A randomized comparison of caspofungin versus antifungal prophylaxis according to investigator policy in acute leukaemia patients undergoing induction chemotherapy (PROFIL-C study)

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Background: Invasive fungal infections (IFIs) are considered a major problem among patients undergoing acute leukaemia (AL) induction treatment. PROPhylaxis of Fungal invasive Infections in Leukaemia-Caspofungin (PROFIL-C) is a multicentre study aiming to assess the comparative yield of using caspofungin versus standard policy (SP) regimens and the overall impact of IFI in routine clinical care conditions.

Methods: All AL patients receiving IFI prophylaxis according to local SP were prospectively included in the study by Northern Italy Leukaemia Group (NILG) centres. To allow the comparison of caspofungin versus SP regimens as prophylaxis strategies, caspofungin treatment was assigned via a centralized randomized procedure. The study was registered at http://www.clinicaltrial.gov (NCT00501098).

Results: Over a 2 year period, 175 patients were included. The overall incidence of IFI was 32/175 (18.3%) [10/175 (5.7%) probable/proven and 22/175 (12.6%) possible], with no statistically significant differences between caspofungin-based versus SP-based regimens [overall: 15/93 (16.1%) versus 17/82 (20.7%), relative risk (RR) 0.78, 95% confidence interval (CI) 0.42–1.46; probable/proven: 7/93 (7.5%) versus 3/82 (3.7%), RR 2.06, 95% CI 0.55–7.7; possible: 8/93 (8.6%) versus 14/82 (17.1%), RR 0.5, 95% CI 0.22–1.14]. Only one IFI-related death was recorded (10%).

Conclusions: The incidence and mortality of IFI were lower than expected in this strictly sequential cohort representative of the routine care in the NILG network. The efficacy and safety of caspofungin were similar to other prophylactic regimens.

Keywords: invasive fungal infections, IFIs, echinocandins

Introduction

The need for antifungal prophylaxis to prevent invasive fungal infections (IFI) in haematological patients is still debatable, considering its potential role in inducing resistant strains and impairing the diagnostic accuracy of Aspergillus galactomannan (GM) antigen detection and its cost–efficacy ratio.1,2 On the other hand, a recent meta-analysis3 showed a reduction of mortality among cancer patients receiving antifungal prophylaxis. Patients with acute myeloid leukaemia (AML)4–6 are specifically considered for targeted antifungal prophylaxis because of the higher incidence of IFI and particularly invasive aspergillosis (IA) during induction chemotherapy.7–10

The efficacy of anti-Aspergillus azole prophylaxis, including itraconazole and posaconazole, may be reduced by inadequate plasma levels due to impaired gastrointestinal absorption as a result of mucositis or food interactions and interaction with concomitant drugs. The interest of focusing on caspofungin as a prophylactic agent was motivated by its spectrum of action against Candida spp. and Aspergillus spp., its safety record and the lack of
interaction with the metabolism of other drugs. The safety and tolerability of caspofungin have been proven both as empirical therapy during neutropenia by Walsh et al. and as primary prophylaxis in patients undergoing haematopoietic stem cell transplantation (HSCT) by Chou et al.

PROPhylaxis of Fungal invasive Infections in Leukaemia-Caspofungin (PROFIL-C) is a multicentre study aiming to assess the efficacy and safety of caspofungin as prophylaxis for pulmonary IA in patients undergoing induction treatment for newly diagnosed acute leukaemia (AL) and the overall impact of IFIs in routine clinical conditions of care.

Patients and methods

Trial design

The PROFIL-C study was implemented from January 2007 to January 2009 as a multicentre Phase II parallel group study with a randomized comparison (1:1) between caspofungin and standard policy (SP) regimens. The study was registered at http://www.clinicaltrial.gov (NCT00501098).

Participants

All consecutive patients aged ≥18 years with de novo acute lymphoblastic leukaemia (ALL) or AML were registered into PROFIL-C at the start of induction chemotherapy, after giving their informed consent. Patients were not considered eligible if they had signs or symptoms of suspected IFI at enrolment, history of hypersensitivity to echinocandin, acute hepatitis or moderate/severe hepatic insufficiency. Other exclusion criteria were concomitant treatment with any systemic antifungal therapy or recent prior use of caspofungin and pregnancy or breast-feeding.

