Clinical and Pharmacoeconomic Evaluation of Antifungal Prophylaxis with Continuous Micafungin compared to Posaconazole with Micafungin Bridging in Patients Undergoing Allogeneic Stem Cell Transplantation: A six-year Cohort-Analysis

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Abstract

Background
Patients undergoing allogeneic stem cell transplantation (aSCT) are at high risk of invasive fungal disease (IFD). Optimization of antifungal prophylaxis strategies may further improve patient outcomes and reduce treatment costs.

Methods
We performed a retrospective single-center pharmacoeconomic evaluation comparing patients who received either posaconazole oral solution plus micafungin as intravenous bridging as required (POS-MIC) to patients who received only micafungin (MIC) as antifungal prophylaxis after aSCT at the University Hospital of Cologne. Epidemiological, clinical, and direct treatment cost data extracted from the Cologne Cohort of Neutropenic Patients (CoCoNut) were analyzed. Revised 2008 EORTC/MSG criteria were used for classification of IFD.

Results
During the observation period from 01/2010 to 12/2015, 313 patients (97 patients in the POS-MIC and 216 patients in the MIC group) fulfilled inclusion criteria. Most patients were male (n= 174; 56%) and median age was 52 years (range: 18 – 75 years). Acute myeloid leukemia was the most common underlying disease (n= 146; 47%). In the POS-MIC and MIC group, median overall length of stay (LOS) was 42 days (IQR: 35 – 52 days) vs. 40 days (IQR: 35 – 49 days; P= 0.296), resulting in median overall direct treatment costs of €42,964 (IQR: 35,040 - €56,348) vs. €43,291 (IQR: €37,281 vs. €51,848; P= 0.993), respectively. In both groups, possible IFD occurred in 6 patients (6%) vs. 16 patients (7%; P= 0.696) and probable/proven IFD occurred in 5 patients (5%) vs. 3 patients (1%; P= 0.051). Overall in-hospital mortality rates in the POS-MIC and MIC group were 10% (n= 10) and 4% (n= 9; P= 0.035). Kaplan-Meier analysis showed improved outcome of patients who received MIC at day 100 (P= 0.037) and at day 365 (P< 0.001) following aSCT. Multivariable cox-regression model demonstrated treatment on ICU as the most important independent covariate for mortality at day 100 (HR: 8.08; P<0.001) and at day 365 (HR: 4.70; P<0.001).

Conclusion
We observed a higher mortality in patients receiving POS-MIC instead of MIC, which was not explained by breakthrough IFDs. The higher drug acquisition costs of micafungin compared to posaconazole oral solution did not translate into higher overall direct treatment costs.

Introduction

Invasive fungal diseases (IFDs) are a major cause of morbidity and mortality in patients undergoing allogeneic stem cell transplantation (aSCT), resulting in a significant healthcare burden and a 12-week mortality rate of up to 50% [1,2].

This is mainly represented by a prolonged hospital length of stay (LOS) especially on the intensive care unit (ICU) and the need of expensive new class antifungal agents. Past studies reported additional direct treatment costs of patients with IFDs of up to €33,000 [3-5].

Especially long-term immunosuppressed patients, such as patients undergoing aSCT, are at high risk to develop an IFD [6]. Effective antifungal prophylaxis strategies after aSCT are needed to improve patient outcome as well as to prevent high treatment costs for each healthcare system.

Two recently published studies demonstrated cost-effectiveness of an antifungal prophylactic regimen using posaconazole oral solution in combination with micafungin bridging (e.g. due to severe mucositis/low posaconazole plasma levels) [7, 8]

The use of azole-class antifungals is associated with interactions with typical immunosuppressants [9]. Especially during engraftment, stable drug levels of immunosuppressants are considered important to avoid acute Graft-versus-Host-Disease (GvHD) or graft rejection.

Our current health economic evaluation analyzed the economic and clinical impact of uninterrupted, continuous micafungin for antifungal prophylaxis after aSCT.

Methods

Setting
This monocentric cohort analysis was carried out at the University Hospital of Cologne (UHC).

Patients ≥18 years of age and treated at the Department I of Internal Medicine via aSCT between 01/2010 and 12/2015 and who received posaconazole oral solution with micafungin as intravenous bridging (POS-MIC, standard group) or only micafungin as antifungal prophylaxis (MIC, experimental group).

All patient data (e.g. epidemiology, clinical parameters) were extracted from the Cologne Cohort of Neutropenic Patients (CoCoNut; registered at ClinicalTrials.gov: NCT01821456) and our local hospital information system.

