Itraconazole for Treatment of Oral Candidosis in Pediatric Cancer Patients

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Abstract

Oral candidosis commonly occurs in malignancy children undergoing antineoplastic chemotherapy. Inadequate response to antifungal treatment leads to a risk of disseminated infection. The aim of this study is to evaluate the efficacy and side effects of itraconazole on treatment of oral candidosis. Fourteen children with malignancy undergoing chemotherapy received itraconazole 100 - 200 mg/day for 10 days to treat oral candidosis. The severity of disease was defined as mild and moderate depending on the number of lesions and symptoms. Oropharyngeal lesions and symptoms were recorded initially and daily. Blood chemistries were done on day 0, day 10 and day 16. The overall response rate was 87.5 per cent. The mild group (4 cases) had a response rate of 100 per cent which had lesions and symptoms resolved on day 2 and day 1.5 $\pm$ 0.7 respectively. The moderate group (10 cases) had 8 responders (80%) whose lesions and symptoms resolved on day 6 $\pm$ 2.5 and day 4.1 $\pm$ 2.3 respectively. Side effects and abnormal blood chemistry values were not seen.

Fungal infection emerges as a major problem among patients receiving anticancer chemotherapy especially for acute leukemia and other hematologic malignancy[1,2]. *Candida* spp is the common opportunistic fungus which causes superficial fungal infection. The clinical spectrum of candidosis can be divided into four categories: superficial or localized infection, major organ infection, disseminated infection and candidemia. Oropharyngeal candidosis which presents as white raised exudate adhered to underlying mucosa occurs in about 25 to 30 per cent of adult cancer patients undergoing chemotherapy[3]. The predisposing factors of candida infection in malignancy patients include damage of mucosal membrane due to chemotherapy, neutropenia, prolonged use of antibiotics and steroids and impaired cellular mediated immunity[4]. The treatment of oral candidosis in these patients is more difficult and response rates are lower. In addition, inadequate response to treatment of local infection bears a risk of potentially fatal dissemination of the infection[5].

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Itraconazole is a triazole compound whose mechanism of actions are related to its binding of fungal cytochrome 450 isozyme with resultant inhibition of ergosterol synthesis and pertubation of membrane bound enzyme function and membrane permeability[6]. Toxicity of this drug has been reported to be minimal. Itraconazole was used for treatment and prophylaxis of fungal infection in children in a few studies[7,8].

The aim of our study is to evaluate the efficacy and side effects of itraconazole on treatment of oral candidosis in malignant children.

MATERIAL AND METHOD

Fourteen children with hematologic malignant disease were studied prospectively. There were 10 boys and 4 girls with age ranging from 5 to 11 years. Minimum patient's weight was 20 kilograms. All patiênts were receiving antineoplastic chemotherapy course of treatment. Oral candidosis was diagnosed by the appearance of a white patch on oral or pharyngeal mucosa with positive presence of yeast with pseudomycelium by KOH preparation. Fungal cultures were performed to confirm the diagnosis. Severity of oral candidosis was defined as mild for lesions without symptoms or one lesion with symptoms and moderate for more than one lesion with symptoms. Severe dysphagia was not included in this study because it was more likely related to candida esophagitis. The other exclusions were systemic candida infection, abnormal liver function tests above twice the normal values, receiving fluconazole or amphotericin B, history of hypersensitivity to itraconazole, and oral herpes simplex infection which was excluded by rapid diagnosis method.

The specific symptoms usually related to oral candidosis such as mouth pain, sore throat and dysphagia were recorded. Non-specific symptoms related to either oral candidosis or patients's underlying or complicating disease including fever, abdominal pain, vomiting, anorexia, constipation and diarrhea were also recorded. Oropharyngeal lesions and symptoms were recorded initially and daily. All patients had base line laboratory studies including liver function tests, BUN, creatinine, triglyceride and electrolytes. These studies were repeated at one day (day 10). Patients received itraconazole orally at a dose of 5 mg/ kg/ day (approximately 100 or 200 mg/day) for 10 days. The side effects of itraconazole (hypertension, jaundice, headache, dizziness, pruritus, skin rash, edema and nonspecific symptoms) were observed during and after therapy. The day that oral lesions disappeared or symptoms were resolved completely was recorded. A patient was considered as a responder if there was disappearing of lesions and symptoms resolved within 10 days after starting therapy. Itraconazole was discontinued earlier if lesions and symptoms became worse or patients had severe adverse reaction such as jaundice or hypertension.