Interventions

Patients were randomized using a central assignment system to an intervention group, given caspofungin 70 mg/day and 50 mg/day intravenously days 3 and 10; 60–65 years, doses of Ara-C 1–2 g/m² according to the protocol form were approved by the Ethics Committee of each of the eight participating institutions, who belong to the network of Haematological Units of the Northern Italy Leukaemia Group (NILG); data were collected by the Mario Negri Sud Institute.

Results

Sample size

By comparing >160 patients the study had a 80% power of detecting a 15% difference in the incidence of proven/probable IFI at a P = 0.05 significance level among the two groups. The sample size was appropriate, considering the possibility of reducing the frequency of IFI among patients with AML and ALL from 20% (according to our previous experience) to 5% with caspofungin prophylaxis.

Randomization

For allocation of the participants, a computer-generated list of random numbers was used through a web-based procedure by the Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud. The detail of the series was unknown to any of the investigators.

Statistical analysis

Patients’ baseline characteristics were reported as proportions (percentages) and median (interquartile range) for categorical and continuous variables, respectively. Moreover, patient characteristics according to the caspofungin prophylaxis and SP were compared using Fisher’s exact test and χ² test for categorical variables and Mann–Whitney U-test for continuous variables.

P values <0.05 were considered statistically significant. All analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, IL, USA), File Maker Pro Advanced 8.5 and SAS Statistical Package Release 9.1 (SAS Institute, Cary, NC, USA).

Patient characteristics

One hundred and seventy-five patients (138 AML and 37 ALL) met the inclusion criteria and agreed to participate in the PROFIL-C protocol (Figure 1). Their baseline characteristics are summarized in Table 1. Table 1 also summarizes the baseline characteristics according to the assigned prophylactic regimens. Local SP included oral itraconazole (67), fluconazole (10), posaconazole (1) and no prophylaxis (4).

Age was the only parameter that significantly differed between subgroups.
Comparative assessment of caspofungin and SP prophylaxis

The incidence of IFIs was 16.1% with caspofungin prophylaxis and 20.7% with SP [relative risk (RR) 0.78, 95% confidence interval (CI) 0.42–1.46]. Probable/proven and possible IFIs were diagnosed in 7.5% and 8.6% of patients with caspofungin versus 3.7% and 17.1% of patients with SP (RR 2.06, 95% CI 0.55–7.7 and RR 0.5, 95% CI 0.22–1.14, respectively) (Table 2). In the SP subgroup there were no differences in the incidence of IFIs according to the different type of prophylaxis received. Three probable/proven IFIs occurred during itraconazole (2/67, 3%) or fluconazole (1/10, 10%) therapy. Fourteen possible fungal infections occurred during itraconazole (12/67, 17.9%) or fluconazole (2/10, 20%) therapy.

The incidence of pulmonary IFIs was 12.9% with caspofungin prophylaxis and 19.5% with SP (RR 0.66, 95% CI 0.33–1.31). Probable/proven IA and possible pulmonary IFIs were diagnosed in 5.4% and 7.5% of patients with caspofungin versus 3.7% and 15.9% of patients with SP (RR 1.47, 95% CI 0.36–5.96 and RR 0.47, 95% CI 0.2–1.13, respectively) (Table 2).
Incidence of IFIs and pulmonary IA

Among 175 patients, 117 episodes of fever were recorded. Overall 32 IFIs (18.3%, 95% CI 12.6–24) were observed in the entire cohort a median of 3 weeks after commencement of chemotherapy. There were 10 (5.7%, 95% CI 2.3–9.1) probable/proven and 22 (12.6%, 95% CI 7.7–17.5) possible IFIs. IFIs were more common in AML (29/138; 21.0%) [9 proven/probable (8.1%) [1 proven (2.7%) and 2 possible (5.4%)]. A pulmonary IFI was diagnosed in 28/32 cases (87.5%). Probable/proven pulmonary IA occurred in AML only in 8/138 cases (5.8%). Possible pulmonary IFI was diagnosed in 18/138 (13.0%) AML patients and in 2/37 (5.4%) ALL patients. These differences were not statistically significant (P=0.19).

