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EFFICACY OF DIFFERENT PROPHYLACTIC ANTIFUNGAL REGIMENS IN BONE MARROW TRANSPLANTATION

Claudio Annaloro, Alessandro Oriani, Elena Tagliaferri, Vanda Bertolli, Aldo Della Volpe, Davide Soligo, Adalberto Ibatici, Ermanno Pozzoli, Giorgio Lambertenghi Deliliers

Centro Trapianti di Midollo, Ospedale Maggiore di Milano, I.R.C.C.S.,Università degli Studi di Milano, Italy

ABSTRACT

Background. **Fungal infections still represent a major clinical problem in neutropenic patients; the recent availability of active imidazole derivatives, particularly fluconazole and itraconazole, has increased interest in prophylaxis.**

Materials and Methods. **Fifty-nine consecutive bone marrow transplant (BMT) recipients were randomized to receive either itraconazole 400 mg/day or fluconazole 300 mg/day as oral antimycotic prophylaxis during the pancytopenic phase; they were retrospectively compared with a historical control group of 30 patients who had received fluconazole 50 mg/day. Every febrile episode was treated with the same empirical antibiotic combination; amphotericin-B was added after 4-5 days in the case of persistent fever. Proven or suspected mycotic infections and the empirical use of amphotericin-B were considered as failures of prophylaxis.**

Results. **There were no differences in the number of febrile episodes in the three groups. Five patients died of bacterial sepsis: two in the fluconazole 300, two in the itraconazole and one in the fluconazole 50 group. The addition of amphotericin-B was required in 12, 16 and 11 cases, respectively, in the three groups. There were four documented fungal infections in the itraconazole and one in both fluconazole groups; three suspected fungal infections were observed in the fluconazole 300 group and two in both the itraconazole and the fluconazole 50 group. None of the differences were statistically significant.**

Conclusions. **The present results indicate that high-dose fluconazole and itraconazole are equivalent; neither of them was superior to low-dose fluconazole, which is regarded as being devoid of prophylactic activity against systemic mycoses.**

Key words: BMT, antifungal prophylaxis, itraconazole, fluconazole

Systemic fungal infections are an important cause of morbidity and mortality in granulocytopenic patients, including bone marrow transplantation (BMT) recipients.[1,2]

Treatment relies mainly on amphotericin-B, which is characterized by considerable toxicity.[3] Since microbiologically documented mycoses account for about 10%[4] of all febrile episodes in granulocytopenic patients, amphotericin-B is generally delivered on an empirical basis after 4-7 days of ineffective broad spectrum polyantibiotic therapy because on the assumption that most of these patients have a fungal infection.[1,2,5,6]

In order to reduce the need for amphotericin-B treatment and overcome the objective difficulties inherent in diagnosing deep fungal infections, considerable effort has devoted to designing effective antimycotic prophylaxis schedules.[1,2,7-10] However, despite marked improvement in the prevention of superficial mycoses, the controversies in the field of systemic mycoses are still far from being resolved, and the question of whether any effective prophylactic regimens exist at all can even be asked .[3,6]

The older azole compounds, such as myconazole[11] and ketoconazole,[12,13] are considered to be

Correspondence: Prof. Giorgio Lambertenghi-Deliliers, Centro Trapianti di Midollo, Ospedale Maggiore di Milano - I.R.C.C.S. via Francesco Sforza 35, 20122 Milano, Italy.
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either insufficiently active or too toxic after dose escalation.[6] It has been claimed that aerosolized amphotericin-B reduces the risk of systemic mycosis, but conclusive evidence is still lacking.[14] Fluconazole is an active and well-tolerated agent against many yeast species, but its limited antifungal spectrum could lead to an unacceptable increase in infections from filamentous fungi and intrinsically resistant yeasts.[6] In some studies dose escalation was proposed in order to achieve an acceptable degree of activity against filamentous fungi, but these proposals have not been universally accepted.[1,2,15] Itraconazole, another of the interesting newer azole compounds, is characterized by considerable activity against filamentous mycetes;[16] however, at present it is routinely available only in capsule form, and drug absorption is affected by meals and rendered unpredictable by the coexistence of mucositis.[8,17]

In the present study, a group of consecutive BMT recipients were randomized to receive either itraconazole or high-dose fluconazole, and the results were compared with those obtained in historical controls treated with low-dose fluconazole.