RESULTS

The underlying disease of fourteen children was ALL (7), AML with neutropenia (5), lymphoma (1) and adenoid cystic carcinoma with neutropenia (1). Ten patients had fever and received broad spectrum antibiotics (ceftazidime, amikacin) for treatment of suspected bacterial infection or prophylaxis of infection in febrile neutropenia. Fungal cultures had 4 positive Candida albican, 1 Candida non-albican and 9 negative results. Descriptions of patients are summarized in Table 1. There were 4 mild severity patients, of which 2 had no symptom. Ten patients had moderate severity. The specific symptoms were mouth pain (11), sore throat (6), and dysphagia (2). The nonspecific symptoms were fever (10), anorexia (6), vomiting (2) and diarrhea (1) (Table 2). The mild group had lesions disappear and symptoms resolved on day 2 and day 1.5 ± 0.7 respectively. In the other group, eight patients were responders whose symptoms were resolved on day 4.1 ± 2.3 and lesion disappearance on day 6 ± 2.5. Of two nonresponders, patient No. 7 with diagnosis of ALL had fever and was treated with ceftazidime and amikacin. Fungal culture from oropharyngeal lesions demonstrated positive Candida albican. He had mouth pain, sore throat, dysphagia, fever and vomiting. Itraconazole was discontinued after 4 days of treatment due to symptoms and worsening oral lesion. Patient No. 8 with underlying ALL had mouth pain and sore throat without fever. After receiving itraconazole for 10 days, symptoms and oral lesions persisted. The overall response rate was 87.5 per cent. Blood chemistry studies performed at day 0, day 10 and day 16 were normal. No side effects were seen during 17 days of studying each patient.

Table 1. Descriptions of patients.

Case	Age (y)	Diagnosis	Severity	Symptoms resolved (d)	Lesions disappeared (d)	Result
1	5	AML	mild	no symptom	2	improved
2	5	ALL	mild	no symptom	2	improved
3	5	ALL	mild	2	2	improved
4	10	ALL	mild	1	2	improved
5	5	ALL	moderate	3	6	improved
6	10	ALL	moderate	8	9	improved
7	9	ALL	moderate	-	-	not improved
8	4	ALL	moderate	-	-	not improved
9	5	AML neutropenia	moderate	2	3	improved
10	10	AML neutropenia	moderate moderate	2	6	improved
11	11	AML neutropenia	moderate	6	7	improved
12	4	AML neutropenia	moderate	2	2	improved
13	8	lymphoma	moderate	4	6	improved
14	9	adenoid cystic carcinoma neutropenia	moderate	6	9	improved

Table 2. Specific and non-specific symptoms.

Symptom	case (n)
Mouth pain	11
Sore throat	6
Dysphagia	2
Fever	9
Anorexia	6
Vomiting	2
Diarrhea	1

DISCUSSION

Itraconazole is an antifungal drug which is effective in treating superficial fungal disease, blastomycoses, histoplasmosis, aspergillosis and cryptococcosis[1,4]. Information on the efficacy of itraconazole in the treatment of serious invasive candida infection on children with malignancy disease is limited. Itraconazole was reported to be more effective than placebo in treating oral candidosis for adult patients with malignancy or receiving immunosuppressive therapy[9,10]. It is not widely used to treat candida infection in children with malignancy disease. Ninane J et al studied children with prolonged granulocytopenia to evaluate the prophylactic antifungal activity of itraconazole and ketoconazole. There was no statistical difference between both medications[8]. Caselli D et al reported a prospective, randomized, controlled study of antifungal chemoprophylaxis in 40 immunocompromised children with hematologic malignancy, receiving itraconazole, ketoconazole, amphotericin B and no prophylaxis. Fungal isolates were significantly less frequent in the ketoconazole group of patients than any other group[7]. Our study demonstrated the efficacy of itraconazole for treatment of oral candidosis in 14 malignancy children which showed a response rate of 85.7 per cent. In the mild group, the response rate was 100 per cent in which specific symptoms were resolved and oral lesions disappeared on day 1.5 ± 0.7 and day 2 respectively. In this group, the duration of treatment should be probably shorter than 10 days. The response rate was 80 per cent in the moderate severity group and oral lesions disappeared on day 6 ± 2.5, so duration of treatment of at least 10 days was appropriate. There was limited data of itraconazole in treatment of candida esophagitis and disseminated candida infection in children, therefore it was discontinued on day 4 of treatment in patient No. 7.