Proven/probable IFIs consisted of eight pulmonary IAs, one candidaemia and one Geotrichum capitatum fungaemia. Aspergillus antigen serum positivity was detected in every case of probable IA (Table 3). Possible IFIs were localized to the lung in all cases, except one possible sinus mycosis and one possible mycotic pharyngeal abscess (Table 4).

The incidence of IFIs was not influenced by the type of chemotherapy administered in AML patients. The incidence was 18/88 (20.5%) after ICE compared with 11/50 (22.0%) after the more aggressive HDS-1/2 induction (P=0.83). There were no differences between ALL 09/00 and ALL 10/07 induction treatments.

Using the new diagnostic criteria for IFIs,17 the number of proven/probable IFIs and IAs found did not change, whereas the incidence of possible IFIs and IAs was reduced from 12.6% to 8.6% and from 11.4% to 7.4%, respectively.

Outcome of IFIs/IA

Fifteen of the 175 (8.6%, 95% CI 4.4–12.8) patients died (caspofungin: 9.7%; SP prophylaxis: 7.3%) (RR 1.32, 95% CI 0.49–3.56). In only one case, G. capitatum sepsis, was death attributable to probable/proven IFI. None of the eight patients with probable/proven IA died. Other causes of death included septic shock (five cases), cerebral haemorrhage (four cases), progressive disease (three cases), possible mycotic sinusitis (one case) and possible pulmonary aspergillosis (one case).

Table 3. Clinical and laboratory features of probable/proven IFIs

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Pathogen</th>
<th>Site of infection</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 fluconazole</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s)</td>
</tr>
<tr>
<td>2 caspofungin</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s)</td>
</tr>
<tr>
<td>3 caspofungin</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s+b)</td>
</tr>
<tr>
<td>4 caspofungin</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s)/cytological (b)</td>
</tr>
<tr>
<td>5 caspofungin</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s)</td>
</tr>
<tr>
<td>6 caspofungin</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s)</td>
</tr>
<tr>
<td>7 itraconazole</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s)</td>
</tr>
<tr>
<td>8 itraconazole</td>
<td>Aspergillus spp.</td>
<td>lung</td>
<td>Aspergillus Ag(s)</td>
</tr>
<tr>
<td>9 caspofungin</td>
<td>Candida spp.</td>
<td>blood</td>
<td>blood culture</td>
</tr>
<tr>
<td>10 caspofungin</td>
<td>G. capitatum</td>
<td>blood</td>
<td>blood culture</td>
</tr>
</tbody>
</table>

Ag, antigen; s, serum; b, BAL.

Table 4. Clinical and laboratory features of possible IFIs (according to the criteria published in Clinical Infectious Diseases 200226)

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Site of infection</th>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 caspofungin</td>
<td>sinonasal infection</td>
<td>CT+maxillary oedema</td>
</tr>
<tr>
<td>2 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+chest pain</td>
</tr>
<tr>
<td>3 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT (infiltrate fulfilling major criteria)</td>
</tr>
<tr>
<td>4 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
<tr>
<td>5 caspofungin</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
<tr>
<td>6 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
<tr>
<td>7 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+pleural rub</td>
</tr>
<tr>
<td>8 itraconazole</td>
<td>sinonasal/pharyngeal infection</td>
<td>upper respiratory symptoms+black necrotic lesion palate</td>
</tr>
<tr>
<td>9 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+dyspnoea</td>
</tr>
<tr>
<td>10 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
<tr>
<td>11 caspofungin</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
<tr>
<td>12 caspofungin</td>
<td>lower respiratory tract</td>
<td>CT+dyspnoea+cough+haemoptysis</td>
</tr>
<tr>
<td>13 caspofungin</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
<tr>
<td>14 caspofungin</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
<tr>
<td>15 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+cough</td>
</tr>
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<td>16 itraconazole</td>
<td>lower respiratory tract</td>
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<td>19 itraconazole</td>
<td>lower respiratory tract</td>
<td>CT+chest pain</td>
</tr>
<tr>
<td>20 fluconazole</td>
<td>lower respiratory tract</td>
<td>CT (infiltrate fulfilling major criteria)</td>
</tr>
<tr>
<td>21 caspofungin</td>
<td>lower respiratory tract</td>
<td>CT+pleural rub</td>
</tr>
<tr>
<td>22 fluconazole</td>
<td>lower respiratory tract</td>
<td>CT (infiltrate fulfilling major criteria)</td>
</tr>
</tbody>
</table>

Safety of caspofungin

None of the patients receiving caspofungin died of toxicity, whereas one patient receiving itraconazole died of hepato-renal failure, possibly due to prophylaxis-related toxicity. Globally, five patients experienced WHO grade ≥2 toxicity (three hepatic, one skin, and one hepatic and renal), with three receiving caspofungin and two itraconazole.

