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Safety and efficacy of caspofungin and liposomal amphotericin B, followed by voriconazole in young patients affected by refractory invasive mycosis

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Abstract: *Objective*: Data on the use of combination of liposomal amphotericin B and caspofungin followed by voriconazole, as maintenance or further rescue treatment, in 10 patients with invasive mycosis are reported. *Material and methods*: The diagnoses were acute leukemia (7), myelodysplastic syndrome (1) and Hodgkin's lymphoma (1). All patients developed an invasive mycosis (proven, 3; probable, 6; and possible, 1) refractory to first-line antifungal treatment (liposomal amphotericin B in all patients except one who received fluconazole). *Results*: Rescue therapy with a combination of caspofungin and liposomal amphotericin B was well tolerated, hypokalemia, and thrombophlebitis being the most common side-effects. Combination therapy was administered for a median of 17 d, range 6–40. Among the nine patients with proven or probable mycosis, one was not evaluated because of early death caused by massive hemoptysis whilst in the remaining eight patients, the response was classified as complete, stable and failure in four, three, and one patients, respectively. Complete response was also observed in patient with possible mycosis. Eight of nine patients received voriconazole for a median of 75 d, range 42–194. Voriconazole was well tolerated although some drug interactions were observed during treatment with methotrexate and digoxin. After a median follow-up of 125 d, nine of 10 patients are alive. Overall, a favorable response to antifungal treatment (including the case of possible mycosis) was obtained in eight of 10 patients.
Conclusion: These data suggest that medical antifungal treatment may be intensified in severely ill patients without significantly compromising patient safety. The combination of synergistic antifungal drugs as well as their sequential use warrants further investigation by a larger randomized controlled study.

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Key words: invasive mycosis; aspergillosis; caspofungin; voriconazole; liposomal amphotericin B; malignancy; children

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Invasive aspergillosis is a life-threatening complication of intensive chemotherapy and hematopoietic stem cell transplantation for hematologic malignancies. Several factors account for the highly reported mortality of 50–90%, including the difficulty of making a rapid and definite diagnosis, the immunosuppression because of the underlying disease and/or the concurrent chemotherapy, the toxicity of amphotericin B deoxycholate which often precludes administration of the full therapeutic dose, and until recently, the limited therapeutic options available (1–4).

Caspofungin and voriconazole are two novel antifungal drugs which inhibit the synthesis of the β-(1,3)D-glucan and ergosterol components of the fungal wall and membrane, respectively (5–7).

The efficacy of both drugs in the treatment of invasive aspergillosis has been demonstrated (8–11), the safety and tolerability profile of caspofungin being excellent (5, 11–13). However, the availability of new antifungal drugs has presented clinicians with the challenge of defining the best antifungal treatment especially in patients with invasive aspergillosis refractory to first-line therapy. The unique mechanism of action of caspofungin, and its broad spectrum of activity, good safety profile, and minimal drug–drug pharmacokinetic interactions, make it an appealing agent for use in combination with amphotericin B or liposomal amphotericin B (14). However, voriconazole, with its favorable pharmacokinetic properties, enables an effective antifungal treatment to be administered orally, thereby reducing the need for prolonged hospitalization and daily intravenous therapy. Data on the safety, tolerability, and efficacy of the combination of caspofungin with liposomal amphotericin B or triazoles in the treatment of invasive mycosis in pediatric patients affected by hematological malignancy, are limited. We report data on 10 consecutive patients (nine children and one young adult), with invasive mycosis, (mainly aspergillosis), who were treated with a combination of liposomal amphotericin B and caspofungin followed by voriconazole as maintenance or further rescue treatment.

Materials and methods

Ten patients were recruited during a 12-month period from December 2002, using the following criteria: (i) diagnosis of proven, probable or possible invasive mycosis according to international guidelines (15); (ii) failure (F) to improve or progression of infection after an effective antifungal treatment that was previously started empirically and given for a minimum of 7 and 4 d, respectively; (iii) no known allergy to the study drugs; (iv) patient expected to survive >7 d according to the status of the underlying disease; and (v) parental informed consent. Diagnostic work-up for mycosis was based on chest X-ray, lung CT scan, and abdominal ultrasound for all patients who did not respond or who deteriorated after empiric antifungal treatment given for at least 7 and 4 d respectively.The progression of infection was defined as the rapid worsening of clinical conditions (higher and more frequent febrile spikes, hemodynamic instability, oxygen desaturation) with instrumental evidence (X-ray, CT scan, ultrasound) of new lesions. The failure to improve was defined as the persistence of fever and/or the lack of a significant reduction (at least 50%) of the number and/or of size of known lesions.

