



## ORIGINAL ARTICLE

**Decreased invasive fungal disease but no impact on overall survival by posaconazole compared to fluconazole prophylaxis: a retrospective cohort study in patients receiving induction therapy for acute myeloid leukaemia/myelodysplastic syndromes**Torsten Dahlén<sup>1</sup>, Mats Kalin<sup>2</sup>, Kerstin Cederlund<sup>3</sup>, Anna Nordlander<sup>4</sup>, Magnus Björkholm<sup>1</sup>, Per Ljungman<sup>5</sup>, Ola Blennow<sup>4</sup>

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**Abstract**

**Objective:** Posaconazole prophylaxis during induction chemotherapy for acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) has been shown to significantly decrease the incidence of invasive fungal disease (IFD) and increase overall survival in a trial setting, but only small real-life studies have been published. **Methods:** This was a retrospective cohort study including consecutive patients with AML/MDS treated with intensive induction chemotherapy; 176 patients received fluconazole prophylaxis 2008–2011 and 107 patients received posaconazole prophylaxis 2011–2013. Only proven and probable IFD according to the revised EORTC/MSG criteria were included in the analysis. **Results:** The two cohorts were well matched without significant differences in patient characteristics. At day 100, patients receiving posaconazole had a significantly lower incidence of total IFD (0.9% vs. 10.8%,  $P < 0.01$ ), invasive aspergillosis (0% vs. 5.7%,  $P = 0.02$ ) and invasive candidiasis (0% vs. 4.0%,  $P < 0.05$ ). There was no significant difference in overall survival, neither at day 100 (87% in the posaconazole group vs. 85% in the fluconazole group) nor at end of follow-up (78% vs. 77%). **Conclusions:** Posaconazole prophylaxis decreased the incidence of IFD but did not improve short-term overall survival. Improved treatment efficacy of manifest IFD is likely to explain the lack of survival benefit.

**Key words** posaconazole; fluconazole; prophylaxis; neutropenia; acute myeloid leukaemia; invasive fungal disease; invasive aspergillosis

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Invasive fungal disease (IFD) is a major complication of chemotherapy-induced severe neutropenia during treatment for acute myeloid leukaemia (AML) (1–3). One potential way of reducing the incidence of IFD is the administration of primary antifungal prophylaxis (PAP) during neutropenia. In a randomised controlled trial conducted between 2002 and 2005, the efficacy of posaconazole, an oral triaz-

ole with activity against a broad spectrum of moulds, was compared to fluconazole/itraconazole as PAP in patients receiving intensive induction treatment for AML and myelodysplastic syndromes (MDS) (4). The results showed that posaconazole not only significantly reduced the incidence of IFD from 11% to 5%, but also increased overall survival. As a result, most guidelines for supportive care

during AML treatment support the use of posaconazole as PAP (5–7).

Since then, three cohort studies investigating real-life experiences with posaconazole vs. fluconazole prophylaxis in patients with AML/MDS have been published, all finding decreased incidence of IFD but no effect on overall survival (8–10). However, two of the studies were small and included only 130 and 125 patients, respectively (8, 9). The third study,

a multicenter trial in China, included 234 patients, but young age (median 40 yr of age), lack of information regarding choice and dosing of chemotherapy, short duration of neutropenia (46% of patients had <14 d of neutropenia) and low overall mortality at day 100 (6.0% in fluconazole recipients compared to 21% in the randomised trial by Cornely *et al.*) make generalisation of the results difficult (10). The aim of this retrospective cohort study was therefore to investigate the effect of a change in PAP from fluconazole to posaconazole on IFD incidence and overall survival in a large contemporary cohort of patients with AML/MDS in a real-life setting.

