International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Original Article **CODEN: IJPNL6**

OBSERVATION OF RADIOTHERAPY RELATED ACUTE SIDE EFFECTS´ OCCURRENCE AND MANAGEMENT IN CANCER PATIENTS

Anmar Al-taie[1,*], Aygül Köseoğlu[2], Fikret V.Izzettin[1], Songül Tezcan[3], Tayf Alqozbakr[1], Atin Aksu[2]

[1]Clinical Pharmacy Department, Faculty of Pharmacy, Marmara University, Istanbul, Turkey
[2]Oncology Center, Dr. Lütfi Kırdar Kartal Teaching and Researching Hospital, Istanbul, Turkey
[3]Oncology Center, Pendik-Marmara Teaching and Researching Hospital, Istanbul, Turkey

***Corresponding author e-mail:** altaii1978@gmail.com

Received on: 23-01-2016; Revised on: 14-03-2016; Accepted on: 21-03-2016

ABSTRACT

The aim of this study was to observe the most common radiotherapy related acute side effects and the effective modulating treatment of these side effects in cancer patients undergoing radiotherapy. A randomized retrospective study was carried out on 79 cancer patients admitted at the radiology unit. Radiotherapy related acute side effects and specific therapies were documented and assessed. The major acute side effect was diarrhea 82, 3%. While, 48, 5% of mucositis, and 62, 5% of skin reactions were managed by benzydamine mouth wash and dexpanthenol ointment respectively. A significant correlation observed between gender and skin reactions (males 55, 6%, females 83, 3%); previous chemotherapy with appetite loss (25%) and with metallic taste (60%). Concerning radiation-applied area, mucositis and stomatitis were significantly correlated with both thorax (39, 2%, 33, 1%), and head (31, 4%, 33, 1%) areas respectively. The occurrence of radiation related acute side effects indicates both the essentially for follow-up and the potential role of clinical pharmacist for better outcomes.

Keywords: Radiotherapy. Acute side effects. Diarrhea. Medications

INTRODUCTION

Radiotherapy is an integral part of cancer therapy since ten decades of its first introduction to medical applications. It is considered a choice of treatment for almost one-half of patients suffering from cancer nowadays [1]. It is a useful, time-efficient, and cost-effective intervention that is crucial for the appropriate delivery of palliative oncology care [2].

The medical benefit of radiotherapy in cancer treatment depends upon the interaction between sufficient radioactive dose and tissues' molecules. This will introduce enough energy to break down the chemical bonds between molecules, which in turn produces ions and free radicals. The net result is oxidative DNA and other cell contents damage critical for the viability and/or replication of cells. [3].

In US hospitalized patients, the incidence of serious adverse drug reactions (ADRs) was 6,7 %, and of fatal ADRs 0.32%, making ADRs be the fourth and the sixth cause of death [4]. Factors increase the risk of radiation toxicity are radiation dose, surgical operations, combined chemotherapy administration [5-7], and comorbidities like diabetes mellitus and autoimmune diseases such as lupus [8-10]. One of the main purposes of clinical oncology practice is monitoring of symptoms and other ADRs revealed by the patients during treatment [11]. Radiotherapy–induced toxicity is classified as either early or late. The first type (acute adverse effects) is observed during treatment or just after its completion, and

usually end up through four to six weeks. The second type (late adverse effects) is categorized as permanent and observed within months to years after radiotherapy completion. The disastrous effect of radiotherapy treatment is secondary malignancies, usually manifesting 10 to 15 years following treatment. Those malignancies occur in proportional to radiation duration and dose received and are inversely proportional to the age at which the radiation was received [12]. This study aimed to evaluate radiotherapy related acute side effects occurrence and to assess and follow up the effective treatment modalities of those side effects in cancer patients with different types of cancers undergoing radiotherapy.

METHODS

This was a randomized retrospective study carried out on (79) cancer patients with different types of cancers admitted to the Oncology Unit of Dr. Lütfi Kırdar Kartal Teaching and Researching Hospital in Istanbul, Turkey. The study participants were recruited between January and June 2015. Approval of this study was granted by the Ethical Committee of the Institute of Health of Marmara University. Patients' demographic data were collected according to the patients' data sheets. Radiotherapy-related acute side effects and specific therapy were documented and assessed. These acute side effects were reported depending on those based on American Cancer Society [13]. Inclusion criteria include patients over the age of 18 years, patients who diagnosed with cancer candidate initially for receiving radiotherapy. Exclusion criteria include patients with neoadjuvant chemotherapy and files with insufficient knowledge of the data.

The SPSS version 15 was used for statistical analysis. Socio-demographic parameters were analyzed as descriptive analysis. Correlations were analyzed using Chi-Square test. The level of statistical significance was expressed as $p<0.05$ using a confidence interval of 95%.

