Fluconazole Administration during Irradiation of Head and Neck Cancer

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Abstrak

Radioterapi merupakan pengobatan terpilih pada kanker kepala - leher terutama nasofaring. Untuk memperoleh hasil pengobatan yang maksimal diperlukan pemberian dosis radiasi yang tinggi. Radiasi pada daerah ini juga akan melibatkan mukosa mulut serta faring, sehingga akan timbul efek samping berupa nyeri telan, hilangnya rasa, dan kekeringan mulut. Di samping itu penurunan daya tahan tubuh lokal juga akan mempermudah tumbuhnya jamur patogen. Penelitian prospektif acak berganda ini bertujuan untuk menilai efektifitas tablet Fluconazole dalam mencegah tumbuhnya jamur kandida dalam rongga mulut yang memperoleh radiasi. Tablet Fluconazole 50 mg diberikan setiap hari selama penyinaran, dan tablet 150 mg satu kali setiap minggu sampai akhir penyinaran. Pada pemeriksaan usap mukosa mulut tampak bahwa kelompok perlakuan mempunyai angka infeksi kandida yang lebih rendah secara bermakna daripada kelompok plasebo. Demikian pula kelompok perlakuan menunjukkan keluhan obyektif yang lebih rendah secara bermakna daripada kelompok plasebo. Tidak terdapat perbedaan dalam cara pemberian pengobatan.

Abstract

Radiotherapy is the treatment of choice in head and neck cancer, especially in the nasopharyngeal region. A high radiation dose is needed to achieve maximal results. Irradiation of this region has been known to affect the mucosal layers of the mouth and pharynx causing side effects such as pain during swallowing, loss of taste sensations and dryness of the mouth. Another problem is a reduced resistance to infection in that area, permitting pathogenic fungal growth. This double-blind randomized prospective study was aimed at evaluating the efficacy of oral Fluconazole in preventing oral moniliasis during the irradiation. Two methods of administration, 50 mg Fluconazole daily and 150 mg weekly, were used from the beginning until the end of radiotherapy. Microscopic examinations of mucosal smears showed that the treated group had a significantly lower infection rate than the placebo group. There was also significantly less objective side-effects in the treated group. There was no significant difference in the method of drug administration.

Keywords *Fluconazole; Antimycotic; Head - Neck Irradiation.*

INTRODUCTION

The incidence of head and neck cancer, especially carcinoma of the nasopharynx, is sufficiently high in Indonesia. In addition to surgery, radiotherapy plays an important role in the treatment of this malignancy, and at present, radiotherapy is the treatment of choice for cancer of the nasopharynx. In surgically inoccessible head and neck tumors, high irradiation dose remains the only method of eradication. However, adequate irradiation is limited by the tolerance of the healthy tissue surrounding the tumor, to irradiation. Irradiation of the oral mucosa can cause mucositis, which in turn will cause pain and difficulty in swallowing and worsen the condition of the patient.[1] The general condition of patients with malignant tumors is usually poor, so any disturbances in nutritional status will further deteriorate the condition of the patients.[2] In addition, there is a local decrease in resistance to infection permitting opportunistic fungal growth in the oral mucosa.[3] These opportunistic fungi can easily become pathogenic if predisposing factors, such as malignancy, diabetes mellitus, poor oral hygiene, prolonged administration of corticosteroids, antibiotics, or chemotherapy, and radiotherapy are present.[3,4]

The aim of the study

To prevent complications in patients with malignancy undergoing irradiation, it is important to break the vicious circle caused by oral candidiasis. One way is preventing fungal growth. If mucositis complicated by

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mycosis can be avoided, irradiation can be continued without stopping and better results can be expected from the radiotherapy.

Fluconazole, one of the newer antimycotic drugs in use since 1982, shows potency in controlling local and systemic fungal infections. Its simple method of administration, broad spectrum activity, and minimal side-effects make this drug superior to other antimycotics.[5]

The aim of this study is to find a drug that is effective in preventing pathogenic fungal growth in the oral mucosa of patients with head and neck cancer undergoing radiotherapy. Methods of administration and dosage will also be evaluated.

MATERIALS AND METHODS

This is a double-blind randomized prospective study on head and neck cancer cases receiving irradiation.

Patients aged 15 - 60 years with good oral hygiene were chosen. Those with dental caries were first sent to a dentist. Patients with diabetes mellitus or receiving corticosteroids and/or antibiotics 2 weeks prior to this study were excluded.

Patients were randomly divided into three groups. Each patient will receive capsules containing either Fluconazole or placebo. Seven capsules were given on the first day and on subsequent control visits, which was held after 5 sessions of irradiation, and continued until the patient had undergone 30 sessions of irradiation.

All medication were packed into identical capsules. Batch A contained 7 capsules of 50 mg Fluconazole, batch B contained 7 capsules of placebo, while batch C contained 1 capsule of 150 mg Fluconazole and 6 capsules of placebo. Each batch of capsules was enough for 1 week.

