Effect of Fluconazole as Prophylactic Treatment of Mycotic Mucositis in Patients with Head and Neck Cancers on Radiotherapy

Thesis

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فى العلوم الصيدلية
(الصيدلة الأكلينيكية)

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Contents

List of Abbreviations

Abbreviation	Meaning
2DXRT	Two-dimensional external beam radiotherapy
5-FU	5-fluorouracil
AIDS	Acquired immunodeficiency syndrome
ALT	Serum glutamic-pyruvic transaminase (SGPT).
AST	Serum glutamic-oxaloacetic transaminase (SGOT).
AUC	Area under the plasma concentration-time curve
C max	Peak plasma concentration
CSF	Cerebro-spinal fluid
CT	Computed tomography
CYP450	Cytochrome P450
DNA	Deoxyribonucleic acid
EBRT	External beam radiotherapy
EBV	Epstein-Barr virus
ECOG	Eastern cooperative oncology group performance status
EORTC QLQ-H&N C35	European organization for research and treatment of cancer patients quality of life questionnaire for head and neck cancer module
GI	Gastrointestinal
GY	Gray unit of measuring radiotherapy
HNC	Head and neck cancer
HNSCC's	Head and neck squamous cell carcinomas

Abbreviation	Meaning
IgA	Immunoglobulin A
MANOVA	Mixed design analysis of variance
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OM,MTS	Oral mucositis
OSCC	Oropharyngeal squamous cell carcinomas
PET	Positron emission tomography
QOL	Quality of life
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RT	Radiotherapy
TNF-α	Tumor necrosis factor-alpha
TNM	Tumor- node- metastasis classification for head and neck cancers
TPN	Total parenteral nutrition
ULN	Upper limit of normal
VCA	Anti-viral capsule antigen
WBC	White blood cell count
WHO	World health organization

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Abstract

Background: Oral mucositis is one of the most significant toxicities associated with head and neck radiotherapy. Radiation related mucosal barrier injury allows for microbial colonization and infection, leading, in turn, to amplification of tissue injury.

Aim of work: To evaluate the effect of fluconazole antifungal prophylaxis on the incidence and severity of oral mucositis induced by radiation therapy in patients with head and neck cancer and to determine the impact of this prophylaxis on their nutritional status.

Patients and methods: Eighty patients with head and neck cancer, eligible to receive radiotherapy were categorized into two groups each of 40 patient. Study group received oral fluconazole 100mg/day starting from the sixth irradiation session throughout treatment course as compared to control group with similar radiotherapy characteristics who didn’t receive antifungal prophylaxis. Incidence and severity of oral mucositis and impact of oral mucositis on nutritional status (using malnutrition score) of this patient population were evaluated.

Results: Incidence of clinical oral mucositis was non-significantly lower in patients who received fluconazole

antifungal prophylaxis at the end of radiation therapy (90% vs 100%). However fluconazole prophylaxis showed a very high significant reduction of the severity of mucositis (P=0.00). High incidence of oral mucositis in both groups negatively affected patient's nutritional status, however less significantly in patients who received fluconazole prophylaxis.

Conclusions: Although fluconazole prophylaxis showed no significant effect on the prevention of oral mucositis, it significantly reduced its severity and showed significant improvement in patients' nutritional status.

Keywords: Antifungal prophylaxis; oral/oropharyngeal candidiasis; oral mucositis, radiotherapy; head and neck cancer, malnutrition, clinical pharmacy.

Aim of Work

The main purpose of this study was to assess the efficacy of prophylactic treatment of mycotic mucositis using fluconazole in patients with head and neck cancers on radiotherapy as compared to a control group without fluconazole prophylaxis this aim was achieved by accomplishing the following objectives:

1- To evaluate the effect of fluconazole antifungal prophylaxis on the incidence and severity of oral mucositis induced by radiation therapy
2- To determine the impact of this prophylaxis on their nutritional status.
3- To determine the impact of this prophylactic therapy on the quality of life of this patient population.

