



Low dose weekly Carboplatin (AUC: 2) with radiation is an acceptable alternative for weekly cisplatin with radiation in the treatment of advanced head neck carcinoma: An observational study

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Abstract

Introduction: In general head and neck cancer may be treated with single modality of treatment for early-stage disease but may require multimodality treatment protocol for advanced disease. concurrent chemoradiation is the current standard protocol for patients with locally advanced squamous cell carcinoma of head neck. Carcinoma of head and neck is common clinical entity approximately 4.8% of the total new- cancer cases. In Bangladesh, according to cancer Registry Report NICRH (20015-2017), approximately 2901(10.6%) patients are registered with head and neck cancer.

Study Design and Objective: This prospective observational study is to compare the treatment response and acute toxicities with the treatment of low dose weekly Carboplatin(AUC:2) with radiation versus weekly Cisplatin with radiation therapy for histologically proven advanced squamous cell carcinoma of head neck.

Methods: All the patients were divided in two groups. Arm-A 30 number patients received injection Carboplatin (AUC:2), i/v 30 minutes infusion weekly for 6 weeks and Arm- B 30 number patients received injection Cisplatin 30mg/m², i/v 2 hrs. infusion weekly for 6 weeks. All patients received 66 Gray (Gy) radiation at the rate of 2Gy/day 5# in a week for 6.5 weeks.

Results: In this study ninety percent (90%) patients were smoker. The most common presenting features were cervical lymphadenopathy (Arm A 100% vs. Arm B 100%), pain (Arm A 73.33% vs. Arm B 66.67%), sore throat (Arm A 36.67% vs. Arm B 36.66%), hoarseness of voice (Arm A 36.67% vs. Arm B 36.66%) etc. Complete response of patients treated with concurrent chemoradiation with inj. Carboplatin was 63.33% in comparison to 53.33% complete response achieved in patients treated with concurrent chemoradiation with inj. Cisplatin. This difference was statistically not much more significant. Common toxicities related to treatment were mucositis, skin reaction, vomiting, nausea, weight loss, anemia, leucopenia, thrombocytopenia and diarrhea. The toxicities in Arm-A were more than that of Arm-B, but were manageable.

Conclusion: In this study the clinical response and toxicities produced by weekly low dose carboplatin with radiation in locally advanced squamous cell carcinoma of head and neck cancer were comparable to those of weekly Cisplatin schedule with radiation showed no additional efficacy. So, concurrent chemoradiotherapy with weekly Carboplatin (AUC:2) is suitable when Cisplatin is contraindicated for the patients with renal impairment.

Keywords: Carboplatin and Cisplatin: (are anti-cancer drugs). Gy(Gray): radiation unit. Concurrent chemoradiotherapy: when any anti-cancer drug added during radiotherapy.

Introduction

Head neck carcinoma is the sixth most common cancer in the world. Approximately 50,000 patients are diagnosed annually with squamous cell head neck cancer in United States. Worldwide, approximately 600,000 patients are histopathologically detected. Nearly 60% of this population present with locally advanced but non metastatic disease (Halperin et al. 2013). Head Neck cancer is more common in men. 66% to 95% of cases occur in men. The incidence of head and neck cancer increases with age, especially after 50 years of age. Although most patients are between 50- and 70-years age, younger patients can also develop head and neck cancer (Pazdur et al. 2010). The usual time of diagnosis is after the age of 40, except for salivary gland and nasopharyngeal cancers which may occur in younger age group (Devita and Rosenberg 11th ed. 2019).

Cancer is one of the major causes of morbidity and mortality among the non-communicable diseases in Bangladesh. Each year more than 200,000 people develop cancer and 150,000 patients die from the disease. Cancer is the sixth cause of mortality in Bangladesh and more than half of the cancer patients die within five years of diagnosis. The number of people developing cancer is expected to increase in huge number mainly because of ignorance, poor socioeconomic status and some lifestyle factors. This is a contributory factor for more cancer load in Bangladesh; (National cancer control strategy and plan of action 2009 - 2015). The overall head and neck cancer remains a significant international health problem.

