

Prophylactic use of fluconazole in neutropenic cancer patients

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Summary

This study was carried out on 70 patients with haematological or solid malignancies who were receiving chemotherapy and/or radiotherapy. Forty-one patients were randomly assigned to receive fluconazole, 400 mg/day, while they were neutropenic. Systemic fungal infection developed in four of the 41 patients (9%) receiving prophylaxis in comparison to nine of 29 patients (31%) not receiving prophylaxis. The incidence of systemic fungal infection was significantly different between the groups receiving prophylaxis and those not receiving it ($p < 0.05$). Fluconazole was found to be effective for preventing systemic fungal infections in neutropenic patients with cancer.

Keywords: fluconazole, prophylaxis, fungal infection

Introduction

Fungal infections are becoming an increasing problem in cancer patients and factors that play an important role in this increase include difficulties in establishing the diagnosis and limitations of management. Although amphotericin B is the agent of choice for the treatment of systemic fungal infections, its use is limited by considerable toxicity.¹ These factors and the high mortality rate associated with fungal infections have made prophylaxis more important.² Until now, prophylaxis with nystatin, amphotericin B, clotrimazole, ketaconazole, and miconazole has been tried but found to be unsatisfactory.^{3,4}

Fluconazole is a bistriazole antifungal agent, which is safe, well-tolerated and highly active against most of the pathogens that cause systemic fungal infections.^{5,6} Studies suggest that fluconazole would be effective in neutropenic hosts.^{3,7} This study was conducted to determine the efficacy of prophylaxis with fluconazole in neutropenic cancer patients.

Methods

Of the 70 neutropenic cancer patients enrolled in the study, 20 were female and 50 male. Their ages were 16 to 68 (mean 45 ± 15 , median 49.5) years. The distributions of the primary tumour are shown in the table. Patients were defined as neutropenic when the neutrophil count was

below $2000/\mu\text{l}$. The mean neutrophil counts were $822 \pm 645/\mu\text{l}$ (range 0–1908/ μl).

Patients were randomly assigned to receive or not to receive prophylaxis with fluconazole. Prophylaxis was given to 41 patients; 29 patients did not receive any prophylaxis. Fluconazole was given orally in a dose of 400 mg daily in two divided doses. Treatment was continued until the neutrophil count had increased to $2000/\mu\text{l}$ or until systemic fungal infection was suspected. During the treatment period cultures of throat, feces, urine and blood were obtained twice weekly. In addition, patients were evaluated for signs and symptoms of infection. Systemic fungal infection was considered to be present when the organism was isolated from blood or urine and when yeasts and pseudohyphae were microscopically seen on sterile urine smears.

STATISTICAL ANALYSIS

Student's unpaired *t*-test was used for comparison of variables, eg, absolute neutrophil counts. Nominal results, eg, incidence of *Candida* infection, between groups were compared using the chi-squared test. A *p*-value below 0.05 was considered significant. Data are reported as mean \pm standard deviation (SD).

Results

Systemic fungal infection occurred in four of 41 patients (9.8%) who were given prophylaxis with fluconazole and in nine of 29 patients (31%) who were not ($p < 0.05$).

The absolute neutrophil counts, in the fluconazole group were $763 \pm 91/\mu\text{l}$ for cases

Table Patient characteristics

Patient characteristics	Control	Fluconazole
Number (<i>n</i>)	29	41
Median age (range) (years)	50 (16–67)	49 (17–68)
Sex		
male	20	30
female	9	11
Underlying disease		
acute leukemia	10	13
chronic leukemia	3	2
Hodgkin's disease	4	5
non-Hodgkin's lymphoma	5	9
myelodysplastic syndrome	2	3
aplastic anemia	–	2
solid tumour	5	4
multiple myeloma	–	3

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with systemic fungal infection and $739 \pm 610/\mu\text{l}$ for cases without ($p > 0.05$), while among the controls, the mean neutrophil counts for cases with systemic fungal infection were $949 \pm 727/\mu\text{l}$ and $898 \pm 704/\mu\text{l}$ for cases without ($p > 0.05$). Patients with and without systemic fungal infection were also compared for the duration of neutropenia. The mean duration of neutropenia was 25 ± 17 days for the fluconazole patients and 17 ± 16 for the controls; the difference was significant ($p < 0.05$).