Materials and Methods

All the allogeneic and autologous BMT recipients admitted to our Unit between 1993 and 1994 entered the study. In addition, 30 consecutive patients who had undergone BMT in 1992 and had received fluconazole 50 mg/day p.o. were utilized as controls. Inclusion criteria for all patients were eligibility for BMT, a lack of evidence of infection and no history of infection or antimicrobial medication in the previous two weeks. Pretreatment testing included complete blood count, chemical and enzymatic blood profiles, surveillance cultures, ECG and chest X-ray. All patients stayed in laminar air flow rooms and received treatment through a central venous catheter. Patients were randomized to receive either fluconazole (300 mg/day p.o.) or itraconazole (400 mg/day p.o.) as antifungal prophylaxis, together with topical nystatin and oral polymyxin E 1.5 MU×3/day. Treatment was started at the same time as the pre-BMT conditioning regimen, which included CTX/Ara-C/TBI for patients with leukemia, CTX/VP-16/TBI for those with lymphoma (CTX/VP-16/BCNU in the case of patients not eligible for TBI) and L-PAM/CTX/TBI for those with multiple myeloma. Except for subjects with chronic or acute myeloid leukemia, G-CSF (5 mcg/kg/day s.c.) was administered during the post-BMT phase until peripheral granulocyte recovery (ANC > 0.5×10^9/L).

Any patient with unexplained fever exceeding 38°C was given empirical intravenous polyantibiotic therapy which included ceftazidime 2 g×3/day, amikacin 15 mg/kg/day, and teicoplanin 800 mg on day 1 and 400 mg/day on subsequent days; in the absence of clinical or microbiological evidence, amphotericin-B 0.75 mg/kg/day was added after 4-7 days if the polyantibiotic therapy was not effective, or if the patient again became febrile after a transient fever-free period. Antifungal prophylaxis was discontinued after peripheral neutrophil recovery or after amphotericin-B was started.

The empirical use of amphotericin-B and clinically suspected or microbiologically proven mycosis were classified as failures of the prophylactic antifungal regimen. Suspected mycosis was defined as the presence of antibiotic-resistant fever with imaging pictures suggestive of a fungal localization, albeit in the absence of any microbiological evidence. Microbiologically proved mycosis was defined as the isolation of fungi in blood or organ samples from patients with otherwise unexplainable symptoms or signs of infection.

Toxicity was graded according to WHO criteria. Differences between treatment groups in the achievement of clinical end-points were compared by means of the chi-square test and Fisher's exact test.

Results

Fifty-nine patients were randomized to receive one of the two antimycotic regimens: 28 patients (males 17, females 11; median age 38 years, range 13-56) were treated with fluconazole 300 mg/day (Group 1) and 31 patients (18 males, 13 females; median age 30 years, range

17-53) with itraconazole 400 mg/day (Group 2). The historical control group (Group 3) included 30 patients (19 males, 11 females; median age 31 years, range 12-48). As summarized in Table 1, the three groups were also comparable in terms of diagnosis, the number of patients not receiving G-CSF and the conditioning regimen.

The pre-BMT conditioning regimen was followed by severe pancytopenia in all cases, the duration of which was comparable in the three groups. No toxic effects could be directly attributed to the antifungal prophylaxis. All of the patients developed grade 3-4 mucositis (median duration 7 days) with no differences between the groups; in spite of this, compliance in taking oral medications was good even though eating meals was hindered. Eight of the 59 patients remained afebrile during the whole pancytopenic phase: three in Group 1, two in Group 2 and three in Group 3. Five patients died of sepsis before peripheral blood recovery: two in Group 1 (*P. aeruginosa* in both cases), two in Group 2 (*P. aeruginosa* and *S. faecalis*) and one in Group 3 (*P. aeruginosa*); no other early deaths were recorded (Table 2).

