

Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort

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Background: Large randomized controlled trials have shown significant decreases in morbidity and mortality in leukaemia patients with posaconazole prophylaxis. However, the value of prophylaxis has been questioned in centres with a low incidence of invasive fungal diseases (IFDs) and pre-emptive treatment strategies.

Methods: We prospectively evaluated the epidemiology of IFDs in acute myelogenous leukaemia (AML) patients undergoing first remission-induction chemotherapy before and after posaconazole prophylaxis had been introduced as a standard of care. Patients admitted from January 2003 to December 2005 received topical polyenes as antifungal prophylaxis (first group), while those admitted between January 2006 and December 2008 received 200 mg of oral posaconazole three times daily (second group). Other diagnostic and therapeutic standard operating procedures remained unchanged.

Results: A total of 82 patients in the polyene prophylaxis group and 77 in the posaconazole prophylaxis group were included in the final analysis. Baseline characteristics were well matched between groups. Patients receiving topical polyene prophylaxis were more likely to experience breakthrough IFDs (19.5% and 3.9%; $P=0.003$) or breakthrough aspergillosis (13.4% and 2.6%; $P=0.018$) than patients receiving systemic posaconazole prophylaxis. They also had more febrile days (mean 10.7 ± 9.66 and 7.3 ± 5.73 ; $P=0.007$), longer need for inpatient treatment (mean 53.0 ± 24.16 and 46.0 ± 14.39 ; $P=0.026$) and a shorter fungal-free survival (78.7 and 90.4 days; $P=0.024$). No significant differences were observed for persistent fever, pneumonia, lung infiltrates indicative of invasive pulmonary aspergillosis, or attributable and overall mortality.

Conclusions: After introduction of posaconazole prophylaxis for patients with AML, the number of febrile days, the incidence rate of IFDs and aspergillosis and the duration of hospitalization decreased significantly.

Keywords: antifungals, triazoles, aspergillosis, neutropenia, cytarabine

Introduction

Invasive fungal diseases (IFDs) are an important cause of morbidity and mortality in leukaemia patients. The main pathogens of IFDs in long-term neutropenic patients are *Aspergillus* spp. causing invasive pulmonary aspergillosis (IPA), followed by *Candida* spp.^{1,2} While the incidence of IFDs has been on the rise for the last two decades, treatment results have improved with the growing antifungal armamentarium and new diagnostic strategies.^{3,4} Still, mortality from IPA has remained unchanged, exceeding 10% and sometimes 20% in recent trials.^{3–7} Early

treatment seems to improve outcome, even though a definite diagnosis of aspergillosis is rarely established in early settings.⁸ Until recently, risk-adapted empirical treatment approaches were the strategy of choice for many clinicians.⁹

This situation has changed with results from two trials on antifungal prophylaxis with oral posaconazole.^{10,11} For the first time, overall mortality was reduced in patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) by antifungal prophylaxis. Primary prophylaxis with posaconazole has thus been recommended in international guidelines for patients at a high risk of contracting an IFD.^{12–14} However,

it has been discussed that the clinical effectiveness of this prophylaxis may vary depending on local epidemiology.¹⁵

Department I of Internal Medicine of the University of Cologne is a major German provider of haematology, oncology and infectious diseases services, serving a population of 2.5 million. After becoming aware of the low numbers needed to treat to prevent IFD and death,¹⁰ we replaced topical polyene prophylaxis by 200 mg of posaconazole three times daily. At the same time, an active trial comparing voriconazole prophylaxis with placebo for the same indication was prematurely discontinued, as placebo treatment was no longer considered ethical.¹⁶

To establish the clinical effectiveness of posaconazole in preventing fungal diseases in this hospital, we analysed treatment courses before and after introduction of posaconazole prophylaxis in a prospective cohort study.

Methods

Trial design

The objective of this non-interventional cohort study was to assess the effectiveness of posaconazole prophylaxis by describing changes in fungal epidemiology in AML patients. In 1995, a prospective cohort was established comprising all patients developing neutropenia after receiving chemotherapy for any kind of malignant disease (Cologne Cohort of Neutropenic Patients, CoCoNut). Caspofungin and voriconazole were introduced into clinical practice in 2001 and 2002, respectively. Patients admitted from January 2003 to December 2005 received only topical polyenes (oral solution), but no systemically active antifungal prophylaxis. They serve as a comparator group for those admitted after introduction of posaconazole prophylaxis in January 2006 to December 2008. This trial was initiated and designed by the academic authors.