A breakdown of *Candida* infections in different groups of patients according to the underlying disease revealed that eight of the 13 *Candida*-positive cases were acute leukemia 61.5% (the other cases were one each of non-Hodgkin's lymphoma, Hodgkin's disease, aplastic anemia, solid tumour and chronic leukemia).

Discussion

Invasive fungal infections are important causes of morbidity and mortality among cancer patients. *Candida* and *Aspergillus* are the most common causes of invasive fungal infections and *Candida* species predominate in cancer patients.^{3,8,9} Several autopsy studies have shown that 10–30% of patients with leukemia 10–15% of patient with lymphoma and 5% of patients with solid tumours have invasive candidiasis.⁴ In another report the incidence of systemic *Candida* infection in immunocompromised patients was 37.5% on autopsy.¹⁰ In our study the 31% incidence of systemic fungal infections noted among the patients receiving no prophylaxis, with predominantly acute leukemia as an underlying disease, is parallel to reports in previous studies.⁴ The results of this study are also similar to previous reports on the significance of the duration of neutropenia as a pre-disposing factor for fungal infections.¹¹

Difficulties in diagnosis and management are the major problems encountered in fungal infections. Diagnosis is established by demonstration of tissue invasion histologically or by isolating the fungus from urine or blood.⁴ However, in high-risk patients, isolating the fungus is difficult and blood cultures lack sensitivity.¹² It has been shown that blood cultures of patients with autopsy-proven fungal infection were 50% negative.¹³ In this study, fungus could not be isolated from blood cultures of cases diagnosed as having systemic fungal infection.

According to an autopsy study of systemic *Candida* infections, the kidney is the most frequently involved organ and candiduria may be the first manifestation of systemic infection.¹⁴ In particular, the appearance of pseudohyphae is indicative of invasive *Candida* infection rather than colonisation.¹⁵ In our study patients with microscopical appearance of yeast and pseudohyphae in urine specimens were considered to have systemic *Candida* infection. Although accurate diagnosis of candidiasis relies on histological demonstration, in these patients the use of such invasive procedures is impossible for several reasons.¹⁶

Learning/summary points

- fungal infections are frequent among neutropenic cancer patients
- fluconazole is a highly effective and well-tolerated prophylactic agent in neutropenic patients with cancer

Several problems are encountered in the management of fungal infections, such as establishing a definite diagnosis at an early stage and the high toxicity of antifungal agents. As antifungal agents are initiated empirically, subjects without fungal infection are unnecessarily exposed to drug toxicity. On the other hand, some patients with fungal infection are not given any antifungal therapy or are given it too late. While amphotericin B is the drug of choice for the treatment of systemic fungal infections, it is not always effective, must be given parenterally, and is associated with high toxicity.¹⁷ In several reports failure of amphotericin B has been noted in 40–50% of cases.^{6,9}

The difficulty in establishing the diagnosis, problems with management and the high mortality rates associated with this disease makes prophylactic therapy highly desirable. However, agents for prophylactic use must be effective, safe and well-tolerated.

Fluconazole is a well-tolerated agent which is active against many important fungal pathogens which cause systemic fungal infections in cancer patients. It has a long half-life which allows once-daily administration via either oral or intravenous routes.^{7,8} Experimental studies in granulocytopenic animals have indicated that fluconazole is effective for preventive treatment of systemic *Candida* infection, penetrates well into all tissue sites, has a low toxicity and high doses are effective in prophylaxis against disseminated aspergillosis.³ Clinical studies have shown that prophylaxis with fluconazole reduced the incidence of both superficial and systemic *Candida* infections, but the incidence of colonisation by strains other than *C. albicans* (eg, *C. krusei* and *Torulopsis glabrata*) have increased.^{2,9,16,18–20} Although the *Candida* species were not identified in the present study, it is probable that the systemic infections observed in some of the fluconazole recipients, could be due to fluconazole-resistant non-*albicans* strains. Prophylaxis with fluconazole is associated with the emergence of less virulent *Candida* species but offers the advantage of suppression of more virulent *Candida* species such as *C. albicans*.

In this study the dose of fluconazole was relatively high (400 mg/day) as we hoped that this dose might also offer some protection against *Aspergillus*.

Our findings support the use of highly effective prophylactic agents like fluconazole in neutropenic cancer patients. Studies are still needed to establish more rapid diagnostic methods for systemic fungal infections and to develop more effective, less toxic therapies.

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