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Itraconazole Prophylaxis for an outbreak of Invasive Aspergillosis in a Hematology Ward after Hospital Construction Work

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Abstract

Objective Hospital construction work, among other environmental factors, is a risk factor for invasive aspergillosis (IA).

Methods We retrospectively surveyed the incidence of IA in hematology-oncology patients before and during hospital construction and studied the effectiveness of prophylactic oral itraconazole (ITCZ) treatment.

We compared the rates of galactomannan (GM)-positive cases and probable IA cases among 224 patients discharged before the start of construction work and among 67 patients hospitalized within two months after the start of the construction work.

Results Our results showed that, during the 12 months before the construction work was started, only four patients were GM-positive, and one had a probable diagnosis; in contrast, among patients hospitalized within two months from the start of the construction work, seven patients were GM-positive, and four had a probable diagnosis. Therefore, we started to administer oral ITCZ to 40 patients with hematological diseases. Although the construction work continued, after the ITCZ prophylaxis, no new probable cases of IA were detected.

Conclusion From our experience, GM surveillance among hematological patients is necessary during hospital construction work, and the administration of ITCZ to prophylactically prevent IA is suggested upon detection of an increase in GM-positive patients

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Key words: galactomannan, invasive aspergillosis, construction, prophylaxis, itraconazole

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Introduction

Aspergillus is a genus of filamentous fungi present in natural environments such as soil. *Aspergillus oryzae* is a species of fungi routinely used in the production of certain products such as soy sauce and miso (fermented bean paste). Moreover, *Aspergillus niger* is the main agent in the fermentation of some kinds of Japanese spirits. Aspergillus usually produces spores of less than 5 μm in diameter that are easily carried off by air currents.

Environmental factors such as construction work are known to be risk factors for invasive aspergillosis (IA) (1 -5). Spores existing within various structures, such as concrete, are scattered via air currents during construction work, leading to infections in susceptible patients.

In this report, we undertook IA surveillance for cancer patients with hematological disorders who were mainly receiving chemotherapy either before or during hospital extension construction work. Prophylaxis with itraconazole (ITCZ) was initiated after the confirmation of an increase in the galactomannan (GM)-positive rate and based on the probable diagnosis of IA following the start of construction work.

Patients and Methods

IA was diagnosed according to the 2008 criteria set by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group (6), wherein a probable diagnosis fulfills three conditions: host factors, clinical criteria, and microbiological criteria.

Host factors included prolonged neutropenia (neutrophil count <500/mm^3 for >10 days), treatment with cell-mediated immunosuppressant agents (e.g., cyclosporine, purine analog) for less than 90 days, and treatment with steroids (prednisolone at greater than 0.3 mg/kg/day) for more than 3 weeks. Clinical criteria included specific computed tomography (CT) findings (e.g., air-crescent sign, halo sign), whereas microbiological criteria included GM positivity.

The target subjects consisted of patients who were hospitalized in the Cancer Chemotherapy Center of our institution between November 2007 and April 2009 and who received cancer chemotherapy. Patients with hematologic malignancies or solid cancers with expected deep myelosuppression are admitted to our Chemotherapy Center. Our hospital made a new extension building next to the existing buildings with fourth floors. There are four connection corridors between existing buildings and a new building. The four connection corridors were shuted up by the plastic boards during the construction period. Construction work started at the beginning of November 2008 and was finished at the end of April 2009.

We compared the rate of GM-positive patients and those with a probable diagnosis of IA between 224 patients hospitalized prior to the start of construction work (for 12 months between November 2007 and October 2008) and 124 patients hospitalized during the construction work (for six months between November 2008 and April 2009). The results for the initial two months after the start of construction and for the four months after the start of ITCZ prophylaxis are shown separately (Table 1).

GM was assayed with an enzyme-linked immunosorbent assay using a Platelia Aspergillus EIA kit (Bio-Rad), with the cut-off value set at 0.5 ng/ml. GM and β-D-glucan were measured approximately once weekly in patients with hematological disorders or as judged by the physician under conditions such as fever in solid carcinoma patients. An outbreak was defined as a continuing appearance among multiple patients with an incidence per one month of more than two standard deviations (SD) greater than that for the previous 12 months.

Comparisons between the two groups were performed using Student's t-test (7). In addition, risk ratios were confirmed with 95% confidence intervals (CI). The effectiveness of protective environment was assessed by Chi-squared test.