Setting

All patients were diagnosed and treated according to hospital care standards. Induction chemotherapy regimens were those of the AML Cooperative Group (AML-CG), i.e. high-dose cytarabine and mitoxantrone (HAM), 6-thioguanine, cytarabine and daunorubicin (TAD) and sequential high-dose cytarabine and idarubicin or mitoxantrone (S-HAI and S-HAM). Standard procedures in our hospital demand galactomannan surveillance three times weekly, chest X-rays and two or more sets of blood cultures at fever onset, chest CT after 72–96 h of persistent fever and, in the case of lung infiltrates, bronchoscopy and bronchoalveolar lavage (BAL).

Neutropenic diets were discontinued and replaced by a standard diet in January 2008. No changes in diagnostic and therapeutic standards were made during the observed periods. In particular, hygiene procedures, as well as the wards and rooms in which patients were treated, remained the same throughout the trial. Construction work outside the hospital was ongoing continuously throughout the observation periods. No renovation work was done on the haematological or adjacent wards.

Inclusion and exclusion criteria

All patients undergoing first induction chemotherapy for AML with an expected time of neutropenia, defined as neutrophil counts $\leq 500/\mu\text{L}$, of ≥ 3 weeks were included and no patient was included twice. We excluded patients receiving systemic antifungal treatment prior to chemotherapy and patients receiving systemically active antifungal prophylaxis other than oral posaconazole; oral fluconazole was permissible in patients intolerant of topical polyene prophylaxis. Patients receiving posaconazole before January 2006 as part of clinical trials were excluded from the analysis. There was no age limit for inclusion in our analysis;

however, Department I of Internal Medicine usually treats adult patients only, and elderly patients are often not fit enough to receive full-dose induction chemotherapy.

Documentation

Data capture included demographics, underlying disease, type of cytostatic chemotherapy, duration of neutropenia, length of stay, incidence and duration of fever, administration of antibiotics, antifungals and other anti-infective drugs, use of haematopoietic growth factors, culture results, histopathology, galactomannan antigen from blood and BAL, chest CT imaging studies and survival. To ensure thorough and convenient documentation, a documentation platform based on Microsoft SQL Server[®] 2005 and Microsoft Access 2003 (both by Microsoft Corporation, Redmond, WA, USA) was developed in cooperation with System AG für IT-Lösungen, Lohmar, Germany.

Ethical statement

All study investigators are directly involved in patient care at Department I of Internal Medicine. No interventions were performed as part of this epidemiological cohort study. Data collection and storage were performed on site by site personnel using current techniques of privacy assurance. In this scenario, neither approval by an Ethics Committee nor patient consent is necessary in the state of Northrhine-Westphalia, Germany. This was confirmed by the head of the coordination office of the local Ethics Committee (Dr G. Grass, Executive Officer of the Ethics Committee of the University of Cologne, personal communication).

Data analysis, definitions and endpoints

A positive galactomannan test was defined as two consecutive blood samples or a single BAL fluid sample with an index ≥ 0.5 . Galactomannan was not evaluated when sampled on days with concomitant piperacillin/tazobactam treatment to avoid false positives. The observational period started after commencing chemotherapy and ended after stable recovery from neutropenia or at the time of discharge, whichever was first. Stable recovery from neutropenia was defined as a neutrophil count $\geq 500/\mu\text{L}$ for at least two consecutive days. All patients were followed-up with regard to survival for 100 days after the start of chemotherapy. Patients receiving at least one dose of posaconazole intended as prophylaxis between the start of chemotherapy and recovery from neutropenia were allocated to the posaconazole group.

Primary endpoints were the incidence of probable or proven breakthrough IFDs and breakthrough IPA, as defined by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG).¹⁷ Other efficacy parameters were incidence of fever, persistent fever unresponsive to broad-spectrum antibiotic treatment for ≥ 72 h, pneumonia and lung infiltrates indicative of IPA (i.e. major signs according to EORTC/MSG consensus definitions,¹⁷ as such establishing diagnosis of possible invasive aspergillosis in the observed patients), as well as attributable and overall mortality after 100 days. Pneumonia was defined as fever with positive diagnostic imaging of the lung. Patients dying in the observation period after diagnosis of an IFD were accounted for as attributable mortality. Fungal-free survival was defined as survival without probable or proven IFDs. All chest CT scans of the department are routinely evaluated by infectious disease specialists while being unaware of current patient treatment.