Not only does a good reponse depend on the efficacy of the antifungal drug, but it is also affected by factors including species of candida, neutropenia, type and duration of antibiotics, severity of mucosal injury due to chemotherapy, bacterial infection and nutritional status.

Fungal culture had 5 positive *Candida* spp in this present data. The negative results were possibly due to technical errors in getting good specimens. Unfortunately, we did not identify the species of one Candida non-albican. Although Candida albican accounts for the majority of infections, other non-albican spp (including C. tropicalis, C. parapsilosis, C. krusei, C. guilliermondi) have emerged as important pathogens[11,12]. Neutropenia is the most common predisposing factor to opportunistic mycoses in malignancy patients[3]. Febrile neutropenia usually occurs during and after receiving chemotherapy. Both the degree and duration of neutropenia influence the development of fungal infection when the neutrophil count falls below 100/mm^3 and when this profound neutropenia persists for more than a week. Five cases of febrile neatropenia in this study responded to itraconazole. However, recovery of neutropenia was the other important factor of good response. Broad spectrum antibiotics is usually administered in treatment of suspected sepsis and febrile neutropenia. It has been associated with increases in both the frequency and degree of colonization by *Candida* spp[14,15]. Combination of ceftazidime and amikacin was the increased risk factor in development of oral candidosis in our 10 children.

The incidence of adverse reaction in adults ranges from about 7 per cent in patients on short course of therapy to 17.7 per cent in patients requiring itraconazole for longer than 1 month[6]. Most of the adverse reactions are transient. There was no report of side effects or laboratory abnormality in the children[5]. Initial non-specific symptoms in our study similar to side effects of itraconazole were not progessively worsened after therapy. Our study supports the safety of this drug in children with short course therapy. Itraconazole had good efficacy on treatment of oral candidosis in malignancy children with a response rate of 87.5 per cent without side effects.

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การรักษาภาวะติดเชื้อแคนดิดาในช่องปาก ในผู้ป่วยเด็กที่เป็นมะเร็ง

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การติดเชื้อราแคนดิดา ในช่องปากนั้นเป็นปัญหาที่พบได้บ่อยในผู้ป่วยเด็กเป็นมะเร็งและอยู่ระหว่างการรักษาด้วยยารักษาโรคมะเร็ง ถ้าการรักษาด้วยยาฆ่าเชื้อรามีประสิทธิภาพไม่ดีพอจะทำให้มีโอกาสที่โรคจะแพร่กระจาย การศึกษานี้มีจุดประสงค์เพื่อศึกษาถึงประสิทธิภาพและอาการข้างเคียงของยา itraconazole ในการรักษาโรคดังกล่าว ผู้ป่วยเด็กจำนวน 14 ราย ป่วยเป็นโรค acute leukemia 12 ราย, lymphoma 1 ราย และ adenoid cystic carcinoma 1 ราย ได้รับยา itraconazole ขนาด 100 - 200 มิลลิกรัม ต่อวัน เป็นระยะเวลา 10 วัน เพื่อรักษาเชื้อราในช่องปาก ความรุนแรงของโรคแบ่งออกเป็นน้อย และปานกลางตามจำนวน lesion และอาการ จากผู้ป่วยทั้งหมด 14 ราย ผู้ป่วยหายจากโรค 12 ราย (87.5%) ในกลุ่มผู้ป่วยที่รุนแรงน้อย จำนวน 4 ราย ผู้ป่วยหายจากโรคทุกราย ซึ่ง lesion และอาการหายไป ในวันที่ 2 และ วันที่ 1.5 $\pm$ 0.7 ตามลำดับ ผู้ป่วยที่รุนแรงปานกลางจำนวน 10 ราย ได้ผลการรักษาดี 8 ราย (80%) โดย lesion และอาการหายไปในวันที่ 6 $\pm$ 2.5 และวันที่ 4.1 $\pm$ 2.3 ตามลำดับ อาการข้างเคียงของยารวมทั้งผลเลือดแสดงการทำงานของตับและเกลือแร่ในเลือดไม่พบความผิดปกติ

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