The higher incidence of the disease in Bangladesh thought to reflect the prevalence of risk factors, such as betel nut chewing and use of smokeless tobacco. In United States, the higher incidence among urban males is thought to reflect exposure to tobacco and alcohol. Risk factors for head and neck cancer include tobacco and alcohol use, ultraviolet light exposure, viral infection and environmental exposures (Pazdur et al. 2010). Human Papillomavirus infection (HPV; most

commonly HPV- 16) plays a role in the development of certain head and neck cancers, particularly those in the oropharynx (Devita and Rosenberg 11th ed. 2019). More than 90% of malignancies are of squamous cell histology (Symonds et al. 2012). Cancers of the CNS, the eye, the esophagus, and the thyroid gland, as well as those of the scalp, skin, muscles, and bones of the head and neck, are not usually classified as head and neck cancers. Head Neck cancers encompass a diverse group that are oral cavity, oropharynx, larynx, nasopharynx, hypopharynx, paranasal sinuses, salivary glands and ear. Although the treatment for this area is often highly specialized, they also have many features in common with regard to investigation, diagnosis and management.

Head neck cancers staging is complex and depends on the anatomic location of the tumor for practical purposes, head neck cancers is divided into three clinical stages: early, locoregionally advanced, and recurrent or metastatic. Treatment approaches can vary depending on the disease stage. The majority of patients present with locoregionally advanced disease.

Concurrent chemoradiotherapy has a central role in the management of locoregionally advanced head neck cancers and a survival benefit for this approach in comparison to radiation alone is now widely accepted. Overwhelmingly, trial results indicate that the concurrent addition of chemotherapy sensitizes tumors to radiation and increases locoregional control and thereby survival.

The concurrent administration of chemotherapy and radiation has improved outcomes in a variety of clinical scenarios. These include all but specially locally advanced nasopharyngeal carcinomas, advanced unresectable cancers, organ preservation in locally advanced larynx and base of the tongue cancers, and in high-risk post operative patients. Thus, concurrent chemoradiation is accepted as a standard option for these patients. Meta-analysis demonstrates that the addition of chemotherapy concurrent to radiation therapy results in up to a 4% to 8%

absolute improvement in survival, which amounts to a 12% to 19% reduction in the risk of death, whether in definitive or post operative adjuvant setting (Skeel and khleif 2011).

Radiotherapy and concurrent chemotherapy represents the most commonly used strategy and is a more attractive approach because some chemotherapeutic agents may have both radiosensitize cells and provide additive cytotoxicity (Halperin et al. 2013). Cisplatin improves the anti-tumor efficacy of radiation therapy. Also taxane-based chemotherapies emerged as one of the most powerful compounds that might improve loco-regional control. Carboplatin is one of the most active agents for squamous cell carcinoma of head neck in the metastatic and recurrent setting and has been shown to be a radiosensitizer when low dose Carboplatin (AUC:2) uses concurrently with radiation for human squamous cell carcinoma of head neck cell lines.

In this study, we tried to show the comparative study analysis of response and acute toxicities during the treatment of squamous cell carcinoma of locally advanced head neck cancers with low dose weekly Carboplatin (AUC:2) with radiation (Arm-A) versus low dose weekly Cisplatin with radiation(Arm-B).

Methods

This was a prospective observational study with two comparison group which include low dose weekly Carboplatin (AUC:2) with radiation in arm A and low dose weekly cisplatin with radiation in arm B to observe and compare the treatment effects, response rate and clinical outcome by two modalities of treatment planning.

Table 1: Distribution of the patients according to age

Statistics	Arm A N=30	Arm B N=30	P-value
Age (Mean±SD)	54.2±7.52	50.23±8.73	
Age (Median range) in year	52.50	49.00	0.067
No statistically difference between the age of two group			

Patient with locally advanced squamous cell carcinoma of head neck treated with concurrent chemoradiation either by Carboplatin or cisplatin and had any part of their treatment at Bangabandhu Sheikh Mujib Medical University, Dhaka, June 2021 to December 2022 were enrolled in this study and were convinced to participate in the study after giving written informed consent and satisfying inclusion and exclusion criteria. In this study, total 60 patients of locally advanced squamous cell carcinoma of head and neck cancer were treated. Among them 30 patients who received Carboplatin (AUC:2) I.V 30 minutes infusion weekly for 6 weeks, (Arm A) and the rest 30 patients received Cisplatin 30mg/m², I.V 2 hours infusion weekly for 6 weeks (Arm B). All patients received 66Gy concurrent radiation using a LINAC Machine, at the rate of 2Gy/day, 5 fractions/week, over a period of 6.5 weeks.

