (%)
Dose adjustment	13 (23.2)	11 (84.6)
Change of antifungal agent	12 (21.4)	6 (50.0)
Debatable indication of antifungal treatment	9 (16.1)	3 (33.3)
Discontinuation of antifungal treatment	9 (16.1)	7 (77.8)
Clinically relevant drug–drug interaction	8 (14.3)	6 (75.0)
Initiation of antifungal prophylaxis	4 (7.1)	4 (100.0)
Overall	56 (100.0)	37 (66.1)

Table 3 Reasons for prescriptions classified as not appropriate in the stewardship period and in study I [12]

Category	Stewardship period ($n=145$)		Study I ($n=171$)[a]		p value
	n	%	n	%	
Antifungal prescription not necessary	21	14.5	44[a]	25.7[a]	<0.05
Antifungal selection not appropriate	10	6.9	39[a]	22.8[a]	<0.05
Dosage not appropriate	6	4.1	40[a]	23.4[a]	<0.05
Clinically relevant drug–drug interactions	7	4.8	32[a]	18.7[a]	<0.05

[a]Published data: Lachenmayr et al. [12]

Quality of antifungal treatment in the stewardship period compared to study I

Quality of antifungal treatment after implementation of the antifungal stewardship programme compared to study I is shown in Table 3. In all assessment categories (indication, choice of drug, dosage, drug–drug interactions and duration of posaconazole prophylaxis) we noted an improvement after the initiation of the antifungal stewardship interventions [12].

First of all, empirical therapy was reduced in the stewardship period (77/145 prescriptions, 53.1% vs. 104/171 prescriptions, 60.8% in study I). In addition, the rate of patients switched from prophylaxis to therapy was lower in the stewardship period compared to study I (31.4% vs. 37.5%). Moreover, only six antifungals were not correctly dosed in the stewardship period, compared to 40 antifungals in study I [12]. The most common reasons for antifungal prescriptions classified as incorrect concerning dosage are listed in Fig. 1. Compared to study I with no patient receiving TDM