**Table 1** Patient and disease characteristics

	Fluconazole (n = 176)	Posaconazole (n = 107)	P-value
Age (median; range)	61 (21–85)	58 (21–79)	0.1
Female	81 (46%)	46 (43%)	0.7
Primary leukaemia	142 (81%)	88 (82%)	0.9
AML	154 (87%)	92 (86%)	0.9
Neutropenia after induction therapy (mean days)	19.9	21.8	0.06
Total days of neutropenia (mean days)	38.5	40.6	0.4
Treatment cycles	2.55	2.53	0.9
Follow-up (mean days) <sup>1</sup>	117	119	0.7
Remission, non-allogeneic SCT	78 (44%)	46 (43%)	0.9
Allogeneic SCT	51 (29%)	31 (29%)	0.9
Palliative or dead during active treatment	47 (27%)	30 (28%)	0.9
Neutropenic fever <sup>2</sup>	2.5	2.6	0.7
Bacteraemia <sup>2</sup>	0.8	0.8	0.8
Empirical treatment <sup>3</sup>	50 (32%)	22 (21%)	0.05
Possible IFD	10 (5.7%)	6 (5.6%)	1.0

AML, acute myeloid leukaemia; SCT, stem cell transplantation; IFD, invasive fungal disease.

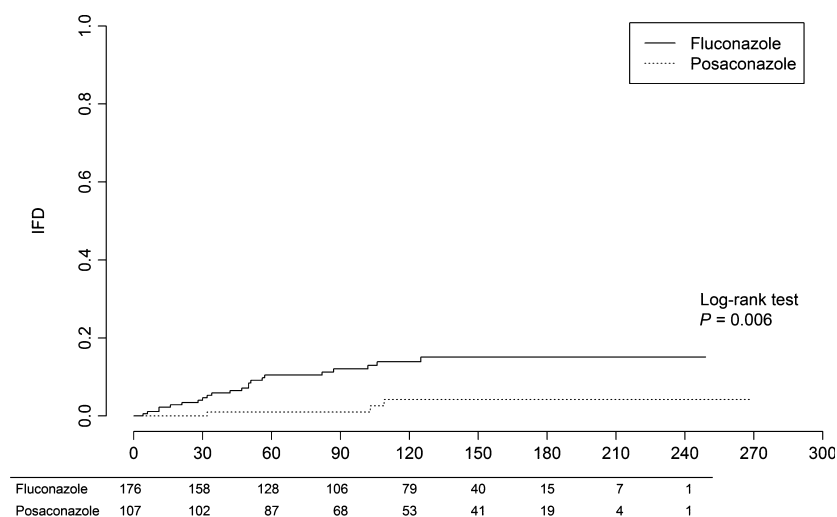
<sup>1</sup>Calculated from first day of induction chemotherapy.

<sup>2</sup>Mean number of episodes per patient.

<sup>3</sup>Patients receiving empirical mould-active treatment without fulfilling criteria for proven or probable IFD.

## Patients and methods

This retrospective cohort study was performed at Karolinska University Hospital, Stockholm, Sweden. Patients were treated at two geographically different hospital sites, both full service hospitals with approximately 650 beds each. The study was approved by the Regional Ethical Review Board in Stockholm (DNR 2012/129-31/1). All patients with AML or MDS who received intensive induction chemotherapy between January 2008 and March 2013 were eligible for inclusion. Exclusion criteria were previous IFD or not receiving the same antifungal prophylaxis during all cycles of chemotherapy (except when prophylaxis was changed to therapy of suspected or proven IFD). Clinical data were collected from the start of induction chemotherapy to 30 d after resolution of neutropenia after the last consolidation chemotherapy, to allogeneic stem cell transplantation (SCT), to conversion to palliative care or to death, whichever occurred first. As both suspected and undiagnosed IFD may influence the decision of conversion to palliative care, all proven and probable IFDs occurring within four weeks after the conversion were included in the analysis. The incidence of bacteraemia (excluding all isolates of *coagulase-negative staphylococci*) was recorded as a non-equivalent dependent variable; a vari-



**Figure 1** Cumulative incidence of invasive fungal disease. The table below graph shows the number of patients at risk.

able independent of changes in fungal prophylaxis but otherwise having similar potential causal variables as IFD (11).

Treatment regimens for AML were similar throughout the whole study period and followed national guidelines (12). Standard induction therapy typically consisted of daunorubicin (60 mg/m<sup>2</sup>) on days 1–3 and high-dose cytarabine (1000–2000 mg/m<sup>2</sup> twice daily) on days 1–5 (12).