Results

A total number of 60 patients were enrolled in this prospective observational study to compare the effectiveness, toxicity of low dose weekly Carboplatin with radiation versus low dose weekly Cisplatin with radiation in the treatment of locally advance head neck carcinoma. Among 60 subjects, 30 subjects were in Arm-A, treated with concurrent chemoradiation with Carboplatin and Arm-B 30 subjects treated with concurrent chemoradiation with Cisplatin. Subjects clinical condition was assessed. Then outcome of these two treatment techniques were studied. Following table showing the distribution of patients on the basis of different parameters/ variables.

Table 2: Distribution of the patients according to the use of Oral Tobacco and Pan Masala

Oral tobacco and pan masala use	Arm A		Arm B		Chi square test	P-value
	n	%	n	%		
Yes	20	66.67	17	56.67	0.150	0.697
No	10	33.33	13	43.33	0.283	0.594
Total	30	100.0	30	100.0		
No statistical difference was found between these two group						

Table 3: Distribution of patients according to the site of Primary Tumour

Site	No. of patients		Total no. of patients and Percentage (N=60)	Chi square test	P-value
	Arm-A (n= 30)	Arm-B (n= 30)			
Oral cavity	07	08	15(25.00%)	0.053	0.817
Nasopharynx	04	06	10(16.66%)	0.343	0.558
Oropharynx	03	02	05(08.33%)	0.184	0.667
Hypopharynx	01	01	02(03.33%)	0	1
Larynx	13	12	25(41.66%)	0.028	0.866
Others	02	01	03(05.00%)	0.317	0.573
No statistical difference was found between these two group					

Table 4: Distribution of patients by Clinical Features (before treatment)

Clinical features	No. of patients		N=60 and %	Chi square test	P-value
	Arm-A (n= 30)	Arm-B (n= 30)			
Cervical lymphadenopathy	30	30	60(100%)	0	1
Pain	22	20	42(70.00%)	0.056	0.812
Sore throat	14	12	26(43.33%)	0.107	0.743
Hoarseness of voice	14	11	25(41.67%)	4.344	0.371
Dysphagia	09	07	16(26.67%)	0.197	0.656
Dyspnoea	07	06	13(21.67%)	0.063	0.801
Cough	03	05	08(13.33%)	0.441	0.506
Otalgia	01	02	03(05.00%)	0.317	0.573

Table 5: Distribution of the patients according to Histopathological Grading

Grading	Arm A		Arm B		Total		Chi square value	P-value
	n	%	n	%	N	%		
Well differentiated (Grade I)	2	6.67	3	10	5	8.33	0.184	0.667
Moderately differentiated (Grade II)	14	46.67	16	53.33	30	50.00	0.088	0.765
Poorly differentiated (Grade III)	11	36.67	9	30.00	20	33.33	0.150	0.698
Not specified	3	10.00	2	6.67	5	8.33	0.184	0.667
Total	30	100.0	30	100.0	60	100.0		
No statistical difference was found between these two group								

Table-6A): Distribution of patients by treatment response in smoker

Response	Arm-A	Arm-B	Chi square test	P-value
	Smoker n-27	Smoker n-27		
Complete response number	16	14	0.085	0.769
Partial response number	11	13	0.115	0.734
No statistical difference was found between these two group				

Table-6 (B): Distribution of patients by treatment response in non-smoker

Response	Arm-A Smoker n-27	Arm-B Smoker n-27	Chi square test	P-value
Complete response number	03	02	0.11	0.740
Partial response number	00	01	0.875	0.349
No statistical difference was found between these two group				