Of the febrile patients, 12/24 in Group 1, 16/29 in Group 2 and 11/26 in Group 3 required the addition of amphotericin-B. Moreover, fever persisted in spite of amphotericin-B and the antimicrobial treatment underwent further modification in one patient in Group 1, two patients in Group 2 and one patient in Group 3; in the other cases the fever resolved after the systemic antifungal agent was added. Of the eleven patients in Group 1 who responded to amphotericin-B, one had a documented fungal infection (*C. krusei*) and three had clinically suspected lung mycosis; of the fourteen responsive patients in Group 2, four had documented fungal infections (*C. glabrata* in two cases, *C. albicans* and *Saccharomyces sp.*) and two had clinically suspected lung mycosis; of the ten responsive patients in Group 3, one had a documentad fungal infection (*Aspergillus sp.*) and two had clinically suspected lung mycosis (Table 3).

There were no statistically significant differences between the three groups in terms of the number of febrile episodes, infection mortality, the need to add amphotericin-B, or the number of possible, suspected or proven mycotic infections.

Table 1. Main characteristics of the patients in the study.

	Group 1 (Flu 300)	Group 2 (Itra 400)	Group 3 (Flu 50)
No. of pts	28	31	30
Median age	38	30	31
range (yrs)	13-56	17-53	12-48
Sex (M/F)	17/11	18/13	19/11
G-CSF	21	19	20
Allogeneic BMT	12	11	8
Autologous BMT	16	20	22
TBI	24	27	25

Table 2: Outcome of the aplastic period.

	Group 1 (Flu 300)	Group 2 (Itra 400)	Group 3 (Flu 50)
Afebrile	3	2	3
Infectious deaths	2	2	1
Amphotericin-B	12	16	11
Median duration of aplasia	19	23	18
range (days)	10-70	10-60	12-48

Discussion

Fluconazole is generally regarded as the most effective azole compound in the management of some systemic fungal infections (especially those sustained by yeasts) in immunocompromized patients.[18-20] These results, along with its low degree of toxicity and the fact that it can be administered orally or intravenously, have prompted investigators to test its possible role as a prophylactic agent in neutropenic and/or immunocompromized patients.[3] Studies on large series are available for evaluation, including some controlled trials; a reduction in the number of systemic mycoses has generally been reported in comparison with historical[2,6] or

Table 3. Outcome of patients requiring amphotericin-B.

	Group 1 (Flu 300)	Group 2 (Itra)	Group 3 (Flu 50)
Amphotericin-B	12	16	11
Antibiotic therapy modified	1	2	1
Deaths	0	0	0
Documented systemic mycosis	1	4	1
[Yeasts]	[1]	[4]	[0]
[Filamentous fungi]	[0]	[0]	[1]
Clinically suspected mycosis	3	2	2

placebo-treated controls,[1,10] although no advantage has been clearly established for patients receiving a dose of 400 mg/day,[2] which could also lead to appreciable activity on filamentous fungi.[1]

