Research Article

Evaluation of Cisplatin Induced Toxicity in Head and Neck Cancer During Concurrent Chemo Radiotherapy and Radiotherapy Alone - A Prospective Observational Study

Dr. Naga Subrahmanyam S[1]*, Dr. Tagoore Vijaya Lakshmi D[1], Dr.G.V.Naga Raju[1], Dr.G.V.Pavan Kumar[2]

[1*]. M.Pharm, Pharm D, Assistant Professor, Department of Pharmacy Practice, Koringa College of Pharmacy, Koringa, Kakinada, A.P, India.

[2]. Associate Professor, Department of medicinal Chemistry Koringa College of Pharmacy, Koringa, Kakinada, A.P, India.

***Corresponding author's E-mail:** subrahmanyamasatupati@gmail.com

Received: 27-08-2018; **Revised:** 28-09-2018; **Accepted:** 10-10-2018.

ABSTRACT

Cisplatin is widely used as radio sensitizer in head and neck cancer (HNC). We conducted this prospective study to evaluate cisplatin induced toxicity as once-weekly regimen during concurrent chemo radiotherapy (CCRT) and radiation induced toxicity alone in HNC to optimize its administration. From December 2016 and May 2017, a data of all eligible patients treated by chemo radiation regimens containing a low dose of cisplatin were collected at the Department of radiotherapy in Government General Hospital, Guntur, Andhra Pradesh. Cisplatin was used weekly at 40 mg/m2 with adequate hydration and premedication in all patients. A complete blood count and renal function tests were done prior to each cycle of chemotherapy to evaluate toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). A total of 74 patients were eligible for the analysis in that 20 members on CCRT and 54 on radiation therapy alone. Mean age, PS, initial weight, enteral nutrition, cisplatin mean dose, use of oral Ondansetron and baseline serum tests did not differ significantly among the types of malignancy. However, weight loss was significantly noted among HNC group compared to radiation therapy patients. Toxicity was observed only in 16 (85%) patients after the 4th week of treatment especially among HNC group. The neutropenia and thrombocytopenia were significantly greater for patients of HNC. However, we did not observe any renal toxicity in CCRT group. Where as in radiation group the adverse drug reaction most commonly occurred was dermatitis 50 (92%), mucositis 52 (96%), xerostomia 53 (98%). Our data have revealed that individuals with HNC were at a significantly higher risk for cisplatin induced toxicity during CCRT and suggest that the once-weekly smaller dose of cisplatin regimen and conventional prophylactic procedures of administration might be effective for protection against the renal toxicity of cisplatin.

Keywords: Cisplatin toxicity; Concurrent chemoradiotherapy; Head and neck cancer.

INTRODUCTION

Head and neck cancers usually begin in the squamous cells that line the moist, mucosal surfaces inside the head and neck (for example, inside the mouth, the nose, and the throat). These squamous cell cancers are often referred to as squamous cell carcinomas of the head and neck).[1-3]

Aim and Objectives

Aim

- To evaluate toxicity profile of cisplatin with radiotherapy in head and neck cancer.

Objective

- To measure the quality of life and pharmaceutical care and toxicity profile of cisplatin with radiotherapy in head and neck cancer.

Plan of work

The work is planned to carry out as following:

- To include head and neck cancer patients.
- To design a patient data collection form and standard questionnaire H& N 35.
- To collect all the data required for the study from radiotherapy out -patient and in patient department.
- To analyse the data and provide the feedback of results to the physician (prescriber) and submit the safety data of cisplatin and adverse reactions of the drug
- To counsel the patients regarding the usage and effects of medications.

METHODOLOGY

Study site

A Non experimental prospective observational study was conducted on head and neck cancer patients in radiotherapy department, GOVERNMENT GENERAL HOSPITAL, Guntur, Andhra Pradesh.

Study duration

The study was carried out between December 2016 and May 2017 at the Department of radiotherapy in Government General Hospital, Guntur, Andhra Pradesh. During that time, a clinical and biological data of all patients treated by chemoradiation regimens containing a low dose (40 mg/m^2) of cisplatin were collected after obtaining oral consent from each patient. Patients were eligible if they had a correct laboratory tests and had an

Eastern Cooperative Oncology Group performance status (PS) of 0 or 1.

Inclusion criteria

- Patient who suffered from various types of head and neck cancer.
- Consented males and females above age 18 years.
- Patient who is concurrent chemoradiotherapy with cisplatin for any cancer of head and neck cancer.