Study objective
Primary objective of the study was to analyze cost-effectiveness of POS-MIC vs. MIC. Therefore, a micro-costing approach was used, meaning that all relevant direct treatment cost factors were analyzed.

Secondary objectives were to compare patients overall length of stay (LOS) from admission to discharge, patient outcome, the duration of antifungal treatment, and incidence of possible, probable, and proven IFD based on EORTC/MSG criteria between both groups [10].

Health economic analysis
The health economic analysis was performed from the German societal perspective as recommended by national guideline [11], whereby indirect costs were disregarded due to the severity of underlying diseases.

Due to a timeframe of >1 year, discounting of all costs with an annual discount rate of 5% was performed. A further sensitivity analysis with different discount rates (0%, 3%, 10% per year) was additionally carried out. All costs were expressed in € (Euro), year 2016 values.

For statistical analysis, IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA) was used.

A Kaplan-Meier analysis and log-rank tests were used for detection of differences in survival rate at day 100 and 365 after aSCT between the two groups.

For multivariable analysis, a cox-regression was carried out to analyze the impact of covariates on survival at day 100 and 365 after aSCT.

Results

Table 1: Patient characteristics (N= 313)

Item	POS-MIC group (n=97)	MIC group (n= 216)	*P*
Age in years, median (range)	50 (18 – 75)	56 (18 - 75)	**0.019***
Female gender, n (%)	44 (45)	95 (44)	0.820**
Height in cm, median (IQR)	173 (165 – 180)	173 (165 – 180)	0.975*
Weight in kg, median (IQR)	71 (62 – 85)	74 (64 – 90)	0.121*
Underlying disease; n (%)			0.169**
- ALL	18 (19)	16 (7)	
- AML	38 (39)	108 (50)	
- CLL	5 (5)	10 (5)	
- CML	6 (6)	9 (4)	
- Hodgkin lymphoma	3 (3)	6 (3)	
- MDS	4 (4)	13 (6)	
- Multiple myeloma	5 (5)	10 (5)	
- Non-Hodgkin lymphoma	9 (9)	29 (13)	
- Other	9 (9)	15 (7)	
Donor type; n (%)			0.183**
- MRD	28 (29)	48 (22)	
- MUD	52 (54)	112 (52)	
- MMUD	16 (17)	43 (20)	
- MMRD	0	10 (5)	
- Monozygotic	1 (1)	3 (2)	
HLA mismatches; n (%)			**0.018****
- 10/10	85 (88)	161 (75)	
- 9/10	8 (8)	46 (21)	
- ≤8/10	4 (4)	9 (4)	
GvHD (intestinal); n (%)			0.083**
- None	79 (81)	178 (82)	
- Grade 1-2	9 (9)	30 (14)	
- Grade 3-4	9 (9)	8 (4)	
GvHD (skin); n (%)			**<0.001****
- None	56 (58)	52 (24)	
- Grade 1-2	32 (33)	119 (55)	
- Grade 3-4	9 (9)	45 (21)	
GvHD (liver); n (%)			0.201**
- None	92 (95)	213 (99)	
- Grade 1-2	3 (3)	2 (<1)	
- Grade 3-4	2 (2)	1 (<1)	
Duration of neutropenia in days; median (IQR)	20 (16 – 19)	20 (14 – 25)	0.158*
Duration of fever in days; median (IQR)	4 (2 – 7)	3 (2 – 7)	0.681*
Patients with mechanical ventilation; n (%)	6 (6)	17 (8)	0.597**
Breakthrough IFD[a]; n (%)			
- Possible	6 (6)	16 (7)	0.696**
- Probable/Proven	5 (5)	3 (1)	0.051**
Inpatient mortality; n (%)	10 (10)	9 (4)	**0.035****

[a]Based on EORTC/MSG criteria (10); *Mann-Whitney U-test; **Pearson's Chi² test (two-sided); significant values are marked in bold

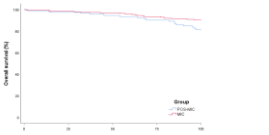


Figure 1: Kaplan-Meier plot shows overall survival rate (in %) until day 100 after a SCT for the POS-MIC group (blue line) and MIC group (red line; log-rank test: **P= 0.037**)

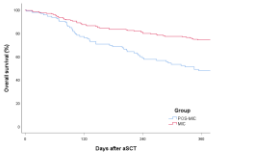
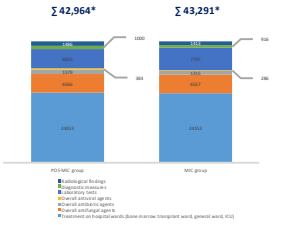