Subjective and objective side-effects were qualitatively assessed (Table 1 and 2). It was carried out each time the patient received a 10-fold Gy dose of radiation.

Table 1: Subjective side-effects on the oral mucosa

Classification of complaint	Pain in swallowing	Loss of taste	Dryness in mouth
Mild	+	-	-
Moderate	+	+	-
Severe	+	+	+

Note: (+) complaints present
(-) no complaints present

Table 2: Objective side-effects on the oral mucosa

Classification	Clinical Manifestation
Mild	Hyperemia
Moderate	Local mucositis
Severe	Diffuse mucositis

An oral smear examination for Candida was made for each patient. It was taken by cotton swab from the right and left buccal mucosa, hard and soft palates, and tongue. The smear was taken before the initiation and at every 10-fold Gy dose of irradiation until the completion of the treatment. It was considered to be positive if a colony of *Candida albicans* was found, and otherwise negative.

Blood was also examined for Candida, before irradiation and on the third and fourth week of irradiation. Two liver function tests were done, before the initiation and after the completion of treatment.

The chi-square test was used to determine if there was any statistical difference between the treatment groups (receiving 50 mg and 150 mg Fluconazole) and the control group (receiving placebo).

All patients received irradiation in the head and neck area covering at least 60% of the entire oral mucosa and cervical lymph nodes. The total dose given was between 55 - 60 Gy, with a maximal dose of 2 Gy, 5 times a week. An external irradiation apparatus of 4 MeV was employed.

RESULTS

There were 59 patients, between the beginning of June 1990 and the end of June 1991, diagnosed with head and neck cancer and indicated for radiotherapy. They fulfilled the criteria required by the study. There were 37 males and 22 females with ages ranging from 17 - 60 years. Seventeen were later excluded, because of deteriorating general conditions and progressive tumors in 2 patients, one patient died of other causes, one patient used unprescribed antimycotics, and 13 patients stopped treatment for known reasons. Therefore only 42 patients were eligible to be included in the study. They were then divided into 3 groups, 18 in group A, 13 in group B, and 11 in group C. The patient characteristics of each group can be found in Table 3.

Subjective complaints

At 40 and 50 Gy, 77.8% of the patients from group A and 92.3% from group B had moderate and severe complaints. Group C (81.8%) had the same complaints, but at a higher irradiation dose (50 and 60 Gy) (Table 4).

Table 3. The patient characteristics of the three groups

	A (n=18)	B (n=13)	C (n=11)
Sex:			
M	15 (83.3%)	7 (53.8%)	6 (54.5%)
F	3 (16.6%)	6 (46.2%)	5 (45.5%)
Age:			
- 20 yrs	1 (5.5%)	1 (7.7%)	1 (9.1%)
21 - 40 yrs	9 (50 %)	4 (30.8%)	6 (54.5%)
41 - 60 yrs	8 (44.4%)	8 (61.5%)	4 (36.4%)
Preradiation oral smear:			
(+)	14 (77.8%)	10 (76.9%)	8 (72.7%)
(-)	4 (22.2%)	3 (23.1%)	3 (27.3%)
SGOT:			
Normal	16 (88.8%)	11 (84.6%)	11 (100 %)
Elevated	2 (11.2%)	2 (15.4%)	0
SGPT:			
Normal	16 (88.8%)	11 (84.6%)	11 (100 %)
Elevated	2 (11.2%)	2 (15.4%)	0
Nasophary carc:	16 (88.9%)	12 (92.3%)	11 (100 %)
Non-nasophary carc:	2 (11.1%)	1 (7.7%)	0

Note : The differences among the 3 groups are not statistically significant.

Table 4. Subjective complaints

Radiation dose	A (n=18)		B (n=13)		C (n=11)	
	I	II	I	II	I	II
10 Gy	12	6	9	4	9	2
20 Gy	10	8	5	8	6	5
30 Gy	5	13	3	10	3	8
40 Gy	4	14	1	12	4	7
50 Gy	4	14	1	12	2	9
60 Gy	6	12	2	11	2	9
						*
						**

Note : A = Group on Fluconazole 50 mg daily
B = Group on Placebo
C = Group on Fluconazole 150 mg weekly
I = no or mild complaints
II = moderate or severe complaints
* = not statistically significant (P = .1)
(Groups A and C compared to group B)
**= not statistically significant (P = .1)
(Group A compared to group C)

There is no significant difference (P = .1) in subjective complaints, when groups A and C were compared to group B. There is also no significant difference (P = .1) due to the method of drug administration, between groups A and C.

Objective symptoms

The objective symptoms assessed at the completion of irradiation show a significant difference between the Fluconazole group (A and C) and the control group (B) (P < .005). No significant difference is found between the two methods of administration (Table 5).