All patients were hospitalized and strictly monitored on a daily basis by clinical examination and biochemical tests (creatinine, electrolytes, transaminases, bilirubin, blood counts), and for patients who had undergone hematopoietic stem cell transplantation, daily serum determination of cyclosporine or tacrolimus levels were performed.

Weekly assessment of serum galactomannan was assessed in all patients who started the empiric antifungal treatment while other diagnostic examinations (central nervous system CT, bronchoalveolar lavage) were performed if clinically indicated.

Previous antifungal prophylaxis was defined as administration of systemic antifungal drugs for at least 7 d before the start of empiric antifungal treatment. Empiric antifungal treatment was based on liposomal amphotericin B, 1–3 mg/kg/d (16–18). Failure to improve or rapid worsening of the patient's clinical condition, was treated by the addition of caspofungin and by increasing the dose of liposomal amphotericin B to 5–6 mg/kg/d if the patient had been previously receiving a low–medium dose of 2–3 mg/kg/d. Caspofungin was administered according to preliminary pharmacokinetic data on children giving a loading dose of 70 mg/m^2 (maximum loading dose, 70 mg) and then 50 mg/m^2/d (maximum daily dose, 50 mg), thereafter (19). Safety was evaluated in patients who received the combination treatment and voriconazole for at least 3 d. Efficacy was assessed in all patients who received the drugs for at least 7 d, and rated as the best clinical–radiological result at the end of caspofungin–liposomal amphotericin B and voriconazole treatment. The criteria adopted for the efficacy assessment were in compliance with those published by Denning *et al.* (1): complete response (CR) was the resolution of all clinical signs and symptoms attributable to mycosis and complete or very nearly complete radiographic resolution; partial response (PR) was a major improvement or resolution of the attributable clinical signs and symptom and at least a 50% improvement in radiologic signs; stable response (SR) was consistent with some improvement but $<50\%$ radiologic improvement; and failure (F) was progression of or death as a result of mycosis. Favorable response encompassed both CR and PR (10). Follow-up data on survival are up to 30 November 2003.

Results

There were seven males and three females, with a median age of 13 yr (range, 6–24), with the following diagnoses: acute lymphoblastic leukemia (ALL), four; acute myeloid leukemia (AML), four; secondary acute myeloid leukemia/myelodysplastic

syndrome (AML/MDS), one; Hodgkin's lymphoma (HL), one.

Before the diagnosis of mycosis, eight of 10 patients had been severely neutropenic (granulocytes $< 0.5 \times 10^9$/L) for a median of 66 d, range 11–253. The status of the underlying disease in the 10 patients was as follows: complete hematological remission in two, partial hematological remission in two; and relapse in six patients. Invasive mycosis was diagnosed after high dose-chemotherapy in six patients, allogeneic stem cell transplant in three, and standard-dose chemotherapy in one patient.

Mycoses were classified as follows: proven, three; probable, six; and possible, one. For proven and probable mycosis, the combination of histology, galactomannan, and culture data were consistent with the diagnosis of aspergillosis in all cases (seven *Aspergillus fumigatus*, one *Aspergillus flavus*), except one, which was because of *Geotricum capitatum*. Nine of 10 patients had multiple lung lesions at diagnosis associated or followed by involvement of the spleen (two patients), liver, skin, sinuses (one patient, each), the last patient having a rhinopharyngeal infection.

Table 1 summarizes the main clinical data of patients. Previous antifungal prophylaxis had been given in six patients: itraconazole (5 mg/kg/d), four; fluconazole (10 mg/kg/d), one; ambisome (1 mg/kg/d), one. All but one of the patients, were treated empirically with liposomal amphotericin B for a median of 7 d, (range 5–28) at a median dosage of 3 mg/kg/d (range 2–6); with one patient receiving fluconazole, 10 mg/kg/d.

Table 1. Main clinical data of the patients treated with combination of caspofungin and liposomal amphotericin B

Patients	Number
Sex (M/F)	7/3
Age median (range)	13 yr (6–24)
Underlying disease	
ALL	4
AML	4
Myelodysplastic syndrome	1
HL	1
Status of disease at time of fungal infection	
Complete remission	2
Partial remission	2
Relapse	6
No. of patients with IFI risk factors	
Severe neutropenia; median duration (range)	8; 66 (11–253)
Steroids (>1 mg/kg/d for 7 d)	5
Allogenic SCT	3 (1 haploidentical, 2 MUD)
ICU admission/mechanical ventilation	4
Site of infection	
Upper respiratory tract	1 (rhinopharyngolaryngitis)
Pulmonary (multiple foci)	7
Disseminated	2 (lungs, spleen, 1; lungs, skin, spleen and liver, 1)
Classification of mycosis	
Proven	3
Probable	6
possible	1
Previous systemic prophylaxis	
Itraconazole	4
Fluconazole	1
Ambisome	1
Previuos empiric antifungal therapy	
Liposomal amphotericin B; median dose/kg/d (range)	9; 3 (2–6)
Fluconazole; dose/kg/d	1; 10

IFI, invasive fungal infection; SCT, stem cell transplantation; MUD, marrow unrelated donor.