Results

A total of 167 patients received a first cycle of high-dose chemotherapy for treatment of AML. Eight of these were excluded

from analysis as they received posaconazole as part of a clinical trial before 2006.¹⁰ Of the remaining 159 patients, 82 received only topical polyene prophylaxis, while 77 received systemic posaconazole prophylaxis. Using a two-sided Fisher's exact test and accepting a type I error of 5%, the study was powered to detect a 19% inter-group difference with a probability of 80%. Patient characteristics are detailed in Table 1. Essentially, gender, age and days of neutropenia were similar between the groups, while patients with topical polyene prophylaxis were more likely to receive granulocyte colony-stimulating factor (G-CSF) and had a longer stay in hospital. All patients were white Caucasians from Europe and the Near East. None of the patients received antifungal treatment or prophylaxis prior to the observational period. No patient in the analysis had presented with a severely immunocompromising condition or treatment before admission to the ward. Chemotherapeutic regimens used were high-dose cytarabine (3000 mg/m²) on days 1, 2 and 3 and mitoxantrone

(10 mg/m²) on days 3, 4 and 5 (HAM), sequential high-dose cytarabine (3000 mg/m²) on days 1, 2, 8 and 9 and mitoxantrone (10 mg/m²) on days 3, 4, 10 and 11 (S-HAM), 6-thioguanine (100 mg/m²) on days 3–9, daunorubicin (60 mg/m²) on days 3–5 and cytarabine (100 mg/m²) on days 1–8 (TAD) and high-dose cytarabine (3000 mg/m²) on days 1, 2, 8 and 9 and idarubicin 10 mg/m² on days 3, 4, 10 and 11 (S-HAI). Patients in the topical polyene and the systemic posaconazole group received the following regimens: HAM, 36.6% and 22.1%; S-HAM, 12.2% and 48.1%; TAD, 37.8% and 18.2%, and S-HAI, 13.4% and 11.7%, respectively ($P < 0.001$). Taken together, 62.2% of the topical polyene and 81.8% of the systemic posaconazole group received high-dose cytarabine ($P = 0.008$). The mean total dose of cytarabine in both groups was 6.7 ± 4.75 g/m² [range 0.8–12, 95% confidence interval (CI) 5.6–7.7] and 9.3 ± 4.21 g/m² (range 0.8–12, 95% CI 8.4–10.3; $P < 0.001$), respectively. Thirteen patients of the topical polyene group were switched to 200 mg of

Table 1. Patient characteristics

	Topical polyene (n=82)	Posaconazole (n=77)	P
Age, years			
mean and SD	52 ± 14.1	54 ± 13.5	NS ^a
median	54	55	
range	18–76	19–75	
Female, n (%)	32 (39.0%)	42 (54.5%)	NS ^b
Duration of neutropenia, days			
mean and SD	31.2 ± 12.99	32.8 ± 11.54	NS ^a
median	28	32	
range	5–89	10–66	
Length of stay, days			
mean and SD	53.0 ± 24.16	46.0 ± 14.39	0.026 ^a
median	48	43	
95% CI	47.7–58.3	42.7–49.2	
range	6–156	23–120	
Administration of G-CSF, n (%)	43 (52.4%)	27 (35.1%)	0.037 ^b
Duration of posaconazole prophylaxis, days			
mean and SD	—	21.7 ± 10.85	
median	—	22	
range	—	1–50	

G-CSF, granulocyte colony-stimulating factor; NS, not significant.

^aP test for independent samples (two-sided).

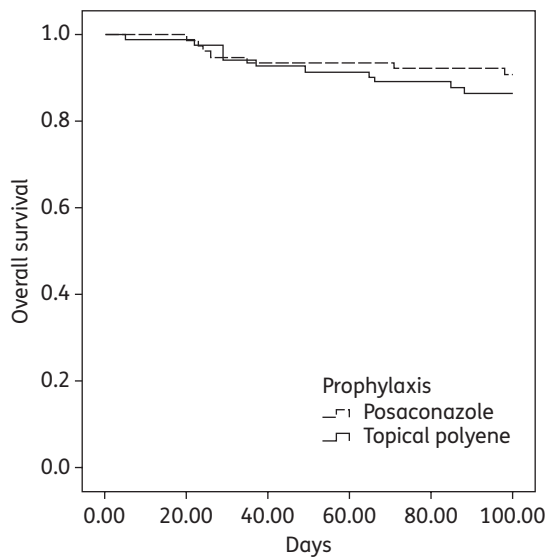
^bFisher's exact test (two-sided).