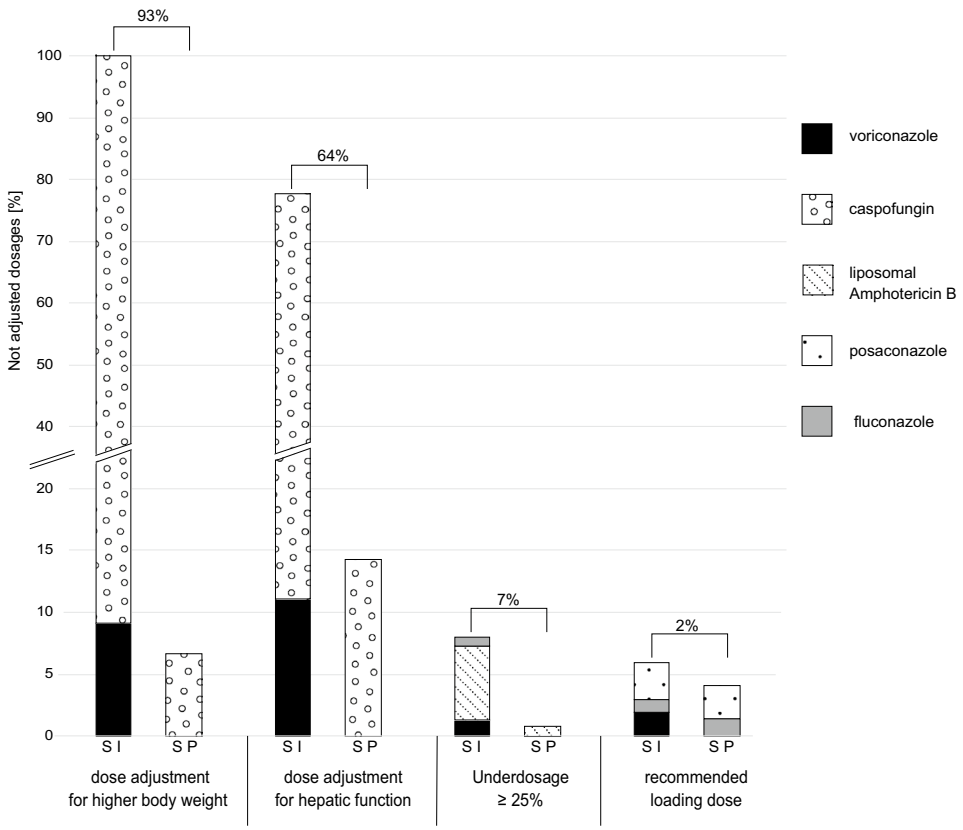

Fig. 1 Decrease of incorrect dosages in the stewardship period compared to study I. Presented are the most common reasons for non-optimal dosages of antifungal agents in the stewardship period (SP) compared to study I (S I; Lachenmayr et al. [12]): prescriptions with lacking dose adjustment for higher body weight (S I: 11/11 prescriptions, S P: 1/11 prescriptions), prescriptions with lacking dose adjustment for hepatic function (S I: 7/9 prescriptions, S P: 1/7 prescriptions) and prescriptions underdosed ≥ 25% (excluding cases counted for higher body weight and hepatic function; S I: 12/151 prescriptions, S P: 1/127 prescriptions), as well as prescriptions with lacking recommended loading dose (S I: 6/102 prescriptions, S P: 3/74 prescriptions)

of antifungal agents, serum concentration of two patients with voriconazole was measured in the stewardship period after recommendation of the stewardship team (due to visual disturbances as an adverse drug reaction).

In the stewardship period, on average 10 drugs (range 0–23) per patient were prescribed in addition to the antifungal agent. In study I, patients received on average 13 medications (range 2–29) additionally. Overall, the amount of potential clinically relevant drug–drug interactions decreased from 32 in study I to 7 in the stewardship period. For a detailed description of identified potential clinically relevant drug–drug interactions see Fig. 2 [12].

Furthermore, we analysed duration of antifungal prophylaxis with posaconazole in patients diagnosed with acute myeloid leukaemia receiving high-dose chemotherapy. In the stewardship period, 45 patients received prophylaxis with posaconazole for this indication, and 43 patients in study I. Overall, 38 out of 45 patients (84.4%) in the stewardship period started posaconazole prophylaxis as per guidelines as soon as they had a neutrophil count of < 500/µL compared to 23 out of 43 patients (53.5%) in study I. We identified 4 patients (8.9%) in the stewardship period starting posaconazole prophylaxis before their neutrophil count was < 500/µL, while this was the case for 20 patients (46.5%) in study I. In addition, the number of patients still receiving posaconazole after neutrophil recovery could be reduced to 5 (11.1%) in the stewardship period, compared to 11 patients (25.6%) in study I [12].

Evaluation of the physicians' satisfaction with the antifungal stewardship programme

Overall 14 physicians were on rotation on the two wards during the study period and were therefore included in the survey. Eight questionnaires were completed and returned (57.1%). The evaluation of the antifungal stewardship interventions was entirely positive (see Table 4).

Discussion

This study demonstrates that antifungal stewardship interventions can successfully optimise quality of antifungal treatment in patients with haematological and oncological malignancies. The antifungal stewardship measures increased dosing accuracy, correct choice of drug, appropriate duration of posaconazole prophylaxis and the awareness of drug–drug interactions—which constitute major issues of drug safety and efficacy. Our analysis shows consistency with previous published literature in different countries analysing antifungal treatment. A French study showed that the prevalence of first-line treatments compliant with the guidelines