Figure 2: Kaplan-Meier plot shows overall survival rate (in %) until day 365 after a SCT for the POS-MIC group (blue line) and MIC group (red line; log-rank test: **P< 0.001**)

Figure 3: Direct treatment costs (median) in Euro (€)



*P= 0.993 (bootstrapped t-test; independent samples, two-sided)

- Our sensitive analysis of different discount rates per year confirmed the result of non-significant differences in overall treatment costs between the POS-MIC and MIC group.
- Cox-regression analyzed treatment on ICU as the most important predictor for mortality at day 100 (HR: 8.08; 95% CI: 4.16 – 15.69; P <0.001) and day 365 (HR: 4.70; 95% CI: 3.04 – 7.26; P < 0.001) subsequent to aSCT.
- Patients in the POS-MIC group had a significantly higher risk for death at day 365 (HR: 2.5; 95% CI: 1.67 – 3.74; P < 0.001), whereby no significant impact of choice of antifungal prophylaxis regimen could be shown 100 days following aSCT (HR: 1.77; 95% CI: 0.91 – 3.44; P= 0.091).
- Occurrence of breakthrough IFD was associated with increased mortality at day 100 (HR: 3.32; 95% CI: 1.57 – 7.01; P= 0.002) and day 365 (HR: 2.02; 95% CI: 1.18 – 3.46; P= 0.011) following aSCT.

Table 2: Treatment durations

Item	POS-MIC group (n=97)	MIC group (n= 216)	*P**
Bone marrow transplant ward (days); median (IQR)	40 (34 – 47)	39 (34 – 44)	0.350
General ward (days); median (IQR)	0 (0 – 8)	0 (0 – 13)	0.701
Intensive care unit (days); median (IQR)	0 (0 – 18)	0 (0 – 16)	0.172
Overall LOS (days); median (IQR)	42 (35 – 52)	40 (35 – 49)	0.296
Duration with posaconazole prophylaxis (days); median (IQR)	19 (13 – 28)	n.a.	n.a.
Duration with micafungin Prophylaxis (days); median (IQR)	15 (10 – 23)	21 (13 – 28)	**<0.001**

*Mann-Whitney U-test; significant values are marked in bold

Discussion

First health-economic evaluation analyzing posaconazole oral solution with micafungin as intravenous bridging compared to patients who received only micafungin as antifungal prophylaxis for IFD.

Cost-analysis
No differences in overall direct treatment costs between the POS-MIC and MIC group, meaning that higher drug acquisition costs of micafungin compared to posaconazole oral solution did not translate into higher overall direct treatment costs (see figure 3).

Clinical outcome
Similar rates of probable/proven IFD between the POS-MIC (n= 5, 5%) and MIC group (n= 3, 1%; P= 0.051) could be shown (see table 1).

Incidence rates of possible IFD were also similar between the two groups (n= 6, 6% vs. n= 16, 7%, P= 0.696; see table1).

In comparison to other studies, the study at hand shows an almost similar incidence of probable/proven IFDs in immunosuppressed patients between 1% – 7% [12, 13].

Improved survival rates of patients in the MIC group. A significantly higher survival rate at discharge (P= 0.035) as well as 100 days (P= 0.037, log-rank test) and 365 days (P < 0.001; log-rank test) following aSCT could be shown (see figure 1 & 2).

Our cox-regression model demonstrated that the choice of antifungal prophylaxis regimen had a major impact on patient outcome. Patients receiving POS-MIC had a significantly higher risk for mortality 365 days after aSCT.

The most important predictor for mortality at day 100 and 365 following aSCT was treatment on ICU, which is in line to other published studies demonstrating high mortality rates of aSCT patients admitted to ICU [14, 15].

Limitations
Because we did not perform a patient matching between the groups, several differences in patient characteristics were found. For example, patients in the MIC group were significantly older and had a significantly higher rate of ≥9/10 HLA-mismatches and skin GvHD.

These differences may lead to e.g. prolonged overall hospital LOS, however, this was not the case in our analysis. This is potentially balanced with the lower rate of probable/proven IFD in the MIC group, well known factors for morbidity and a prolonged hospital LOS [5, 16, 17].

Costs for treating underlying disease and treatment of IFD are sometimes inseparable. Therefore, we cannot rule out that other comorbidities may have influenced our cost result's, although we excluded non-IFD relevant cost factors (e.g. dialysis) from our cost-analysis.

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