Safety and tolerability

The combination therapy (caspofungin + liposomal amphotericin B) was well tolerated despite being administered when the patients were more critically ill. No infusion-related fever and chills or increase of bilirubin, ALT or creatinine more than two times the baseline value were observed; an increase in the bilirubin level between two- and 2.5-fold the upper limit of normal range was recorded in two patients who had moderate veno-occlusive disease after receiving treatment with gentuzomab–ozogamycin, followed, in one case, by allogeneic stem cell transplantation. The most common side-effects were hypokalemia ($K^+ < 2.5$ mEq/L) in eight of 10 patients, possibly related to liposomal amphoterin B, and femoral vein thrombophlebitis and thrombosis in two patients treated during admission to an intensive care unit. In these patients, the peripheral veins had been used to administer complex intravenous therapy. Both patients were treated with subcutaneous low weight heparin.

Treatment with voriconazole was well tolerated too and no abnormalities in liver and renal function tests were observed. Conversely, drug interactions were more frequent: with voriconazole, two patients developed a skin rash and an unusual severe hemorrhagic cheilitis concurrently with therapy with metothexate (70 mg/m^2 and 2 g/m^2, respectively), and two other patients required prompt withdrawal of digoxin therapy for high trough levels despite strict weekly monitoring: one patient had an arrthymia and electrocardiograph abnormalities (ST depression in V6, second degree atrial-ventricular block, Mobitz type I) whilst the other patient was asymptomatic.

Immunosuppression with cyclosporin and tacrolimus was used in two of three patients who underwent T-replete stem cell transplantation. In one patient, cyclosporin was discontinued early, before starting the combination of caspofungin and liposomal amphotericin B, whilst in the other patient, the daily dose of tacrolimus was modulated

according to the blood trough tacrolimus level performed at least weekly. Both patients are alive with no signs of chronic graft vs. host disease.

Efficacy

Combination therapy was administered for a median of 17 d, range 6–40. Nine of 10 patients were evaluated for response data, whilst one patient died from a massive hemoptysis, 6 d after the start of combination therapy. This patient had just received chemotherapy for an extensive relapse of Hodgkin's lymphoma involving lungs, mediastinum, and cervical lymph nodes and had developed lung infiltrates during the subsequent neutropenic phase. The diagnosis was consistent with probable aspergillosis on CT scan evaluation and serum galactomannan test. Definition of the primary cause of death and confirmation of pulmonary aspergillosis was not possible because the parents refused necropsy.

In the remaining eight patients with proven or probable mycosis, the response at the end of combination therapy was classified as CR, SR, and F in four, three, and one patients, respectively. CR was also observed in patient with possible mycosis. Concurrently, recovery of PMNs $> 0.5 \times 10^9$/L and hematological remission of the underlying disease was achieved in six patients (4 CR, 1 SR, 1 F) whilst in two SR and one CR patients, respectively, either the persistence of severe neutropenia or relapse was observed. The median time to PMN recovery was 3 d after the start of combination therapy.

Eight patients received voriconazole after therapy with caspofungin and liposomal amphotericin B in order to consolidate the recovery from invasive mycosis (three patients); as secondary prophylaxis during the subsequent chemotherapy or immunosuppressive treatment (two patients); and as further rescue therapy for the two SR and one F patients (three patients). In one patient with SR, voriconazole was given in combination with caspofungin. As of 30 November 2003, voriconazole had been administered for a median of 75 d, range 42–194; and two patients had treatment still ongoing. During this period, the patient classified as F showed a continuous improvement and achieved a CR in $6\frac{1}{2}$ months, whilst one SR patient obtained a PR. The response of all the other patients did not change. Of note, one CR patient was diagnosed with asymptomatic left heart endocardial vegetation on routine echocardiography. Because of the high risk of embolization in systemic circulation, the vegetation was removed by open-heart surgery; culture and histology was consistent with a vegetation due to *Aspergillus fumigatus*. After surgery, this patient received a 4-wk course of caspofungin in combination with voriconazole.

Survival

After a median follow-up of 125 d, range 9–335, nine of 10 patients are alive, the response to invasive mycosis was complete in seven, partial in one and stable in one of the patients, respectively. Overall, favorable response to antifungal treatment (including the case of possible mycosis), was obtained in eight of 10 patients (80%). Of note, complete recovery from fungal infection was associated with the patient achieving a complete stable hematological remission in seven of eight CR patients, whilst the PR and SR patients remained in relapse. Moreover, two CR patients successfully underwent allogeneic stem cell transplantation from an unrelated HLA matched and family haploidentical donor, 5 and 7 months, respectively, from treatment of the invasive fungal infection.