Introduction

Head and neck cancer (HNC) refers to a group of biologically similar cancers that start in the upper aero-digestive tract, including lips, oral cavity, nasal cavity, para-nasal sinuses, pharynx, and larynx. 90% of HNC are squamous cell carcinomas, originating from mucosal lining of these regions. Each year there are approximately 560,000 new cases diagnosed and about 300,000 deaths ***(Ferlay et al., 2005).*** In Egypt; studies showed that HNC constitutes about 17-20% of malignancie, most of them have metastatic disease at the time of diagnosis ***(Esra et al.., 2010).***

Treatment modalities of HNC tumor is either by chemotherapy or radiotherapy or chemo-radiation and is decided according to the patient tumor-node-metastasis (TNM) classification; which imply anatomic staging along with classification of cancers of head and neck according to National Comprehensive Cancer Network**.** ***(NCCN ,2012).***

Radiation therapy (RT) causes acute side effects which include mouth sores, dysphagia, taste alteration, pain, and most importantly oral mucositis (OM) due to hypo-salivation secondary to destruction of glandular tissue which encourages candida colonization ***(Trotti et al., 2014)***. Candida species (especially; albicans), are commensal inhabitants of oral cavity in

a large proportion of individuals, which due to mucosal tissue destruction, immunosuppression induced by radiation or disease and imbalance in the oral flora (e.g., secondary to antibiotic therapy) develop into oral fungal infection in this population with a significantly higher incidence rate than general population. In fact oral candidiasis being superimposed on the radiation-induced mucositis would be anticipated to contribute to the severity of mucositis in this patient population ***(Nicolatou et al.,2006).***

Mucositis in patients with HNC receiving radiation therapy is severe enough so that it may require narcotics for pain, it severely interfere with oral nutrition resulting in weight loss and affecting patient quality of life, also it may delay scheduled treatment, compromising therapeutic efficacy ***(Elting et al., 2008).***

Late side effects of RT include xerostomia, fibrosis, hearing loss, retinopathy, optic nerve injury and trismus which is a debilitating side effect due to the fibrosis that occurs in the masticatory muscles when they are in the radiation field and has a negative impact on the quality of life of the patients, as it causes alterations in the facial appearance, difficulty in food intake ***(Trotti et al., 2014).***

The high prevalence of candidiasis during head and neck radiotherapy, and the potential role of candidiasis on the severity of mucositis, has led several authors to consider the need for

antifungal prophylaxis, however, the beneficial effect of fluconazole antifungal prophylaxis on RT interruptions ***(Koc & atkas , 2003)*** and severity of resultant oral mucositis was reported ***(Nicolatou et al; 2006)*** in few studies so far.

Fluconazole is the predominant medication utilized to treat oropharyngeal candidiasis. It has also been used effectively to treat this infection in patients receiving head and neck radiation, as the predominant organism has been C. albicans ***(Sonis et al., 2001)***, which also has been reported to be colonized in the oral cavity of HNC patients receiving RT ***(Jham et al.,2007).*** Fluconazole is also indicated as a prophylactic therapy to decrease the incidence of candidiasis in HNC patients receiving RT ***(Nikhil et al., 2013).***

Head and neck cancer

Definition:

Head and neck cancer refers to a group of biologically similar cancers that start in the upper aero-digestive tract, including the lip, oral cavity (mouth), nasal cavity (inside the nose), para-nasal sinuses, pharynx, and larynx. 90% of head and neck cancers are squamous cell carcinomas (SCCHN), originating from the mucosal lining (epithelium) of these regions ***(Ridge et al.,2011).***

Head and neck cancer is more common in men, with 66% to 95% of cases occurring in men. The incidence by gender varies with anatomic location and has been changing as the number of female smokers has increased. The male-female ratio is currently 3:1 for oral cavity and pharyngeal cancers ***(Ridge et al.,2011).***

Annually, it is estimated that 550,000 cases are diagnosed from oral cavity cancer world-wide, of which 96,720 occur in less developed countries. Mortality rates vary in accord with world regions and are lower in developed countries, despite the higher incidence rates observed in these countries ***(Jemal et al.,2011).***