Discussion

Despite the general consensus on the great clinical relevance of IFIs in the overall management of AL patients, both in terms of morbidity and mortality, the cost-effectiveness of antifungal prophylaxis is not fully elucidated. The retrospective nature of many studies and the selected patient populations enrolled in prospective studies18 do not allow a generalization of their results to routine clinical practice.

The use of anti-Aspergillus prophylaxis in AL patients was SP at most NILG centres, with <5% of patients at one single hospital not considered for prophylaxis. Oral itraconazole was the antifungal drug most frequently used. In spite of recent guidelines6,19 based on the results of randomized studies,20...
Posaconazole was used in only one patient. Reasons for this are unclear, but may include economic issues as well as potential deficiencies in the randomized study of Cornely et al., where the control arm was felt to have a disproportionately high incidence of IFI. In PROFIL-C the clinical approach of nearly universal antifungal prophylaxis during induction treatment of AL was associated with a very low incidence of proven/probable IFIs (particularly IA). Figures were higher in other studies; however, data were retrospective and referred to somewhat different haematological populations.

The small number of outcome events makes it difficult to associate statistical significance with the differences found between percentages. The incidence of proven/probable IA was 5.4% in the caspofungin group compared with 3.7% in patients receiving standard prophylaxis with azoles. While the use of mould-active azoles may reduce the sensitivity of GM detection, it is known that echinocandins may paradoxically increase GM levels by inducing hyphal fragmentation and do not negatively affect such an important diagnostic tool. When including possible IFI in the comparison, a condition where strong clinical suspicion of IFI is not formally supported by microbiological evidence of mycosis, patients receiving caspofungin had a lower incidence of IFI compared with patients receiving standard prophylaxis; however, this difference did not reach statistical significance. The cumulative incidence of IFI remained lower with caspofungin, even considering the more stringent 2008 international MSG/EORTC diagnostic criteria of possible IFI, which should better identify real cases of IFI and actually reduced by approximately one-third the number of possible IFIs in PROFIL-C. As a matter of fact, these results show that IFIs, and particularly IA, may at present have less of an impact in patients with AL, even among those treated with more intensive regimens.

Matiuzzi et al. reported the results of a single-institution Phase III study comparing caspofungin with itraconazole during induction. Also in this study, the incidence of events was similar in both arms, but more patients in the itraconazole group were dropped from the study because of drug-related adverse events. In PROFIL-C, with the limitation of a relatively small number of patients, the results obtained in the subgroup randomized to caspofungin seem to support the favourable characteristic of this drug, whose profile in real practice was one of the explicit targets of the study. Considering its efficacy together with its low interaction rate with other drugs and its tolerability, it can be included among antifungal agents that can be used as an alternative in patients undergoing induction treatment for AL.

In conclusion, the PROFIL-C study showed that caspofungin prophylaxis was effective and well tolerated, although it did not show a statistically significant advantage compared with the standard antifungal prophylactic policy adopted by participating centres. It may be particularly suited for patients at risk of impaired intestinal drug absorption and for those with severe hepatic and renal dysfunction. Oral antifungal prophylaxis with azoles is currently the most common practice in large NILG haematological centres during induction treatment of AL. In this context, the frequency of IFI/IA was lower than expected based on recent epidemiological surveys.

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**Transparency declarations**

G. R. acted as advisor in the Hema-e-chart project. Other authors: none to declare.

**Author contributions**

C. C. and G. R. were the principal investigators and are primarily responsible for this paper. A. A., E. A., E. B., L. C., E. C., C. M., R. R., A. S., F. S., L. V., A. L., G. L. D., E. M. P. and A. R. recruited the patients. S. M., C. F. and R. G. participated in the analysis of data and statistical analysis. C. C., S. M., G. T., A. R. and G. R. coordinated the research. C. C., S. M. and G. R. wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

**References**