In our experience, 300 mg/day of fluconazole did not prove to be superior to 50 mg/day in reducing the empirical use of amphotericin-B, or the number of clinically suspected or microbiologically documented mycoses. Since fluconazole 50 mg is generally regarded as a prophylactic agent mainly against superficial mycoses,[2,10] it can therefore be argued that fluconazole 300 mg does not offer any clear advantage over topical agents in the prevention of systemic mycoses. The value of this assumption is limited by the comparison with a historical control group, which implies well-known biases. Nevertheless, the patients included in the control group had undergone BMT one year earlier and they were fully comparable in terms of clinical parameters, conditioning regimen, nursing and supportive care. Furthermore, since the present series is limited with respect to those of the most significant previous publications,[1,2,15,21] any conclusion must be considered with caution. In clinical trials dealing with neutropenic patients and BMT recipients, fluconazole has been prospectively compared mainly with placebo,[1,10,21] historically with no antifungal prophylaxis,[2,6] rarely with topical prophylaxis;[22] in AIDS patients, it has been compared with clotrimazole.[23] The absence of topical antifungal measures in patients being treated with prophylactic antibiotics may account for a substantial portion of the occurrences of colonization and subsequent spread of fungi, as can be deduced from the significant decrease in the empirical use of amphotericin-B in patients receiving fluconazole.[1,2,21] This view is perhaps further supported by the results of the recent GIMEMA study, the only published paper comparing fluconazole with oral amphotericin-B; the authors could not prove any clearcut superiority of fluconazole over topical measures in preventing either systemic fungal infection or the empirical use of amphotericin-B.[22] Furthermore, the advantage of fluconazole prophylaxis is practically restricted to a limited number of fungal species (*C. neoformans* in AIDS patients and *C. albicans* in BMT recipients),[2,23] although it does seem to compare favorably with amphotericin-B and/or 5-fluorocytosine in the treatment of established infections by these agents.[18,20] The question has been raised as to whether the widespread use of fluconazole might lead to an overgrowth of intrinsically resistant yeast species and much attention has been given to reports of an excess of infections by *C. krusei*, but the issue is still being debated.[6,24,25] It should also be kept in mind that prophylactic fluconazole may lead to the emergence of resistant *C. albicans* strains and thus counteract the benefit of antimycotic prevention.[26] The negative results of the antimycotic regimens in our series, though primarily attributable to the limited size of the population, cannot therefore be considered in direct conflict with the literature, and raise some doubts about the appropriateness of the prophylactic use of an agent which, in selected fungal infections, may represent an effective therapeutic alternative to conventional and more toxic treatment schedules.[18-20] Furthermore, the detrimental effect of oral mucositis and impaired enteral nutrition in BMT recipients should not be overlooked.[3] The intravenous route of administration restricts the feasibility of this type of prophylaxis to hospitalized patients. In our study, the intravenous route was intentionally avoided and that may have contributed to the unfavorable outcome of the patients; however, this possibility is contradicted by the absence of any differences between the two considerably different drug doses.

The availability of itraconazole has been considered with some enthusiasm because of experimental evidence concerning its activity against filamentous fungi.[16,27-29] Some studies, mainly anecdotal or ones based on small series, report that it is comparably or even more active than amphotericin-B in the treatment of some mycotic infections in neoplastic or immunocompromized subjects.[16] Itraconazole has been used as a prophylactic agent for neutropenic patients in a limited number of studies:[6,8,30,31] in this situation, it has proven to be superior to ketoconazole[6] but its activity depends on plasma levels[8] that are difficult to reach with oral administration, the presence of mucositis and the impossibility of immunocompromized patients to eat regular meals.[32] These factors are sufficient explanation for the disappointing results in the patients given itraconazole in the present study. The widespread availability of alternative pharmaceutical forms that are more suitable in the presence of mucositis will contribute to overcoming the pharmacokinetic limitations of itraconazole in prophylaxis.[33] Despite lack of statistical support, the increase in the number of yeast infections in our series seems to be worth mentioning as a possible treatment-related event.

The present series included a limited number of homogeneous patients with similar characteristics and cannot be considered suitable for detecting small between-group differences. Early mortality was attributable to bacterial infection in all cases (mainly *P. aeruginosa* sepsis). The raw rate of documented fungal infection was comparable with those generally reported;[1,2] on the contrary, the frequency of the empirical use of amphotericin-B was rather high, although greater variability can be found in the literature.[1-3,6,14,15] This, together with the absence of any differences between the three study groups, suggests that all the prophylactic schedules are equally ineffective and that a primary, although undetermined role should be attributed to the limited suitability of oral antifungal medications for BMT recipients. Nevertheless, as pointed out above, oral administration has been preferred in the majority of comparable studies,[1,2,6,15] and generalized parenteral administration would require a change in the rationale for antifungal prophylaxis.

The present data do not support the efficacy of oral systemic antifungal prophylaxis in transplanted neutropenic patients. The discrepancy with the data reported in the literature is more apparent than real, since these are far less favorable than they appear at first glance. They clearly favor the use of systemic azole in comparison with placebo, but not with topical medications.[1,2,10,22] Selection favoring intrinsically resistant species[6,24,25] and the emergence of resistant strains are primary risks;[22, 34-36] the latter is also involved in the alternative policy of delivering prophylactic aerosolized amphotericin-B, since polyene resistance is a rare but not exceptional phenomenon that should perhaps be of increasing concern.[37,38] The costs and benefits of these risks should be carefully weighed not only in terms of the use of azole compounds in prophylaxis, but also from the perspective that their improper widespread use might compromise the possibility of successfully utilizing them in the treatment of potentially responsive fungal infections.

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