Fungal prophylaxis was, in most cases, administered only during neutropenia (defined as absolute neutrophil count <0.5 × 10<sup>9</sup>/L). Fluconazole, 100 or 200 mg once daily, was used as PAP between January 2008 and March 2011. During April to June 2011, PAP was gradually changed from fluconazole to posaconazole 200 mg three times daily, and after June 2011, only posaconazole was used. Therapeutic drug monitoring was not routinely conducted. The wards were not equipped with HEPA filters. Fungal surveillance with galactomannan or beta-glucan assays was not performed. In case of fever more than 72 h or deterioration, despite broad spectrum antibiotics, the typical diagnostic workup consisted of blood cultures, a thoracic computed tomography (CT) and galactomannan testing in serum. In case of lesions on CT indicative of a fungal infection, investigation by bronchoalveolar lavage was performed if feasible and, in most cases, treatment with voriconazole started. Empiric antifungal treatment was usually initiated after 4–5 d of neutropenic fever even if no infiltrates were seen on thoracic CT and consisted most often of caspofungin. Bacterial prophylaxis with ciprofloxacin, 500 mg twice daily, was used during neutropenia in approximately 80% of patients at the start of study period, increasing to above 90% at the end.

IFD was defined according to the revised 2008 EORTC/MSG definitions (13). An experienced thoracic radiologist (KC) re-examined all thoracic CTs conducted during the study period. Lesions less than 1 cm were recorded as non-significant. Primary outcome was incidence of proven and probable IFD. Secondary outcome was overall survival.

## Statistical methods

All statistical data analysis was carried out in RStudio 0.97.551 (Boston, MA, USA) with R-base version 3.0.2. Differences of proportions were tested using Fisher's exact test and the independent *t*-test for differences in means. Kaplan–Meier curves were calculated for overall survival, and statistical comparisons were performed by log-rank test. All statistical tests were two-tailed, and *P* < 0.05 was defined as statistically significant.

## Results

### Patients

A total of 328 patients were eligible for inclusion. Twenty-one patients that received neither of the two PAP regimens

studied (17 received no prophylaxis, three received voriconazole, one unknown) and 24 patients that changed PAP during treatment cycles (in most cases due to changes in treatment recommendations during the study period) were excluded. Of the remaining 283 patients, 176 received prophylaxis with fluconazole and 107 posaconazole. The cohorts were well matched at baseline (Table 1). The incidence of bacteraemia during neutropenia was the same in both cohorts (0.8 episodes per patient), supporting the notion that besides changing fungal prophylaxis, no other significant changes in treatment were introduced during the study period.

### Incidence of IFD

The incidence of all IFD was significantly decreased in patients receiving posaconazole both at day 100 and at end

**Table 2** Proven and probable invasive fungal disease at day 100 and at end of follow-up

	Fluconazole (n = 176)	Posaconazole (n = 107)	<i>P</i> -value
Total IFD			
Day 100	19 (10.8%)	1 (0.9%)	<0.01
End of follow-up	22 (12.5%)	3 (2.8%)	<0.01
Total mould			
Day 100	11 (6.3%)	1 (0.9%)	0.03
End of follow-up	14 (8.7%)	3 (2.8%)	0.1
<i>Aspergillus</i> spp.			
Day 100	10 (5.7%)	0 (0%)	0.01
End of follow-up	11 (6.3%)	2 (1.9%)	0.14
<i>Candida</i> spp			
Day 100	7 (4.0%)	0 (0%)	<0.05
End of follow-up	7 (4.0%)	0 (0%)	<0.05
Species distribution			
Mould			
<i>Aspergillus fumigatus</i>	2	1	
<i>Aspergillus niger</i>	1		
<i>Aspergillus</i> spp. <sup>1</sup>	8	1	
<i>Rhizomucor pusillus</i>	1		
<i>Rhizomucor miehei</i>		1	
<i>Fusarium solani</i>	1		
Proven mould <sup>2</sup>	1		
Yeast			
<i>Candida albicans</i>	2		
<i>Candida krusei</i>	2		
<i>Candida glabrata</i>	1		
<i>Candida tropicalis</i>	1		
<i>Candida parapsilosis</i>	1		
<i>Blastoschizomyces capitatus</i>	1		

IFD, invasive fungal disease.