Table 2. Incidence of breakthrough infections

	Topical polyene (n=82)	Posaconazole (n=77)	P	95% CI
Breakthrough invasive aspergillosis ^a	11 (13.4%)	2 (2.6%)	0.018 ^b	–12.9 to –2.6
Breakthrough invasive candidiasis ^a	5 (6.1%)	1 (1.3%)	NS ^b	–6.0 to +4.7
Probable or proven invasive fungal disease ^a	16 (19.5%)	3 (3.9%)	0.003 ^b	–18.6 to –7.8

^aDefined as probable or proven invasive fungal disease as per EORTC/MSG criteria.¹⁷

^bFisher's exact test (two-sided).

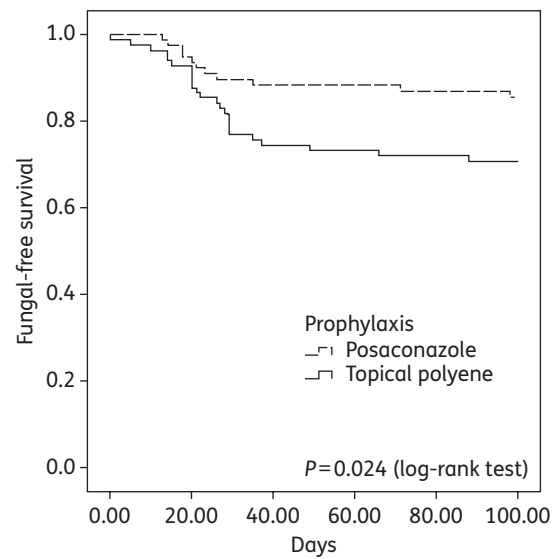


Group	Days					
	0	20	40	60	80	100
Posaconazole (n)	77	76	72	72	71	70
Topical polyene (n)	82	81	76	75	73	71

Figure 1. Overall survival. Follow-up was complete for all patients in the trial (no cases censored). The table shows patients at risk during different time periods.

oral fluconazole once daily due to oral candidiasis or intolerance of treatment.

Assessment of the efficacy parameters in demonstrated in Table 2 showed a significant reduction in probable IPA and probable IFDs for patients receiving systemic posaconazole prophylaxis. Four of the 13 patients (30.8%) in the topical polyene group who were switched to fluconazole contracted a probable IFD compared with 17.4% of those treated with topical polyenes only. Five patients in the topical polyene and one patient in the systemic posaconazole group contracted invasive candidiasis. All of these were diagnosed by detection of *Candida albicans* in blood cultures. All cases of probable IPA were diagnosed by typical lung infiltrates coinciding with positive galactomannan tests from BAL or two consecutive blood samples. The number needed to treat (NNT) to prevent one IFD was 7 (95% CI 4.0–16.6). No cases of proven IPA were diagnosed. Mean febrile days for the secondary endpoints of the topical polyene and the systemic posaconazole groups were 10.7 ± 9.66 (range 0–38, 95% CI 8.62–12.87) and 7.3 ± 5.73 (range 0–26, 95% CI 6.01–8.61; $P=0.007$), respectively. There were no significant differences in the incidence of fever (85.4% and 90.9%, respectively), persistent fever (61.0% and 53.2%, respectively), pneumonia (51.2% and 36.4%, respectively), infiltrates on CT indicative of IPA (22.0% and 13.0%, respectively), attributable mortality (3.7% and 1.3%, respectively) and survival after 100 days (86.6% and 93.5%, respectively). Figure 1 shows a plot of 100 day overall survival. Positive galactomannan values were ignored for seven patients in the topical prophylaxis group and two patients in the systemic posaconazole group because of concomitant



Group	Days					
	0	20	40	60	80	100
Posaconazole (n)	77	72	68	68	67	66
Topical polyene (n)	82	75	61	60	59	58

Figure 2. Fungal-free survival (Kaplan–Meier plot). Follow-up was complete for all patients in the trial (no cases censored). The table shows patients at risk during different time periods.

piperacillin/tazobactam treatment. Allowing use of these values would have established two more cases of probable IPA (one in each group), without changing the statistical significance of the difference between groups for IPA or IFDs. As depicted in Figure 2, estimated fungal-free survival was 78.7 and 90.4 days, respectively ($P=0.024$). There was no grade III or IV CTCAE (‘common terminology criteria for adverse events’) toxicity related to antifungal prophylaxis in either patient group. No patient had to discontinue posaconazole prophylaxis due to adverse events or intolerance.