RESULTS

The characteristics of the study population are presented in Table (1). The mean age of the patients was 58,4±14,8 years with a range of 60-92 years. Most of the participants were males (68,4%), married (94,9%), and had a secondary level of education (49,36%). The majority of the participants were nonsmokers (68,4%), non-alcohol drinkers (97,5%) and had no previous medical history (71,9%).

Lung carcinoma as presented in Table (2) was the most common type of cancer (29,1%), followed by breast cancer (17,7%) and colorectal carcinoma (17,7%). The majority of the study participants had stage IV carcinoma (83,54%) with no previous history of radiotherapy (96,2 %). Most of the patients had received previous chemotherapy regimens (51,3%). The thorax was the most radiation-applied area (40,5 %), while head and pelvis areas constituted (27,8%), (18,9%) respectively.

Table (3) demonstrated some of the acute side effects related to radiotherapy. The majority of cancer patients (n=59) was suffering from diarrhea, which constituted 82,3%, followed by loss of appetite comprised 74,7%, mucositis 64,4%, fatigue 63,3%, skin reactions 63,3%, metallic taste 57%, difficulty in swallowing 54,4%, nausea and vomiting 49,4%, and dry mouth 15,2%.

The management of acute side effects is presented in Table (4), where the only cases with severe and intolerable side effects were managed. It was realized that 18,2% ($p<0.001$) of loss of appetite was treated by the administration of enteral nutrition, 14,2% ($p<0.001$) of diarrhea was treated with diphenoxylate tablet, 48,5% ($p<0.001$) of mucositis was managed by benzydamine mouth wash, 62,5% ($p<0.05$) of skin reactions was treated by dexpanthenol ointment, and 34,4% ($p<0.05$) of nausea and vomiting were treated with granisetron tablet.

Table (5) presented a correlation between certain demographic data of the patients and radiotherapy related acute side effects. There was a significant correlation ($p<0.05$) between gender and skin reactions (males 55,6%, females 83,3%), previous chemotherapy and loss of appetite (25%), previous chemotherapy and metallic taste (60%). Concerning radiation-applied area; there was a significant correlation ($p<0.001$) involving mucositis with both thorax (39,2%) and head (33,1%), stomatitis also with both thorax (31,4%) and head (33,1%) applied areas. Likewise, proctitis was significantly ($p<0.01$) correlated with pelvis applied area (100%). Stage IV carcinoma and alcohol drinking were significantly ($p<0.05$) associated with mucositis (89,8 %), and (50%) respectively. Regarding cigarette smoking, many acute side effects had significant correlation including mucositis (39,2%), dry mouth (46,5%), swallowing difficulty (46,7%) and metallic taste (51,3%).

DISCUSSION

The goal of radiotherapy is to provide maximum benefit to the patients with minimal side effects [14]. The radiation dose that can be given clinically is usually limited by the occurrence and severity of side-effects [15]. In this study, we revealed a higher occurrence of diarrhea (82,3%). The association between diarrhea and radiation therapy is well-documented in the literature, the incidence is higher with concomitant chemotherapy and occurs during or immediately after pelvic or abdominal radiotherapy as the small intestine has the highest cell turnover rate, and bacterial contamination of the small bowel. The results of this study were consistent with the findings of A. Danielsson et al, whose observed a higher frequency of chronic diarrhea in patients previously treated with radiation for gynecological cancer [16-19]. In our study, patients suffered from diarrhea were treated with diphenoxylate tablet. In the literature, management of diarrhea is achieved both by non- pharmacological therapy and the use of oral opiates such as loperamide or diphenoxylate which are effective in mild symptoms. It was reported in some randomized trials that the use of subcutaneous octreotide (100-150 µg tid) is more effective than high dose oral diphenoxylate in grade 2 diarrhea [20]. The second higher observed acute adverse effect was loss of appetite (74,7%) with a significant correlation ($p<0.05$) with previous chemotherapy (25%). This high occurrence may be related to some cancer types (ovarian, pancreatic, and stomach cancers), advanced cancer stage, surgery, chemotherapy, and some complaints like nausea and vomiting, mucositis, fatigue and depression [21].