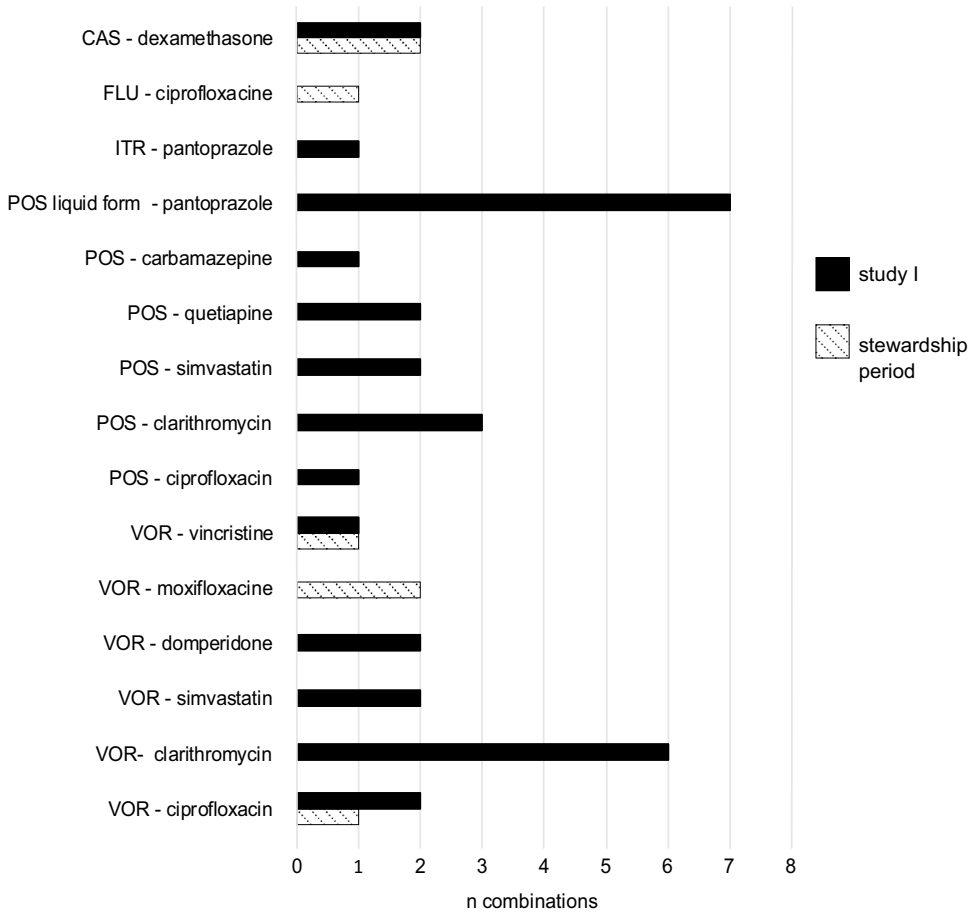

Fig. 2 Number of possible drug–drug interactions identified in the stewardship period compared to study I [*n*] (Lachenmayr et al. [12]). *CAS* caspofungin, *FLU* fluconazole, *ITR* itraconazole, *POS* posaconazole, *VOR* voriconazole

Table 4 Results of the questionnaire regarding physicians' satisfaction with the antifungal stewardship programme (eight questionnaires were completed)

Question	Strongly agree [*n*]	Agree [*n*]	Neutral [*n*]	Disagree [*n*]	Strongly disagree [*n*]	Total [*n*]
1. The project facilitated therapeutic decisions concerning antifungal therapy	3	4	1	0	0	8
2. For the future, the establishment of an antifungal stewardship programme would be desirable	6	2	0	0	0	8
3. The cooperation between physician and pharmacist was classified as constructive	5	3	0	0	0	8

improved, and a Spanish study reported that choice of drug could be optimised in 29% of the cases through stewardship interventions [17, 20]. Our study focuses on patients with haematological and oncological malignancies. These patients often suffer from a complex underlying disease and side effects such as mucositis or nausea/emesis, as well as from multiple comorbidities what often leads to a variety of concomitant medication. All these factors affect rational antifungal treatment. Avoiding unnecessary treatment, choosing the appropriate drug and the correct dose as well as reducing the risk of possible drug–drug interactions, are important strategies to achieve rational antifungal use.

For our antifungal stewardship programme, we chose a model that focused on a multimodal concept with a pharmacist as representative of the team. After analysing the effects of the consulting-pharmacist on different aspects of antifungal therapy, we found that a pharmacist can have an impact on choice of drug, dosage and potential drug–drug

interactions. Common drug–drug interactions of azole antifungals include interactions with calcineurin inhibitors and tyrosinkinase inhibitors [21–23]. Frequently, prescription of an azole antifungal agent is the only alternative, particularly in outpatient treatment. Therefore, the most appropriate azole compound has to be chosen, with regard to the potential of each azole to cause drug–drug interactions. In this context a pharmacist can provide valuable support.

