Prevention of Invasive Fungal Infection during Chemotherapy-Induced Neutropenia in Patients with Acute Leukemia

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Abstract

This is a retrospective study comparing the methods of preventing fungal infection in a total of 420 episodes of chemotherapy-induced neutropenia of more than 10 days’ duration between 1986 and 1992 in 104 patients with acute leukemia and 62 patients who underwent bone marrow transplantation.

The episodes were divided into five groups according to the prophylactic regimens (group 1, oral amphotericin B (OA) only; 2, OA and nebulization of amphotericin B (NA); 3, OA and NA with a laminar air flow system (LAF); 4, oral fluconazole (OF) and NA; 5, OF, NA, and LAF. The total numbers of neutropenic episodes were 115, 141, 95, 37, and 32, respectively.

A total of 15 episode of invasive fungal infections were documented. Aspergillosis was seen on two occasions each in groups 1 and 2, while none was seen in the patients who were under the LAF system.

Nebulization of amphotericin B did not have a significant preventive effect in this study and it needs to be evaluated further by a randomized study.

Introduction

Fungal infection is one of the main problems in treating the hematological malignancies. Invasive aspergillosis especially is a serious complication of intensive chemotherapy1-3). Because aspergilli invade through the respiratory system, preventive methods, such as nebulization or nasal spraying of amphotericin B, have been investigated with favorable results4,5).

This is a retrospective study comparing the methods of preventing fungal infection used comparing the methods of preventing fungal infection used in the Hematology Division at the Tokyo Metropolitan Komagome Hospital between 1985 and 1992. We started nebulization of amphotericin B on the general ward in 1986. Since 1989, almost all patients have been treated prophylactically by nebulization of amphotericin B. The compact type of laminar air flow (LAF) system was also initiated, in 1990.

Material and Methods

The records of all adult patients who were admitted to the Hematology Division at the Tokyo Metropolitan Komagome Hospital and received intensive chemotherapy for acute leukemia between
January 1985 and October 1992 were reviewed. Granulocytopenia of less than $0.5 \times 10^9/L$ of more than 10 days’ duration was used as the inclusion criterion and the episodes of neutropenia exceeding 90 days were excluded from the analysis.

Sixty-two patients who underwent bone marrow transplantation (BMT) for hematological diseases were also included in the analysis.

**Antifungal prophylactic regimen**

Nebulization of amphotericin B, 5 to 10 mg three times a day, was given by means of an ultrasonic nebulizer (Sonilizer 305, ATOM, Tokyo, or an Acoma ultrasonic nebulizer, model EN-3, Acoma, Tokyo), starting in January 1986. After January 1988, all patients except those who could not tolerate nebulization received nebulization of 7.5 mg three times a day.

Between January 1986 and March 1990, all patients received amphotericin B, 800 mg, three times a day orally. After May 1990, patients received amphotericin B or fluconazole, 200 mg, once a day according to our prevention protocol (manuscript in preparation).

The patients were treated under conventional ward conditions. A compact high-efficiency particulate air (HEPA) filtered laminar air flow system (Bed Isolator LI30-S, Toyo Netsu Kogyo Kaisha, Ltd., Tokyo) was used after May 1990 in selected cases. All the patients who underwent BMT received oral amphotericin B and nebulization of amphotericin B in the LAF room.

**Definition of invasive fungal infection**

Invasive fungal infection was defined as the fulfillment of one of the following criteria: (1) positive blood culture, (2) isolation of fungi from a biopsy or autopsy specimen with histological evidence of invasion.

**Results**

**Patient characteristics**

During the study period, 366 episodes of neutropenia were documented in 104 patients with acute leukemia, aged 16 to 74 years. Eight episodes were excluded because of prolonged neutropenia (four episodes each in groups 1 and 2) but none of these patients developed documented invasive fungal infection. The remaining episodes were divided into five categories according to the preventive regimen, as follows: (1) oral amphotericin B (OA) without nebulization of amphotericin B (NA) or laminar air flow (LAF); (2) OA with NA, without LAF; (3) OA with NA and LAF; (4) oral fluconazole (OF) with NA, without LAF, and (5) OF with NA and LAF.

The numbers of neutropenic episodes analyzed in each group are 115, 141, 33, 37, and 32, respectively. The median durations of neutropenia are 22.0, 21.2, 20.0, 16.1, and 21.9 days, respectively. The 62 patients who underwent BMT were also assigned to group 3.

**End point analysis**

Between 1986 and 1992, 15 episodes of invasive fungal infection were documented. According to the preventive regimen, their categories were (1) for 7 patients, (2) 6, (3) 1, (4) 1, and (5) none.

Table 1 shows the fungal genera identified in each group. *Aspergillus* was responsible in two patients who were not receiving nebulization and two who were receiving nebulization. Comparison of groups 1 and 2 shows that there is no significant difference between them. The incidence of invasive fungal infection and the genera identified were almost the same, as was the temporal incidence over the study period (Fig. 1).

In group 3, in contrast, no case of aspergillosis was documented, even if the 62 patients who underwent BMT between 1989 and 1992 were included in the analysis. If we added the episodes in group 5, no case of aspergillosis was found in the 127 episodes that occurred when the LAF system was used.
Table 1  Cases of invasive fungal infection according to preventive method

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive method</td>
<td>oral</td>
<td>nebulization</td>
<td>LAF</td>
<td>Episodes of neutropenia</td>
<td>No of IFI</td>
</tr>
<tr>
<td>A*</td>
<td>A</td>
<td>A</td>
<td>F**</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>115</td>
<td>141</td>
<td>33(62)</td>
<td>37</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fungal genus</td>
<td>Trichosporon</td>
<td>Aspergillus</td>
<td>Candida</td>
<td>Torulopsis glablate</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
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<td>1</td>
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</table>

A*: amphotericin B, F**: fluconazole, LAF#: laminar air flow system, IFI*: invasive fungal infection, (): patients with bone marrow transplantation.