Our data showed that fatigue comprised (63,3%) among the most common acute side effects in this study. It is the most distressing acute side effect characterised by extreme tiredness and decreased physical and mental capacity, and affects treatment adherence [22]. Acute fatigue due to radiotherapy occurs in 80% of patients while chronic fatigue occurs in 30% of radiotherapy-treated patients. This may be attributed to gender (females), active cancer, and radiotherapy applied area as brain, head and neck, breast, lung, and pelvis [23,24]. Therefore, all patients with cancer should be assessed for fatigue at regular intervals. A dose-dependent radiation dermatitis is another common issue of radiotherapy and complicated by local infection as a potential progression of this side effect. It is observed more in patients who are obese, have a high body mass index, undergo treatment with concurrent chemotherapy notably doxorubicin, fluorouracil, and paclitaxel [25-27]. Our results found that skin reaction constituted about (63,3%), and manifested more in females (83,3%) than in males (55,6%) as erythema, itchy, peeling skin, and ulceration. Most clinical reports stated that the majority of these complications arise within 1–4 weeks of radiotherapy, persist for the duration of therapy, and may require 2–4 weeks for healing after therapy completion. In this study, we observed that most patients suffering from dermatitis were treating with dexpanthenol ointment and this coincides with other reports that topical steroids and dexpanthenol-containing emollients are most effective for the management of radiation dermatitis [28].

Early nutritional intervention in cancer patients is important to maintain an acceptable weight, prevent or treat protein-calorie and micronutrient deficiencies. These interventions can result in positive outcomes leading to better tolerance of treatment and its side effects, more rapid healing and recovery, reduced risk of infection during treatment, enhanced overall survival. [29-31]. The management of patients' appetite loss in this study was performed by the administration of enteral nutrition supplementation which is preferable to parenteral nutrition in most cancer patients [32].

The findings of our study also showed the occurrence of nausea and vomiting as another common acute side effect and represented about (49,4%). This high percentage might be related to radiotherapy-related factors such the administered dose and patient-related factors such as (gender, age, health status), recent chemotherapy, psychological state, and tumor stage. [33]. Patients in this study were treated with a combination of granisetron and pantoprazole tablets. Generally, the management of radiation-induced emesis is achieved by the application of both non-pharmacological and pharmacological strategies through the administration of 5-hydroxytryptamine3 (5-HT3) receptor antagonists, such as ondansetron or granisetron plus dexamethasone to provide additional benefit for prophylaxis [34,35].

Radiotherapy-related mucosal damage in our study was observed as mucositis (64,4%), metallic taste (57%), difficulty in swallowing (54,4%) and dry mouth (15,2%) arising during the application of radiotherapy for head and neck. Radiotherapy severely affects any mucosal surface exposed, from lips to cervical esophagus. However, chemotherapy-induced stomatitis is typically less severe and of shorter duration (3-12 days) than that associated with radiotherapy (3-12 weeks). Furthermore, the use of concurrent chemotherapy with radiotherapy shortens the onset, exacerbates the severity, and prolongs the

duration of mucositis. Mucosal damage occurs more in relation to certain risk factors, including age, gender, genetic predisposition, oral health, tobacco smoking, alcohol, co-morbidities, head and neck mucosa irradiated, rate of radiation dose accumulation and schedules, and concurrent chemotherapy [36,37]. These risk factors explain the significant correlation ($p<0.001$) between mucositis with radiation-applied area involving both of thorax (39,2%) and head (31,4%) applied areas respectively as well as the significant relationship between cigarette smoking and the occurrence of many acute side effects, including mucositis (39,2%), dry mouth (46,5%), swallowing difficulty (46,7%) and metallic taste (51,3%) as presented in Table (5). Importantly, treatment of mucositis can be performed by the basic oral care as a standard practice to prevent infections and potentially help alleviate mucosal symptoms. Treatment also involves the application of viscous lidocaine [38], amifostine [39], systemic and topical formulations of antimicrobial agents as polymyxin B, tobramycin, and amphotericin B pastilles [40], and nonsteroidal anti-inflammatory agents such as topical benzydamine. In our study, patients suffering from this acute side effect were treating with topical benzydamine because of its anti-inflammatory, analgesic/ anesthetic, and antimicrobial properties [41].

CONCLUSIN

The results of this study clearly revealed that the occurrence of radiation-induced acute side effects places the essentiality for more evaluation and follow- up. However, prospective studies are required to further demonstrate the important role of the clinical pharmacist for better outcomes in cancer patients treated with radiotherapy.

Acknowledgment

Great thanks, deep appreciation to Ass. Prof. Dr. Mesut Sencar and Dr. Betul Okyan (Department of Clinical Pharmacy-College of Pharmacy-Marmara University) for guidance and support.

Funding: The authors did not receive any financial support

Conflicts of Interest: No conflicts of interest have been declared.