<sup>1</sup>Diagnosed with positive galactomannan test. None of the patients had received piperacillin + tazobactam within four days of the positive test. Five patients had a positive galactomannan test in BAL, two patients had positive tests both in BAL and serum, one patient had two positive tests in serum, and one patient had a single positive test in serum.

<sup>2</sup>Hyphae in lung biopsy, culture negative.

of follow-up (0.9% vs. 10.7%,  $P < 0.01$ , and 2.8% vs. 12.5%,  $P < 0.01$ , respectively) (Fig. 1) (Table 2). The incidences of invasive aspergillosis and invasive candidiasis were both significantly decreased in posaconazole recipients at day 100 (0% vs. 5.7%,  $P = 0.01$ , and 0% vs. 4.0%,  $P < 0.05$ , respectively) (Table 2). There was no difference in invasive mould infections between patients with primary and relapsed leukaemia (fluconazole recipients 11/142 vs. 3/34,  $P = 0.74$ , posaconazole recipients 2/88 vs. 1/19,  $P = 0.45$ , all 13/240 vs. 4/53,  $P = 0.53$ ).

Five of 17 invasive mould infections occurred during the first induction therapy, four during re-induction therapy, four during the first consolidation therapy, three during the second consolidation therapy and one during the third consolidation therapy. There was a trend towards longer mean time to first fungal episode in patients receiving posaconazole (81 vs. 48 d,  $P = 0.3$ ). Antifungal therapy was used more often in the fluconazole group than in the posaconazole group, measured both as mean days with antifungal therapy (4 vs. 25,  $P < 0.01$ ) and proportion of patients receiving antifungal therapy (23% vs. 40%,  $P < 0.01$ ).

### Overall survival

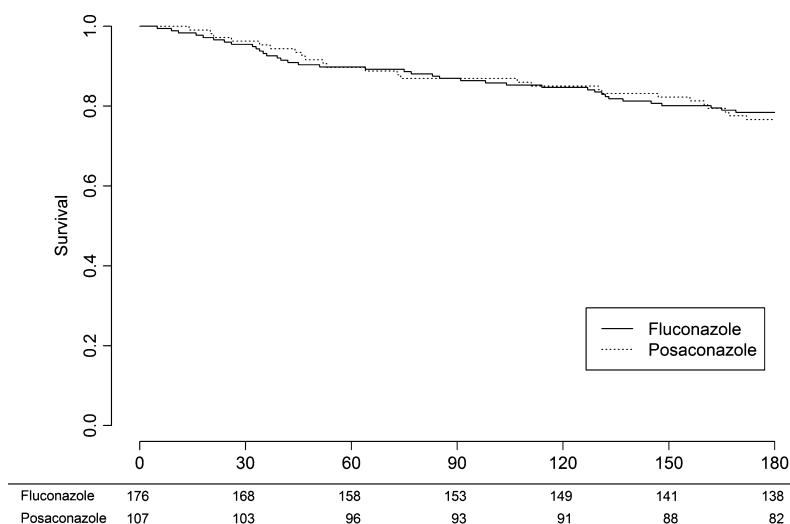
There was no significant difference in overall survival at day 100 (87% in the posaconazole group vs. 86% in the fluconazole group [relative risk (RR) 0.99, 95% CI 0.90–1.09]) and at end of follow-up [78% in the fluconazole group vs. 77% in the posaconazole group (RR 1.02, 95% CI 0.90–1.17)] (Fig. 2). Four patients in the fluconazole group with proven or probable IFD died within 100 d: one patient died because of mucormycosis; one patient in a combination of invasive aspergillosis and refractory leukaemia; one patient in a combination of candidemia and refractory leukaemia; and one patient with candidemia died because of brain oedema of unknown origin. In the posaconazole group,

one patient died from a combination of mucormycosis and refractory leukaemia.