Exclusion criteria

- Patients who suffered from cancers, other than head and neck cancers.
- Patients with head and neck cancer below 18 years are excluded.
- Patients who have recurrent and remission of head and neck cancers.
- Female patients with pregnancy are excluded.
- Patients with severe heart disease and lung disease are excluded.

Study design

A Non Experimental prospective observational study.

Cisplatin administration

Cisplatin-based chemoradiation was used in our department weekly at 40 mg/m^2 with a maximum of 70mg per cycle. It was administered in 500 mL of 0.9% normal saline over 30 minute. All patients were pre hydrated with 1L of 0.9% normal saline and post hydrated with 1L of 0.9% normal saline, which was administered over 1h. Oral hydration with 2 - 3 L the night before and the day after treatment was recommended for all patients. Antiemetic prophylaxis with 5-HT3 serotonin receptor antagonists (Ondansetron) plus dexamethasone was administered 15 min before the onset of chemotherapy in all cases. A supplemented oral antiemetic treatment during the 3 days was prescribed for all patients.

Toxicity evaluation

Complete blood count and renal function tests were done prior to each cycle of chemotherapy.

Nephrotoxicity indicating the postponement of the treatment was defined as a creatinine clearance (CC) less than 50ml/min according to the Cockcroft-Gault equation or 50 ml/min/1.73 m^2 by MDRD eGFR for patients over 65 years. Nephrotoxicity was also defined as an increase in the serum creatinine concentration of grade 2 or higher, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0).

According to the same criteria, anemia was noted grade 2 when the hemoglobin (Hb) is less than 10.0 - 8.0 g/dl and grade 3 indicating a transfusion; when Hb is lower than 8.0 - 6.5 g/dl. Neutropenia was noted grade 2 when the neutrophil rate is <1500-1000/mm^3, grade 3 if <1000-500/mm^3 and grade 4 if < 500/mm^3. Thrombocytopenia was noted grade 1 when the platelet count is <150,000-75,000/mm^3 and grade 2 if <75,000-50,000/mm^3, whereas, we practically postponed the treatment when the platelet count is less than 100,000/mm^3. Finally, vomiting was noted grade 1 when the patients report between 1 to 2 episodes (separated by 5 minutes) in 24 hours and grade 2 between 3 to 5 episodes (separated by 5 minutes) in 24 hours, while an increase of 4-6 stools per day over baseline was noted grade 2 diarrhea.

Statistical analysis

Qualitative variables were presented as number and percentages.

RESULTS

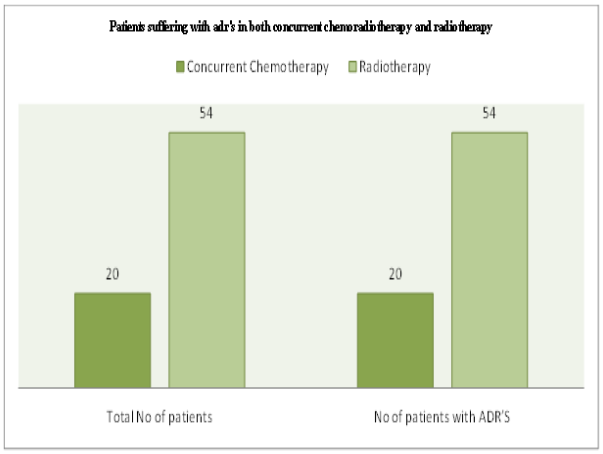

Figure 1: Categorization based on both chemotherapy and radiotherapy induced ADR'S

Table 1: categorization based on both chemotherapy and radiotherapy induced ADR'S

Type of treatment	Total No of patients	No of patients with ADR'S
Concurrent Chemotherapy	20	20
Radiotherapy	54	54

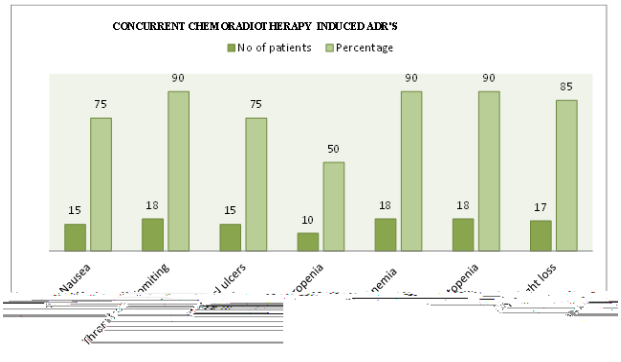

Figure 2: Categorization based on chemotherapy induced ADR'S

Table 2: categorization based on chemotherapy induced ADR'S

Type of reaction	No of patients	Percentage
Nausea	8	40
Vomiting	8	40
Oral ulcers	15	75
Neutropenia	10	50
Anemia	18	90
Thrombocytopenia	18	90
Weight loss	17	85