Fig. 1  Temporal incidence of cases of invasive fungal infection over the study period 1985 to 1992. (-): more than ten episodes in that year. (- - - -): ten or fewer episodes in that year. Arrows: cases of invasive fungal infection. T: Trichosporon, A: Aspergillus, C: Candida, G: Torulopsis glablate.

In the patients receiving fluconazole, fungemia due to Torulopsis glablate was documented on one occasion. No candidemia was observed when the patients were on fluconazole while it occurred four times in 289 episodes in patients on amphotericin B. Trichosporon was responsible on five occasions, three in group 1 and one each in groups 2 and 3. On two occasions, patients developed fungemia despite the empiric use of amphotericin B. The patients treated with fluconazole did not develop fungemia due to this organism.

Discussion

Fungal infection is still one of the main problems in treating the hematological malignancies. Invasive aspergillosis especially is a serious complication of intensive chemotherapy. Several clinical studies using intranasal spraying or nebulization of amphotericin B showed a preventive effect of amphotericin B against aspergilli, although no randomized study has shown a definitive benefit of these methods yet.

Also, there is a question regarding the effect of nebulization and intranasal manipulation of amphotericin B because the nasal cultures of the patients with aspergillosis did not show any significant increase of colonization by aspergilli.

A recent randomized placebo-controlled trial in leukemia patients also failed to show a protective effect of amphotericin B nasal spray against invasive pulmonary disease.

In comparing group 1 and group 2 in our study, no apparent beneficial effect of nebulization was
demonstrated either, even though the incidence of invasive fungal infection was rather low. The dose of
amphotericin B used for nebulization in this study was reasonable according to recent reports and the
ultrasonicator used would make droplets 1 to 5 μm in diameter which should be small enough to distribute
the medicine through the respiratory system. Compliance was also checked by the nursing staff each
time. Although we could not evaluate the efficacy of this method in eradicating the colonized aspergilli
from the nasal area because we do not have data regarding surveillance culture of the nasal area, no
methodological failure was suspected in this study.

On the other hand, if we add all episodes in which the LAF system was used, invasive fungal infection
developed in only two of 127 episodes and no case of aspergillosis was documented. Because the LAF system
seemed to have prevented infection due to aspergilli even though the patients also received nebulization of
amphotericin B, we believe that our data have confirmed the efficacy of the LAF system in preventing
aspergillosis and also support the hypothesis that the patients probably obtained the responsible agents
directly during respiration, with or without colonization in their respiratory system.

The compact type of LAF system also turned out to be effective in preventing respiratory fungal
infection, even though the patients were not under LAF all the time. Considering its price, it might be a
cost-effective way to prevent fungal infection compared to the construction work necessary to install a new
HEPA system on the floor.

Considering the relationship between each preventive method and the observed fungal genus,
fluconazole effectively prevented candidal infection but Torulopsis glabata emerged as a new agent to cause
invasive infection. Considering the high incidence of colonization by this organism (manuscript in
preparation) and the high incidence of fungemia due to Candida krusei reported in patients receiving
fluconazole, it seems to be necessary to manipulate the method of preventing fungal infection further even
when fluconazole is used.

Trichosporon was observed only in the patients receiving amphotericin B, which may suggest a
preventive effect of fluconazole. The sensitivity of this organism, however, suggests that it might be
difficult for fluconazole to prevent infection efficiently.

The preventive effect of nebulization of amphotericin B, therefore, needs to be evaluated further by a
randomized study and meantime it might be reasonable to use intranasal spraying or nebulization of
amphotericin B if the LAF system is not available.

Acknowledgments

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1990.
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Prevention of Fungal Infection


急性白血病患者の化学療法に伴う顆粒球減少時の真菌感染予防法の検討

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要 旨
当科に於て、急性白血病患者の化学療法後の顆粒球減少時に真菌感染予防のために試みられた、Ampicillin B（Amp B）のネプライザーによる経気道投与（A 吸入）、Laminar air flow system（LAF）、Amp B 経口投与（A）、Fluconazole 経口投与（F）の臨床的予防効果について retrospective に検討した。
1985年から1992年の7年間に当科に入院した急性白血病患者104例と骨髄移植患者62例に観察された延べ420回の顆粒球減少のエピソード（顆粒球数500/μ1以下の期間が10日間以上続いたもの）を対象とした。それぞれのエピソードについて A 吸入（1回5～10mg を超音波ネプライザーにて1日3回投与）、LAF の使用、A（2,400mg/日、分 3）、F（200mg/日、分1）の有無と真菌感染症の有無について検討した。真菌感染については、血液培養、あるいは剖検や生検により確認されたもののみを確認例として扱った。真菌感染確診例の頻度は、(1) A 単独：7/115（6.1%）、(2) A＋A 吸入：6/141（4.2%）、(3) A＋A 吸入＋LAF：1/95（1.1%）、(4) F＋A 吸入：1/37（2.7%）、(5) F＋A 吸入＋LAF：0/32（0%）であった。このうち invasive aspergillosis については(1)群及び(2)群に於いてそれぞれ2回ずつ観察されているが、他群では観察されなかった。
LAF の使用は、他の方法と併用することにより真菌感染症をさらに減少させうると思われた。A 吸入については invasive aspergillosis の予防効果を含め併用効果は明らかではなかった。