Discussion

Invasive aspergillosis has been increasingly recognized during the last decade, and together with *Candida* spp., accounts for 90% of all nosocomial fungal infections (20). Amphotericin B is a broad-spectrum antifungal agent that, for years, represented the gold standard of therapy but its poor safety and tolerability profile was often detrimental to the recovery of severely ill patients. Despite the introduction of liposomal amphotericin B, which significantly reduced these unwanted side-effects (16–18), mortality from invasive aspergillosis still remained as high as 50–90% (2). The recent introduction of new antifungal drugs makes possible an alternative strategy for the treatment of invasive mycosis. Voriconazole is a broad-spectrum triazole that is effective as both first-line or rescue treatment of invasive or refractory aspergillosis, respectively (9, 10, 21, 22). However, caspofungin is currently licensed only for the treatment of refractory aspergillosis (8). Apart from the efficacy of these new drugs as single antifungal agents, limited data are available on their use in combination, especially in pediatric patients (14, 23, 24). The mechanism of action of caspofungin, i.e. inhibition of fungal cell wall, makes it synergistic with the action of either amphotericin B and triazole which in turn damage or inhibit the synthesis of fungal cell membrane (5).

The aim of our study was to test the safety and efficacy of a new strategy of medical treatment of fungal infections which had proved refractory or were rapidly worsening whilst on first-line empiric antifungal treatment. The study was based on an

'attack phase' where the treatment was intensified for at least 2 wk with the addition of caspofungin to liposomal amphotericin B, followed by voriconazole as 'maintenance phase' or further rescue treatment. The potential advantages of this strategy would be the increase of the response rate and/or the reduction of the time to obtain a favorable response allowing an early discharge with oral voriconazole for responsive patients or the opportunity to change the antifungal treatment in non responding patients. The major finding of this study is that the combination of caspofungin and liposomal amphotericin B has been shown to be well tolerated and did not cause further organ toxicity apart from that expected, such as hypokalemia, a well-known side-effect of therapy with (liposomal) amphotericin B. Moreover, no detrimental effect was observed on the hepatic or renal function of any of the patients, including the four severely ill patients who started the combination therapy whilst in the intensive care unit on mechanical ventilation and the three patients whose invasive mycosis occurred after allogeneic stem cell transplantation. Two patients developed femoral vein phlebitis and thrombosis. Several factors may have contributed to the pathogenesis of this: the irritative drugs (including caspofungin) or solution administered through the peripheral vein, immobilization, and procoagulant abnormalities due to the inflammatory status of the patient. However, this complication was not recorded in any of the other patients where it was possible to use the central venous catheter for the administration of intravenous therapy.

From the point of view of efficacy, our data are consistent with that of Aliff *et al.* (14) who found a favorable response of 60% in a group of 30 adults patients affected by refractory invasive aspergillosis. The response rate was 75% (15/20) in the subgroup of leukemic patients. Of note, the good results in terms of survival, favorable response and CR which we are reporting, were obtained in a group of severely ill patients, as indicated by baseline patient characteristics of infection. The high response rate seen in our study may in part be explained by the fact that most patients (7/10) achieved a complete myeloid recovery and hematological remission after the diagnosis of invasive mycosis. Another intriguing hypothesis that deserves further investigation, is the potential beneficial effect of the early shift to combination therapy with caspofungin and liposomal amphotericin B. This might partly explain the difference of our results with those of Kontoyiannis *et al.* (25) who found retrospectively an overall lower favorable response rate (42%) in a group of 48 hematological patients treated with the combination of caspofungin and liposomal amphotericin B. Moreover, the response rate in their patients with documented aspergillosis was as low as 18% (25). Apart from the above-mentioned authors, no other large series has reported on the combination of caspofungin and liposomal amphotericin B. In pediatric patients, to date, there is only one case report of successful treatment which was given over nearly 12 weeks without any major clinical or laboratory side-effects (24). The choice of using voriconazole as maintenance or third-line therapy was based mainly on safety data, because of the worry about undesired toxicity or drug interactions in this severely ill group of patients (11, 26). However, its inclusion in our strategy alone or in combination with caspofungin, allowed an effective antifungal treatment to continue orally (and mainly without hospitalization in responsive patients) and to rescue completely and partially two patients, respectively, who had failed or who had had a SR to caspofungin and liposomal amphotericin B.

In conclusion, our data suggest that medical antifungal treatment may be intensified in severely ill patients with refractory invasive mycosis without significant compromise of safety. The combination of synergistic antifungal drug as well as their sequential use showed encouraging results overall but warrants further investigation by a larger randomized controlled study.

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