Results

Table 1 shows the patient characteristics, GM-positive rate, and probable diagnosis of IA for each time period. For the 12 months prior to the start of construction, 4 of 224 patients were GM-positive and one patient had a

Table 1. Patient's Characteristics

	before the start of construction	during the construction without prophylaxis	during the construction with prophylaxis*[1]
duration	12 months	2 months	4 months
number	224*[2]	67*[3]	85*[4]
hematological disease	163	52	67
solid cancer	53	15	18
median age (range)	63 (27~80)	62 (37~81)	64 (41~78)
male	120	36	48
female	104	31	37
GM*[5] positive cases (%)	4 (1.8)	7 (10.4)	2 (2.4)
probable cases (%)	1 (0.4)	4 (6.0)	0 (0)

*1 prophylaxis: After the confirmation of increased probable cases without prophylactic period, we started oral daily 200mg Itraconazole administration. *2: Inpatients in the cancer chemotherapy center from November 2007 to October 2008. GM were measured 2218 times and CT scan were conducted 1203 times in this period.

*3: Inpatients from November 2008 to December 2008. GM were measured 483 times and CT scan were conducted 138 times in this period. *4: Inpatients from January 2009 to April 2009. GM were measured 885 times and CT scan were conducted 311 times in this period. There were 29 cases of overlap with *2 and *3, and 28 overlap with *3 and *4. *5 GM: galactomannan

possible diagnosis of IA. The EORTC/MSG guidelines were applied to the diagnosis of all cases, including those preceding publication of the guidelines.

Within two months of the start of construction, 7 of 67 patients were GM-positive (two in November 2008 and five in December 2008), and a probable diagnosis of IA was made in four patients; all the probable diagnoses were made in December 2008. Moreover, all GM-positive patients and patients with a probable diagnosis of IA had hematological disorders.

Based on the data for the 12 months prior to the start of construction work, the incidence rate of probable diagnosis was 0.1 ± 0.3 cases/1000 patient-days (one case/28 beds × 365 days), which increased to 4.6 cases/1000 patient-days (four cases/28 beds × 31 days) in December 2008. As this rate markedly exceeded 2 SD, an outbreak was considered to have occurred. In addition, a statistical examination of GM positivity also showed that the seven patients identified in December 2008 greatly surpassed the previous mean by 2 SD (0.33 + 2 × 0.85), and thus also had a significantly high frequency.

Therefore, as a preventative measure, we began the administration of ITCZ oral solution at 200 mg/day to patients with hematological disorders who were considered to be at high risk. In this situation, we considered the patients with hematological disorders and a neutrophil count that could be reduced to less than 1000/mm^3 (including those receiving cyclophosphamide, adriamycin, vincristine, and prednisolone) as high-risk; this group included 40 patients over a four-month period. Granulocyte-colony stimulating factor prophylaxis was administered according to the American Society of Clinical Oncology guidelines, for example, to at-risk patients aged 65 years or over with malignant lymphoma.

In the four months after the start of ICTZ prophylaxis, only 2 of 85 patients were GM-positive (November–December 2008 vs. January–April 2009; risk ratio, 0.14; 95%CI, 0.03–0.67), and none of the patients had a probable diagnosis of IA. Thus, after prophylaxis, the probable diagnosis rate fell to 0/1000 patient-days (0/28 beds × 122 days) from a rate of 4.6/1000 patient-days for the month prior to the start of prophylaxis.

In total, 36 of 40 patients received interventional administration of ITCZ, with the remaining four patients unable to receive prophylaxis due to gastrointestinal symptoms. Prophylaxis was discontinued at the cessation of construction work; however, follow-up over the next three months identified only one GM-positive patient and no patients with a probable diagnosis of IA (data not shown).

All four probable diagnosis patients identified prior to ICTZ prophylaxis showed CT findings, fever, and increased C-reactive protein levels, and they were treated with single-agent voriconazole (VRCZ). Symptoms and CT findings (All patients showed angio-invasive pulmonary aspergillosis type with halo sign) were resolved within one month in all four patients.

Table 2 shows the number of GM-positive patients by diagnoses. GM positivity was detected in patients with multiple myeloma, malignant lymphoma, and acute leukemia, and no solid cancer patients were positive for GM antigens. No patients received hematopoietic stem-cell transplantation during the study period. In addition, all acute leukemia patients were controlled in a protective environment under a laminar air flow environment equipped with high-efficiency particulate air filters (HEPA- filtration).

Table 3 shows the rate of GM positivity with and without the protective environment. Indication for the protective environment was based on an expectation of the patient having neutropenia (<500/mm^3) for over one week or on the judgment of the physician. The results show that even though many of the protective environment-controlled patients had severe neutropenia, only 6% were GM-positive, whereas 12% of patients without the protective environment were positive for GM antigens.

Discussion

There have been many reports of increases in IA due to construction work (1-5). It has also been reported that the incidence of IA is reduced to one-sixth when patients are managed with HEPA filtration after hematopoietic stem-cell transplantation (8,9). Although prevention of IA by HEPA filtration has been established, not all hematology wards are equipped with a sufficient number of rooms with HEPA filters.