Discussion

We conducted a prospective cohort trial to observe the effect of posaconazole in a standard clinical setting. Patients undergoing remission-induction chemotherapy for AML after introduction of posaconazole prophylaxis in January 2006 were compared with patients treated prior to introduction of systemically active prophylaxis. The groups were well matched in all assessed parameters except G-CSF usage and the chemotherapeutic regimen; patients in the posaconazole group were more likely to receive high-dose cytarabine, an established risk factor for contracting IFDs.^{18,19} Although posaconazole patients were thus at a higher risk of contracting an IFD, the results of our study confirm findings from a large randomized trial,¹⁰ showing a marked reduction in the incidence of IPA and IFDs. We additionally showed a reduction in febrile days, shorter inpatient stays and a longer fungal-free survival for the group receiving posaconazole prophylaxis.

The NNT to prevent one IFD was 7, which may be considered low compared with other, more established areas of prophylaxis.^{20,21} It was also lower than projections made based on the randomized trial on posaconazole prophylaxis in a comparable patient group, probably owing to a more effective comparator arm.^{22,23} The incidence of IFD in the group receiving topical polyene prophylaxis was in line with expectations for this high-risk patient group in the absence of effective systemic prophylaxis.²⁴

Lacking reliable means to establish a diagnosis of IPA, we included a number of secondary outcome parameters (persistent fever, pneumonia, 'specific' lung infiltrates, and attributable and overall mortality) in the analysis. In particular, the overall incidence of lung infiltrates has been discussed as a sensitive marker of prophylactic efficacy in a previous trial.¹⁶ All showed a concordant trend towards a reduction in adverse events for the group receiving posaconazole prophylaxis, though statistical significance was not achieved for these less specific variables. As the difference between the topical polyene group and the systemic posaconazole group for these secondary parameters was $\leq 15\%$, our trial was not powered to detect a significant difference. To establish a significant difference for the incidence of overall pneumonia (difference 14.8%) with reasonable power, we would have had to observe 189 patients in each group, which is clearly beyond the possibilities of our single-centre observation. The 51.2% rate of lower respiratory tract infections in the group with topical polyene prophylaxis was remarkably high compared with data from other publications,^{25,26} probably owing to the rigorous implementation of diagnostic standards in our institution. While overall mortality was low, the survival difference for patients with and without posaconazole prophylaxis was numerically on a par with results from the first trial on posaconazole prophylaxis.¹⁰

Being non-interventional by nature, cohort trials are subject to a number of shortcomings. At our institution, therapy of AML/MDS and supportive care follow detailed protocols. Nevertheless, a level of standardization concerning treatment and documentation, as is inherent in prospective interventional trials, cannot be achieved in a cohort study. Thus, there may have been changes in IFD epidemiology during the observation period of which the authors are unaware. The advantage of observational trials lies in the possibility of describing the actual effectiveness of establishing an intervention as standard of care, outside the controlled environment and highly selected patient collective of an interventional trial.²⁷

In an editorial¹⁵ addressing the recently published large posaconazole trials,^{10,11} the authors advocate use of early pre-emptive treatment in hospitals with a low incidence of IFDs, as proposed by another study.²⁸ However, many centres may have only limited knowledge of their local fungal epidemiology. We ourselves did not expect the high incidence of IFDs uncovered by implementation of rigorous diagnostic standards and prospective documentation.

It should be kept in mind that patients who have developed IFDs on any occasion remain at a high risk of relapse during later chemotherapy cycles or allogeneic stem cell transplantation.²⁹ Many patients contracting an IFD early in their treatment course stay on antifungal treatment for many months.^{30,31}

Future research in this setting should examine the best treatment for breakthrough fungal diseases and the role of empirical antifungal treatment in patients receiving posaconazole prophylaxis.

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Transparency declarations

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