Table 5. Objective symptoms

Radiation dose	A (n=18)		B (n=13)		C (n=11)	
	I	II	I	II	I	II
10 Gy	16	2	9	4	9	2
20 Gy	8	10	4	9	5	6
30 Gy	9	9	3	10	5	6
40 Gy	9	9	4	9	5	6
50 Gy	11	7	5	8	4	7
60 Gy	12	6	4	9	8	3
						*
						**

Note: A = Group on Fluconazole 50 mg daily
B = Group on Placebo
C = Group on Fluconazole 150 mg weekly
I = no or mild complaints
II = moderate or severe complaints
* = P < .005
(Groups A and C compared to group B)
**= not statistically significant (P = .475)
(Group A compared to group C)

Oral swab preparations

Fourteen patients in group A and 8 in group C showed positive signs for *Candida albicans* before treatment was initiated, that became 11 and 6, respectively, after the completion of treatment. All but one patient in group B had candidiasis at 20 Gy, which remained until the completion of irradiation.

There is a significant difference in positive oral smear preparations between the groups receiving Fluconazole and the group receiving placebo (P < .005) (Table 6).

Table 6. Oral smear preparations

Radiation dose	A (n=18)		B (n=13)		C (n=11)		
	(+)	(-)	(+)	(-)	(+)	(-)	
0 Gy	14	4	10	3	8	3	
10 Gy	14	4	10	3	9	2	
20 Gy	12	6	12	1	7	4	
30 Gy	12	6	12	1	7	4	
40 Gy	10	8	12	1	5	6	
50 Gy	12	6	12	1	8	3	
60 Gy	11	7	12	1	6	5	*
							**

Note: A = Group on Fluconazole 50 mg daily
B = Group on Placebo
C = Group on Fluconazole 150 mg weekly
* = P < .005
(Groups A and C compared to group B)
** = not statistically significant (P < .475)
(Group A compared to group C)

It can be seen from Table 7, that the administration of Fluconazole did not influence the response of cervical lymph nodes to irradiation. Blood specimens showed no systemic mycosis. There were also no abnormal changes in liver function values.

Table 7. Cervical lymph node is response to irradiation

Group	Response	
	(+)	(-)
A	7	0
B	11	0
C	6	1

Note: A = Group on Fluconazole 50 mg daily
B = Group on Placebo
C = Group on Fluconazole 150 mg weekly
Response (+) tumor involution found
Response (-) no tumor involution found

DISCUSSION

Healthy tissue damage due to irradiation in the head and neck region will predispose that area to candidial infection,[6] which could lead to systemic candidiasis and death.[3] Che reported that 47.9% of his patients with negative pre-radiation cultures became positive during irradiation,[6] and Rossie reported that 46.6% of his patients became positive.[3] All their patients had received no antifungal treatment.

In the placebo group, 3 patients who had negative pre-radiation oral smears, became positive after irradiation was completed. In the Fluconazole groups, 4 (57%) out of 7 patients with negative smears prior to irradiation became positive after irradiation. Almost all of those in the placebo group developed positive oral smears (Table 6). There was a significant overall difference (P < .005) between the groups receiving Fluconazole and the group receiving placebo. The treated group, had a significantly lower infection rate than the placebo group. No significant difference was found, however, between groups A and C (P = .475).

There was no significant difference in subjective complaints between the 3 groups. It was therefore assumed, that these complaints were directly caused by the effects of irradiation, and not by the fungal infection itself. Symptomatic treatment with analgesics was found to alleviate the complaints.

Clinical examination of the oral mucosa showed a significant difference (P < .005) between the Fluconazole groups and the placebo group (Table 5). It can therefore be concluded, that Fluconazole is effective in indirectly preventing severe mucositis by suppressing fungal growth.

Since no significant difference was found in the results of oral smears from both Fluconazole groups, the weekly single dose is recommended because it is relatively simpler and cheaper.

Tolerance to Fluconazole was generally good. No clinical symptoms of abnormal liver functions developed during the treatment. Bodey has reported that only 2 out of 115 cases, treated with Fluconazole, developed abnormalities in liver function tests[5]. In this present study, no abnormal changes in the liver function tests developed after treatment with Fluconazole.

No difference was found in the response of cervical lymph nodes to irradiation in all three groups. It was concluded that Fluconazole did not exert any influence on the response of these nodes to irradiation (Table 7).

Even though at present no report is available on the recommended dose of Fluconazole for cancer patients undergoing radiotherapy, Bodey has reported that the use of Fluconazole can inhibit fungal growth in cancer patients[5]. Fluconazole could also be given before initiating radiotherapy so that Candida will be minimal at the onset of irradiation.

CONCLUSIONS

1. The administration of Fluconazole to patients with malignancies of the head and neck was proven effective in reducing the incidence of oral candidiasis when compared to placebo (P < .005).
2. Fluconazole was not found to affect the severity of subjective side-effects on the oral mucosa when compared to placebo.

3. Fluconazole was found to significantly decrease the severity of objective symptoms caused by irradiation on the oral mucosa.
4. Since no significant difference was found between the two methods of Fluconazole administration, the weekly single dose of 150 mg is recommended because it is relatively simpler and cheaper for the patient.
5. Fluconazole did not affect the effectivity of radiation on cervical lymphatic nodes.

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