In contrast, recommendations concerning indication of antifungal therapy were only marginally accepted by the prescribing physicians. Therefore, we concluded that a senior physician or even an infectious disease specialist is needed to evaluate indication and give advice to the prescribing physicians. As every profession has its focus and expertise, the multidisciplinary team is a major goal for optimal antifungal treatment.

Comparing the certainty of invasive fungal infections according to EORTC/MSG criteria, fewer patients received antifungal treatment without fulfilling EORTC criteria after the implementation of the antifungal stewardship measures (28% vs. 50%, see Table 1). Possible explanations could be that the antifungal stewardship programme lead physicians to more critically evaluate the clinical situation, i.e. if the patients actually fulfil criteria for an invasive fungal infection or not before starting or switching to empirical therapy. This hypothesis is supported by the finding that a higher number of patients received prophylaxis only in the stewardship period (34%) compared to study I (23%), and that less patients were switched from prophylaxis to therapy in the stewardship period (31.4% vs. 37.5% in study I).

Additionally, duration of posaconazole prophylaxis was optimised in the stewardship period. More patients started posaconazole prophylaxis in accordance with our local guidelines and prophylaxis was stopped after neutrophil regeneration on the basis of our local guidelines in more patients than during study I. A shorter duration of posaconazole prophylaxis reduces patient's drug exposure thereby decreasing the risk of drug toxicity and drug–drug interactions.

There was no difference in DDD/100 patient days after implementation of the stewardship programme. Analysis of antifungal consumption represents an effective option to gain an overview of the quantity of antifungal treatment; however, it does not reflect the quality of treatment.

It is important to establish antifungal stewardship measures in routine care, as junior physicians regularly rotate between different wards and departments. The evaluation of the questionnaires (see Table 4) shows that the physicians were satisfied with the programme and that they prefer continuous support. The establishment of daily pharmaceutical counselling on haematological and oncological wards regarding antifungal use, can in our opinion be a key factor in ensuring a long-lasting effect of an interdisciplinary-based antifungal stewardship programme.

Moreover, areas for further improvement of our antifungal stewardship programme could be infection consultation rounds, on-call-service (24/7), regular benchmark analyses, assistance of the antifungal stewardship team by a microbiologist to incorporate optimal strategies on fungal diagnostics and/or an economist to support an interdisciplinary approach.

Limitations

This is a single-centre study, investigating the effect of antifungal stewardship strategies only on general haemato-oncological wards. We did not measure patient-related outcomes due to our small number of patients and the limited definition of outcomes for invasive fungal infections. To analyse patient-relevant outcomes like morbidity, break-through infections or intensive care unit stays, patients with antifungal stewardship should be matched to patients without antifungal stewardship. Moreover, there are still some questions that could not be resolved in this analysis. Duration of antifungal therapy was not assessed as there are—except for therapy of candidemia—only vague recommendations given in current guidelines. Exact stop criteria for antifungal therapy or how to evaluate indication for long-term antifungal treatment or secondary prophylaxis do not currently exist.

The long-term effects of an antifungal stewardship programme should be further investigated as this was not possible in our study due to a short observation period. This study may be used as a template for the implementation of further antifungal stewardship programmes in Germany.

Conclusion

This study demonstrates that an antifungal stewardship programme based on drug reconciliation by a pharmacist on the ward can successfully optimise quality of antifungal treatment concerning choice of drug, dosing, duration of posaconazole prophylaxis and drug–drug interactions. However, for recommendations concerning indication and duration of antifungal treatment, the expertise of an infectious disease specialist is necessary to give advice to the attending physicians. As junior physicians frequently rotate to different wards, a permanent antifungal stewardship programme needs to be established to improve and standardise quality of antifungal treatment. Further research needs to be conducted concerning duration of antifungal therapy and defining helpful stop criteria to ensure safe drug therapy.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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