Both VRCZ and caspofungin have been reported as IA prophylactic drugs that can be given during hospital construction work (1,2). On the other hand, the anti-fungal agents fluconazole and ITCZ are widely used in hematopoietic stem-cell transplantation recipients, and there are many reports of clinical trials showing the effectiveness of ITCZ in preventing IA (10,11,12). We often administer fluconazole, micafungin, and ITCZ for prevention of IA in hematopoietic-stem cell transplantation recipients. In addition, as part of the Hokkaido Hematology Study Group, we have previously reported the effect of ITCZ (13). Accordingly, we selected ITCZ for prophylaxis.

Table 2. Positive ratio of galactomannan and probable cases during the construction in respect to disease without prophylactic itraconazole

Disease	GM positive	Probable
Myeloma	44% (4/9)	22%(2/9)
Lymphoma	9% (2/23)	9%(2/23)
AML	11% (1/9)	0%(0/9)
ALL	0% (0/3)	0%(0/3)
MDS	0% (0/8)	0% (0/8)
Solid cancer	0% (0/15)	0%(0/15)

AML: acute myelocytic leukemia, ALL: acute lymphocytic leukemia,
MDS: myelodysplastic syndrome, GM: galactomannan.
All cases in myelosuppression with AML and ALL entered under the protective environment.
This data is a summary from November 2008 to December 2008.

Table 3. The positive ratio of galactomannan during the construction in relation to protective environment without prophylactic itraconazole

Protective environment	(+)	(-)
GM positive	6% (1/16)	12% (6/51)*1
probable cases	0% (0/16)	8% (4/51) *2

All cases in myelosuppression with acute leukemia were controlled under the protective environment.
GM: galactomannan.
*1, *2: These were statistically not significant analyzed by Chi-squared test (p=0.08 and p=0.30).
This data is a summary from November 2008 to December 2008.

We suspected an increase in IA in relation to the construction work, and our surveillance confirmed an increase in both the GM-positive rate and the rate of patients with a probable diagnosis of IA. Accordingly, we began the administration of prophylactic ITCZ two months after the start of construction work. Prophylactic ITCZ of 200mg may be relatively low dose compared with those with the previous reports which showed the effect of ITCZ as prophylaxis (12). This 200mg dose is the Japanese insurance approval dose.

Our results confirmed a decrease in the incidence of GM and the disappearance of cases of probable IA diagnosis four months after the start of prophylaxis. GM may be the most adequate as a surrogate marker for IA. Positive result of GM may be interpreted with caution, and intimate survey including CT scan will be recommended. The GM-positive sensitivity is known to be decreased during treatment with an anti-aspergillus agent such as ITCZ (14). GM sensitivity is generally around 70%, but this falls to 50% during administration of the abovementioned antifungal treatment. Even allowing for a decrease in the detection rate, the fall in detection of GM from 7 cases in 2 months prior to prophylaxis to 2 cases in 4 months post-prophylaxis appears to be a good result. In addition the absence of new cases of probable IA diagnosis after prophylaxis suggests that the prophylaxis was effective.

None of the solid cancer patients were positive for GM, with all GM-positive cases found exclusively among those with hematological disorders. Therefore, anti-IA measures may not be required for solid cancer patients during hospital-related construction work. Instead, the onset of GM-positive cases in those with hematological disorders may be related to the high doses of steroids, severe myelosuppression, and decreased normal human immunoglobulin levels.

Among patients with hematological disorders, 44% of those with myeloma were GM-positive and 22% had a probable diagnosis of IA, which is regarded as a particularly high frequency. The reason for this is thought to be the long-term high doses of dexamethasone given in the treatment of myeloma, although we cannot deny that our high rate of GM in the patients with myeloma may be false positive (15).

On the other hand, GM positivity was not increased in cases of acute leukemia, despite the severe myelosuppression associated with this condition. In agreement with previous reports, we believe that this is due to the effectiveness of the protective environment.

Therefore, the current study suggests the usefulness of ITCZ prophylaxis during hospital construction work.

However, ITCZ inhibits cytochrome P450 3A4 (CYP3A4), and the blood concentration of several chemotherapeutic drugs may consequently increase (16). Such anticancer drugs include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, vinorelbine, vinblastine, vincristine, and bortezomib. In addition, attention should be paid to possible increases in the serum concentration of drugs used after hematopoietic stem-cell transplants, such as tacrolimus and cyclosporine.

A further limitation is that ITCZ may lead to digestive symptoms, such as nausea or diarrhea, in some patients and to a decrease in patient quality of life.

Our experience indicates that patients with hematological disorders need to be monitored, particularly for GM, during construction work in hospitals, and ITCZ or another anti-aspergillus drug considered to be used as a prophylactic for high-risk patients when an increase in the incidence of GM positivity is confirmed.

Conflicts of interest

The authors declare that they have no conflict of interest.

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