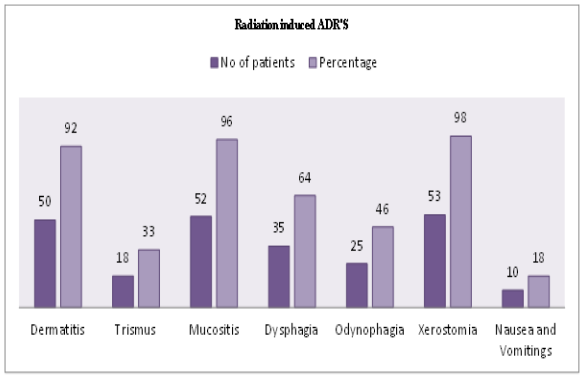

Figure 3: Categorization based radiation induced ADR'S

Table 3: Categorization based radiation induced ADR'S

Type of reaction	No of patients	Percentage
Dermatitis	50	92
Trismus	18	33
Mucositis	52	96
Dysphagia	35	64
Odynophagia	25	46
Xerostomia	53	98
Nausea and Vomitings	10	18

DISCUSSION

Head and neck cancers usually begin in the squamous cells that line the moist, mucosal surfaces inside the head and neck (for example, inside the mouth, the nose, and the throat). These squamous cell cancers are often referred to as squamous cell carcinomas of the head and neck).

During a 6 months study, 74 patients who were diagnosed with head and neck cancer and who met the inclusion criteria were taken as study subjects. The prevalence of ADRs varies from subject to subject because of the inter subject variability towards the drugs administered

Subjects were recruited based on criteria that were set in protocol. Subjects for concurrent chemo radiotherapy were selected based on performance status of the patient that assess the capability of the patient to withstand the chemotherapy drugs and their ADR's. ECOG (Eastern Cooperative Oncology Group) performance status scale, which provides with the grading and relative description is used in this study.

As similar to the study which is conducted by Maghous .A,et.,(2017)– This is a prospective study to evaluate cisplatin induced toxicity as once-weekly regimen in HNC during concurrent chemoradiotherapy (CCRT) to optimize its administration. From 01 January 2015 to 11 May 2015 study was conducted, and of all eligible patients treated by chemoradiation regimens containing a low dose of cisplatin were collected at the Department of radiotherapy in National Institute of Oncology in Morocco. Cisplatin was used weekly at 40 mg/m2 with adequate hydration and premedication in all patients. A complete blood count and renal function tests were done prior to each cycle of chemotherapy to evaluate toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). A total of 96 patients were eligible for the analysis. Mean age, PS, initial weight, enteral nutrition, cisplatin mean dose, use of oral Ondansetron and baseline serum tests did not differ significantly. However, weight loss was significantly noted among HNC group compared with 6.06 ± 2.92 kg respectively. Toxicity was observed only in 16 (20%) patients after the 4th week of treatment especially among HNC group. The neutropenia and thrombocytopenia were significantly greater for patients of HNC. In multivariated analysis, only a subtype of HNC (OR, 1233; 95% CI, 16-95 103; P=0.001) and grade 2 emetogenicity (OR, 34.8; 95% CI, 2.1-583; P=0.014) were significantly associated with an increased risk for cisplatin toxicity. Whereas, less than 4 weekly cisplatin treatment (OR, 0.4; 95% CI, 0.1-0.9; P=0.046) was associated with a significantly reduced risk. The data have revealed that individuals with HNC were at a significantly higher risk for cisplatin induced toxicity during CCRT and suggest that the once-weekly smaller dose of cisplatin regimen and conventional prophylactic procedures of administration might be effective for protection against the renal toxicity of cisplatin[5-9].

In the present study the patients who are under concurrent chemoradiotherapy of all eligible patients treated by chemoradiation regimens; cisplatin was used weekly at 50 mg with adequate hydration and premedication in all patients for six cycles. A complete blood count and renal function tests were done prior to each cycle of chemotherapy to evaluate toxicity under the guidance of physician. A total of 20 patients were eligible for the analysis. However, weight loss was significantly noted among 17 out of 20 HNC group compared with percentage of 85%. Toxicity was observed patients after the 3rd week of treatment among HNC group. The neutropenia and only in 10 (50%) thrombocytopenia only in 18 (90%) were significantly greater for patients of HNC and grade 1 emetogenicity only in 8(40)were significantly associated with an increased risk for cisplatin toxicity. Patient whose performance status is very poor then prefer the regimen cisplatin only for four weeks

.Whereas, less than 4 weekly cisplatin treatments was associated with a significantly reduced risk. The data have revealed that individuals with HNC were at a significantly higher risk for cisplatin induced toxicity during CCRT and conventional prophylactic procedures of administration might be effective for protection against the renal toxicity of cisplatin.