Table 1: Patients´ demographic data

Parameter	N= no. of Patients	(%)
Gender		
Male	54	68,4
Female	25	31,6
Age (year)	mean=58,4±14,8 (range=60-92)	
Education		
Primary	18	22,78
Secondary	39	49,36
High School	22	27,84
University	0	0
Civil State		
Single	4	5,1
Married	75	94,9
Cigarrate Smoking		
Yes	25	31,6
No	54	68,4
Alcohol Drinking		
Yes	2	2,5
No	77	97,5
Medical History		
No	60	71,9
DM	1	3,8
COPD	13	16,5
HT	1	2,5
Chronic Renal Failure	1	1,3
CHF	1	1,3
Bronchititis	1	1,3
Dsypne	1	1,3

Table 2: Types and characteristics of cancer

Parameter	No. of Patients (79)	(%)
Cancer Type		
Lung CA	23	29,1
Breast CA	14	17,7
Colorectal CA	10	12,7
Skin CA	9	11,4
Prostate	3	3,8
Pelvis	3	3,8
Others	13	16,45
Cancer Stage		
Stage I	1	1,26
Stage III	12	15,18
Stage IV	66	83,54
Radiation-applied area		
Thorax	32	40,5
Head	22	27,8
Pelvis	15	18,9
Vertebra	6	7,59
Abdomen	1	1,26
All Body	3	3,7
Previous Chemotherapy		
Yes	40	51,3
No	38	48,7
Previous Radiotherapy		
Yes	3	3,8
No	76	96,2

Table 3: Occurrence of radiotherapy related acute side effects

Side Effect	No. of Patients (79)	(%)
Fatigue	50	63,3
Headache	31	39,2
Hair Loss	12	15,2
Loss of Appetite	59	74,7
Bleeding	1	1,3
Skin Reactions	50	63,3
Mucositis	51	64,6
Stomatitis	3	3,8
Dry Mouth	12	15,2
Swallowing difficulty	43	54,4
Metalic Taste	45	57,0
Nusea and Vomiting	39	49,4
Diarrhea	65	82,3
Proctitis	1	5,1

Table 4: Management of radiotherapy related acute side effects

Side Effect	Management	No. of suffering patients	No. of treating patients (%)		p-value
Loss of appetite	Enteral nutrition	59	12	18,2	*p<0.001*
Skin reactions	Dexpanthenol	50	40	62,5	*p<0.05*
Mucositis	Benzydamine	51	31	48,5	*p<0.001*
	Amoxycillin+ Clavulanic acid		1	1,6	
Metallic taste	Benzydamine	45	1	1,6	*p<0.001*
Nausea and Vomiting	Granisetron(alone)	39	22	34,4	*p<0.05*
	Pantoprazole (alone)		15	23,4	
	Granisetron+ Pantoprazole	65	14	21,9	*p<0.001*
Diarrhea	Diphenoxylate		9	14,2	

** P<0.05 siginificance at 95% Confidence Interval*

Table 5: Correlation of radiotherapy related acute side effects with patients´ demographic data

Parameter	Side Effects	No. of Patients	%	p-value
Gender	Skin reactions			
Male		30	55,6	*p<0.05*
Female		20	83,3	
Previous Chemotherapy	Loss of Appetite			
Yes		10	25	*p<0.05*
No		1	2,6	
	Metallic Taste			
		24	60	*p<0.05*
		14	36,8	
Previous Radiotherapy	Dry Mouth			
Yes		0	0	*p<0.05*
No		43	56,6	
Radiation-applied area	Mucositis			
Thorax		20	39,2	
Head		16	31,4	*p<0.05*
Pelvis		8	15,7	
Vertebra		6	11,8	
Abdomen		1	2	
All Body		0	0	
	Stomatitis			
Thorax		1	33,3	
Head		1	33,3	
Pelvis		0	0	
Vertebra		0	0	*p<0.001*
Abdomen		1	33,3	

All Body		0	0	
Pelvis	Proctitis	4	100	*p<0.01*
Cancer Stage	Mucositis			*p<0.05*
Stage 1		1	2	
Stage 3		4	8,2	
Stage 4		44	89,8	
Alcohol	Stomatitis			
Yes		1	50	*p<0.001*
No		2	2,6	
Smoking	Mucositis			
Yes		20	39,2	*p<0.05*
No		31	60,8	
	Dry mouth			
		21	46,5	*p<0.01*
		24	53,5	
	Swallowing difficulty			
		21	46,7	*p<0.01*
		24	53,3	
	Metallic Taste			
		20	51,3	*p<0.0001*
		19	48,7	
Civil State	Skin Reactions			
Single		0	0	*p<0.01*
Married		50	67,6	
	Stomatitis			
		1	25	*p<0.01*
		2	2,7	
Medical History	Dry mouth			
Yes		15	78.9	*p<0.05*
No		28	46,7	
	Swallowing difficulty			
		15	78,9	*p<0.05*
		30	50	

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