### Discussion

Primary prophylaxis with posaconazole has, in contrast to fluconazole, been shown to reduce IFD in neutropenic AML/MDS patients, both in a large randomised trial and in small real-life cohorts (4, 8–10, 14, 15). In the Nordic countries, including Sweden, the incidence of mould infections has been thought to be low and many centres have continued using fluconazole as primary prophylaxis. Prophylaxis guidelines were changed at our institution during 2011, based on a perceived increase in the number of patients with IFD, possibly due to building activities at the hospital sites. This change enabled us to perform this large real-life study investigating posaconazole vs. fluconazole as primary fungal prophylaxis in consecutive patients with AML/MDS receiving induction therapy. We found a significantly lower incidence of proven and probable IFD in patients receiving posaconazole compared to fluconazole prophylaxis, both at day 100 and at end of follow-up. The decrease in incidence was even larger than that observed in the randomised trial by Cornely *et al.* (present study 11 to 1%, Cornely study 11 to 3% when excluding itraconazole recipients) (4). In accordance with earlier reports, prophylaxis with posaconazole significantly reduced the requirement for other antifungal treatment (8). Interestingly, 47% of the mould infections were diagnosed during consolidation therapy. Earlier studies and guidelines have often focused on the risk for mould infections and need for mould-active prophylaxis during induction therapy (4, 7). The results in this study indicate that it might be appropriate to use mould-active prophylaxis during all periods of neutropenia.

We did not find any trend towards an improvement of overall survival with posaconazole prophylaxis. This was



**Figure 2** Kaplan–Meier estimates of overall survival. There was no difference in overall survival between the groups using the log-rank test. The table below graph shows the number of patients at risk.

somewhat unexpected because the decrease in mould infections in posaconazole recipients at day 100 was similar to that in the Cornely study: 6.3 to 0.9% in the present study and 7.1 to 1.0% in the Cornely study. A likely explanation could be the lower attributable mortality of IFD in the current study compared to the Cornely study (1.7% vs. 5%) (4). Other real-life studies in patients with AML/MDS have also reported a significant decrease in IFD incidence in patients receiving posaconazole prophylaxis with no impact on overall survival (8–10). One possible explanation for the lower attributable mortality is that treatment with voriconazole is associated with improved prognosis of invasive aspergillosis (16, 17). This was not known when the trial by Cornely was initiated and patients with proven or probable breakthrough infections were treated at the discretion of the local physicians. Another contributing factor might be the continuing improvement of supportive care, whereas earlier diagnosis of invasive aspergillosis appears to be a less probable explanation because no fungal surveillance with galactomannan (or beta-glucan) tests was performed during the study period. However, it is important to acknowledge that one effect of reducing the frequency of IFD is that patients eligible for allogeneic SCT could be transplanted without delay due to IFD. Since the patients were censored at the time of allogeneic SCT, the potential positive effect of this factor could not be analysed. In addition, postponing of consolidation therapy because of IFD has been shown to negatively impact long-term survival (18). Considering that the number of patients needed to treat to avoid one probable or proven mould infection was relatively low, 19 at day 100, the severity of invasive-mould infections and the low frequency of severe side effect of the drug, we believe that prophylaxis with posaconazole during chemotherapy-induced neutropenia in patients with AML/MDS is indicated despite no clear beneficial effect on short-term survival.

There are limitations to the study, the most important being its retrospective nature. We surmised that the short time span (5.5 yr) together with inclusion of all patients receiving induction chemotherapy would render the two cohorts comparable. This is supported by the fact that the cohorts were well matched at baseline. In addition, the incidence of bacteraemia during the two study periods was found to be unchanged. A lower dose of fluconazole, 100 or 200 mg, was used compared to the 400 mg in the Cornely study. This might explain the significant difference in the incidence of candidemia seen in the present study, especially as several of the strains isolated were *Candida albicans* sensitive to fluconazole. The sensitivity of the galactomannan test has been shown to be decreased by mould-active prophylaxis (19). This might decrease the number of probable cases with a corresponding increase of possible cases, as, in most studies, a positive galactomannan test is the most common mycological criterion to be fulfilled. Such an effect may have been true also in the present study with the major-

ity of the probable aspergillosis infections in fluconazole recipients being diagnosed with a positive galactomannan test, even if there were no difference in possible invasive-mould infections between the groups.

To conclude, we found that primary posaconazole prophylaxis significantly decreased the incidence of IFD, but had no impact on short-term overall survival, seemingly due to a low attributable mortality of IFD in patients receiving fluconazole.

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## Conflict of interest and Sources of funding

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