Table 7: Distribution of the patients by Treatment Response

Status at last follow-up (After 24 weeks of	Arm A		Arm B		Total	
	N	%	N	%	N	%
Complete response	19	63.33	16	53.33	35	58.33
Partial response	11	36.67	14	46.67	25	41.67
No response	0	0	0	0	0	0
Progressive disease	0	0	0	0	0	0
Total	30	100.0	30	100.0	60	100.0
X² = 0.061, Pvalue=0.432						

Table 8: Distribution of the patients on Treatment Related Haematological and Non-Haematological Toxicities

Variable	Arm-A n=30		Arm-B n=30		(Chi square test) p-value
	No. of patients	(%)	No. of patients	(%)	
Anemia					
Gr-I	07	23.33	10	33.33	0.613
Gr-II	02	6.67	03	10.00	
Gr-III	00	00	00	00	
No statistical difference between these two group					
Leucopenia					
Gr-I	04	13.33	06	20.00	0.895
Gr-II	03	10.00	04	13.33	
Gr-III	00	00	00	00	
No statistical difference between these two group					
Nausea					
Gr-I	04	13.33	07	23.33	0.010
Gr-II	08	26.67	14	46.67	
Gr-III	01	3.33	02	6.67	
No statistical difference between these two group					
Vomiting					
Group I	01	03.33	07	23.33	0.511
Group II	05	16.67	12	40.00	
Group III	02	06.67	03	10.00	
No statistical difference between these two group					
Mucositis					
Group I	00	00.00	00	00.00	0.369
Group II	05	16.67	08	26.67	
Group III	05	16.67	07	23.33	
No statistical difference between these two group					
Diarrhea					
Gr-I	01	03.33	02	06.67	0.595
Gr-II	00	00	02	06.7	
No statistical difference between these two group					
Weight Loss					
Gr-I	07	23.33	10	13.33	0.605
Gr-II	03	10.00	06	20.00	
No statistical difference between these two group					
Skin reaction					
Group I	08	26.66	18	60.00	0.240
Group II	07	23.33	16	53.33	
Group III	06	20.00	05	16.66	
No statistical difference between these two group					

Discussion

The head and neck malignancies constitute about 05% of all cancer worldwide. Head and Neck hampers three of the vital functions such as voice, and swallowing by virtue of its anatomical location, local infiltration and direct extension.

Incidence of head and neck cancer increases with age, especially after 50 years of age. Most patients are between 50 to 70 years old (Pazdur et al. 2010). In this study the patients aged between 17 years to 69 years with a mean age of 53.4 years. This is consistent with the above statement.

Head and Neck cancer is a predominantly male disease. As regards to sex of head and neck cancer have shown male and female ratio was 5:1 (Bomford et al. 2003) 66% to 95% of case occur in men (Pazdur et al. 2010).

Head and neck tumors occur six times more often among cigarette smokers than nonsmokers (Stupp R. et al. 1994). In this study, among 60 patients 54(90%) were found smokers, which reflects the strong association of smoking with head and neck cancer.

Pain, sore throat and hoarseness of voice are the cardinal presenting symptoms of head and neck cancer. In this study, among the 60 cases 42(70%) cases presented with pain, 26(43.43%) cases presented with sore throat and 25(41.67%) cases presented with hoarseness of voice.

All the patients (100%) of this study presented with cervical lymphadenopathy. As only locally advanced head and neck cancer cases were taken as study population.

Dyspnoea occurs with advanced exophytic carcinoma where growth narrows the airway. Here 13 (21.67%) cases presented with dyspnoea. 8 (13.33%) with cough and 3 (5%) with referred otalgia.