Out of 74 subjects 16 subjects were observed toxicity with cisplatin at the dose of 40 mg/m^2 after 4th week of therapy in the above said study and in the present study we observed the toxicity with cisplatin at the dose of 50 mg after 3rd week of therapy. We have taken preventive measures to prevent the oral infections like candidiasis by prescribing medication flucanazole and to maintain dental hygiene mouth washers are made to be used by patients. Due to high incidence of neutropenia and thrombocytopenia antibiotics like ciprofloxacin and metronidazole are administered who are suffering with fever and systemic infections.

Apart from above mentioned study we have noticed oral ulcers in 15 (75%) and anemia in 18 (90%) of total 20 members .Even we considered the adverse reactions occurred during radiation alone. Besides concurrent chemo radiotherapy there are 54 patients under the radiation. Subjects after receiving second week of radiation had encountered with different types of toxic reactions such as Dermatitis in 50(92%), Trismus in 18(33%), Mucositis in 52(96%), Dysphasia in 35(64%), Odynophagia in 25(46%), Xerostomia in 53(98%) and Nausea and Vomiting in 10 (18%) of total 54 patients.

Hence a supportive therapy for symptomatic relief was suggested to the patients where by the physician accepted the suggestions of the clinical pharmacist prescribed the supportive medications for ADR's which helped the patient to cope up with them. This had a major hand on improving the quality of life of the patient and progression in the performance status. Apart from this, we, clinical pharmacists counseled the patients regarding disease, medication and diet that could taken viz., buttermilk, porridge, malts, non-irritant jucies like cane sugar, banana, etc. they helped the patient to gain physical strength and cooperate with the treatment. This made patient to recover faster.

CONCLUSION

Our study concluded that the incidence of ADRs associated with drug toxicities in concurrent chemotherapy patients and patients on radiotherapy alone. Regular follow up and provision of pharmaceutical care is a key factor to manage the ADRs and complications. By creating awareness and providing pharmaceutical care on disease and usage of drugs, medication adherence and quality of life of the patient was improved. The need of provision of pharmaceutical care is necessary to improve quality of life of both concurrent chemotherapy patients and patients on radiotherapy alone to manage all the possible ADRs and complications associated with the drugs and disease progression. Prescription errors, administration errors, possible ADRs were avoided due to strict follow-up by the pharmacist. Along with physicians, nurses and clinical pharmacists has a great role in management of ADRs and improvement of patient's quality of life.

REFERENCES

1. Boeckman HJ,Trego KS, Turchi JJ, Cisplatin sensitizes cancer cells to ionizing radiation via inhibition of nonhomologous end joining. Mol Cancer Res, 3, 2005, 277-285.
2. Maghous A, Marnouche E, Loughlimi H, Rais F, Benhmidou N, et al. Evaluation of Cisplatin Induced Toxicity in Head and Neck Cancer and Cervical Cancer During Concurrent Chemoradiotherapy. Experience of National Institute of Oncology in Morocco. J Cancer Sci Ther, 9, 2017, 314-318. doi:10.4172/1948-5956.1000434
3. Marcu L,Bezak E, Olver I, Scheduling cisplatin and radiotherapy in the treatment of squamous cell carcinomas of the head and neck: A modelling approach. Phys Med Biol 51, 2006, 3625-3637.
4. Marcu L,Van Doorn T, Olver I Cisplatin and radiotherapy in the treatment of locally advanced head and neck cancer-a review of their cooperation. ActaOncol 42, 2003, 315-325.
5. Pabla N, Dong Z Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. Kidney Int 73, 2008, 994-1007.
6. Pignon JP, Le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17, 346 patients. RadiotherOncol 92, 2009, 4-14.
7. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, et al. () Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340, 1999, 1144-1153.
8. Rosenberg B, VanCamp L, Trosko JE, Mansour VH Platinum compounds: A new class of potent antitumour agents. Nature, 222, 1969, 385-386.
9. Rozencweig M, Von Hoff DD, Slavik M, Muggia FM Cis-diamminedichloroplatinum (II). A new anticancer drug. Ann Intern Med, 86, 1977, 803-812.

Source of Support: Nil, **Conflict of Interest:** None.