Multimodality therapy is required for management of locally advanced head and neck cancer (stage III and stage IVA). Currently four multimodality treatment approaches are used. They are concurrent chemo-radiation. Induction chemotherapy followed by radiotherapy. Radiotherapy alone and surgery followed by adjuvant concurrent chemo-radiotherapy

Concurrent chemoradiotherapy is the standard care for patients with unresectable locally advanced squamous cell carcinoma of head and neck cancer. The optimal chemotherapy agents and their dose schedules have yet to be defined. Cisplatin improves the anti-tumour efficacy of radiation therapy with 5-year loco-regional control rates between 35-70%. The last decade witnessed the introduction of new chemotherapeutic agents, among these, low dose Carboplatin (AUC:2)/ Paclitaxel/5-FU based chemotherapies emerged as one of the most powerful compounds that might improve loco-regional control. The aim of this study was to compare the outcome and toxicity of weekly Carboplatin with weekly Cisplatin-based concurrent chemoradiation in locally advanced squamous cell carcinoma of head and neck cancer. Patients were evaluated weekly by history, physical examination and laboratory investigation during treatment period. The response evaluation was performed 6 weeks after the completion of concurrent chemo-radiotherapy and every 6 weeks thereafter for six months. For the evaluation of tumor response, physical examination, radiologically image and panendoscopy when it was indicated, were performed, as well as CT and/or MRI for objective evaluation. The primary end point of our study was response rate. For the evaluation of the response to concurrent chemo-radiotherapy, tumor response criteria of the World Health Organization (WHO) was applied.

In this study, total 60 patients of locally advanced squamous cell carcinoma of head and neck cancer were treated. Among them 30 patients who received Carboplatin (AUC:2) I.V 30 minutes infusion weekly for 6 weeks, (Arm A) and the rest 30 patients received Cisplatin 30mg/m², I.V 2 hours infusion weekly for 6 weeks (Arm B). All patients received 66Gy concurrent radiation using a Tele Cobalt 60 Machine, at the rate of 2Gy/day, 5 fractions/week, over a period of 6.5 weeks. Complete response was achieved in 63.33% cases of Arm-A where only 53.33% of cases of Arm-B showed complete response.

While partial response was achieved in 36.67% in Arm-A and 46.66% in Arm-B. Thus, the objective

overall response was with no statistically significant difference. So, the results of weekly Carboplatin schedule in the treatment of locally advanced squamous cell carcinoma of head and neck cancer were comparable to those of weekly Cisplatin schedule with no additional efficacy.

It was also observed that patients having a good performance status showed better treatment response. In Arm A. patients with Kamofsky scale of 100, 90 and 80 had a complete response rate of 100%, 66.67% and 40% respectively. In Arm B, patients with Kamofsky scale of 90, 80 and 70 had a complete response rate of 85.71%, 54.54% and 33.33% respectively. This indicates that there was a gradual decrease in complete response with decrease in performance status of the patients.

Toxicities were evaluated by history, physical examination and laboratory blood cell counts and serum tests. Laboratory and clinical toxicities were considered acute if discovered during the first 12 weeks after the initiation of therapy. The grading system was based on the Radiation Therapy Oncology Group (RTOG), acute radiation morbidity scoring criteria for the following in-field toxicities.

Mucositis, nausea and skin reaction were the common treatment related toxicities in both arms. The patients of Arm-A, suffered from vomiting less often (26.67%) than that of Arm-B (73.33%). Other toxicities like weight loss and haematological toxicities (anaemia, leucopenia) were more common in Arm-A. All the toxicities were managed effectively by conservative management.

Treatment related toxicities were more in patients treated with chemoradiation. About 81% suffering from severe toxicities effects compared to 61% of patients treated with radiation only. Two patients developed Grade I nephrotoxicity in Arm-B at first follow-up after 6 weeks of completion of treatment. So, chemotherapy given concomitantly with radiation causes more toxicity. The result of the study supports the above fact.

Survival in head and neck cancers depends on treatment response and locoregional control of the

disease. Recent studies have demonstrated that concurrent chemoradiation is superior in head and neck malignancies regarding local tumor control and perhaps overall survival. This study also shows that weekly carboplatin is suitable when cisplatin is contraindicated in the patients of renal impairment.

Conclusion

In this study the clinical response and toxicities produced by weekly low dose Carboplatin with radiation in the treatment of locally advanced squamous cell carcinoma of head and neck cancer were comparable to those of weekly Cisplatin with radiation schedule with no additional efficacy. So, concurrent chemoradiotherapy with weekly Carboplatin is feasible when contraindication to Cisplatin for contraindicated as the patients with renal impairment.

Conflict of Interest: We can declare there was no conflict of interest in this study.

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