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Original Research Paper

Oncology

A PROSPECTIVE STUDY OF CARBOPLATIN VERSUS CISPLATIN IN 3-WEEKLY SCHEDULE CONCURRENTLY WITH RADIOTHERAPY IN LOCALLY ADVANCE HEAD AND NECK CANCER PATIENTS: RESPONSE AND TOXICITY ANALYSIS

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ABSTRACT **Objective:** To compare the effect and toxicity of carboplatin to cisplatin as a concurrent chemoradiation agent in locally advanced squamous cell carcinoma of head and neck (H&N) region. **Materials and methods:** Hundred patients diagnosed with stage III and Stage IVA locally advanced H&N squamous cell carcinoma were taken in this study. 50 patients in study (carboplatin) arm and 50 patients in control (cisplatin) arm were administered with carboplatin Area under the curve 6 Area under the curve 6 (AUC 6) and cisplatin 100 mg/m^{2}respectively with one hour infusion four hour before radiation, repeated three weekly for 3 cycles. Patients of both the arms received a total dose of 70 gray (Gy) by external beam radiotherapy in 7 weeks at the rate of 200 cGy/fraction, 5 fractions/week. **Result:** Acute higher grade renal toxicity and nausea were reported more in number of cases in control arm in comparison to study arm. There was no significant difference observed in both the arms in terms of treatment response and failure pattern. On follow-up, up to 6 weeks, 60% of cases are disease free in the study arm and 56% of cases in the control arm. **Conclusion:** Three weekly carboplatin concurrent with external beam radiation therapy is comparable to concurrent cisplatin in locally advanced H&N squamous cell carcinoma in terms of efficacy. There is lower incidence of severe renal toxicity and vomiting with concurrent carboplatin than with cisplatin.

KEYWORDS : Carboplatin, cisplatin; concurrent chemoradiation; head and neck squamous cell carcinoma

INTRODUCTION

The treatment of patients with locally advanced head-and-neck squamous cell carcinoma (HNSCC) is very difficult to cure. Poor clinical outcome and survival results are found when we treated patient with radiotherapy (RT) alone.[1]

Different studies on concurrent chemoradiotherapy schedules have been done to enhancement of results. Different trials evaluating concurrent chemoradiotherapy have utilized different radiosensitizing agents, such as hydroxyurea, cisplatin,and carboplatin.[2-6]

Phase II studies from the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) has been done with better survival and good response to patients utilizing high-dose cisplatin regimens in concurrent radiotherapy.[7,8]

A follow-up phase III Intergroup study showed improvement in overall survival of patient with concurrent chemotherapy-radiotherapy (CTRT) with high dose cisplatin in comparison to RT alone.[9]

Radiation with three weekly cisplatin yields promising results but nephrotoxicity becomes limiting factor in patients. Cisplatin is most common agent used in combination with radiotherapy in most studied. It has radiosensitizing property and its toxicities does not overlap with radiotherapy.

Carboplatin is a platinum group of drug, generally its tolerance is better than cisplatin, It has lower toxicity profile and similar mechanisms of action as cisplatin. Carboplatin is a second-generation cisplatin analog with lower gastrointestinal toxicity, nephrotoxicity and neurotoxicity compared with cisplatin.Carboplatin can be used in patients having more toxicity with cisplatin or with compromised renal function.[10]

This study has been carried out with the objective of evaluating the response of locoregional tumor control, disease free as well as overall survival in this setting.

MATERIALS AND METHODS

Prospective comparative study of newly diagnosed biopsy proven patients with locally advanced, nonmetastatic stage III–IVa, according to American Joint Committee on Cancer 8th edition HNSCC. Total hundred patients were included with Karnofsky performance status of >70 from august 2019 - February 2021. Patients should have measurable or evaluable disease, absolute neutrophil count of at least 1800/mm^3, serum creatinine less than 1.6 mg %, haemoglobin > 9 g%, platelet count >1 lakh. All patients gave informed consent and their age range between 19 to 70. Patient not willing to give consent, age more than 70 years, and metastatic tumour were not included in study.

These 100 patients were divided into 2 groups, study arm and

control arm. Study arm received carboplatin Area under the curve6 (AUC6) three weekly as concurrent chemotherapy whereas control arm receive cisplatin 100 mg/m^{2}three weekly, both arm treated with external beam radiotherapy (EBRT) up to 70 gray (Gy) in 35 fractions and 5 fractions per week using reduced field technique. The EBRT was delivered by Co-60 Teletherapy machine Theratron 780C (Best Theratronics Ltd., Kanata, Canada). Patient details have been given in table 1.

Table 1: Characteristics of patients treated in study (carboplatin) and control (cisplatin) arm

Patients characteristics		Study arm	Control arm
Total Patient		50	50
Male		35	33
Female		15	17
Stage (T) Stage	T3	33	30
	T4a	17	20
N(Node)	N1	15	17
	N2	30	28
	N3	5	5
Location	Buccal mucosa	30	28
	Tongue	5	7
	Lip	7	5
	GBS and Alveolus	8	10

Renal toxicity and haematological toxicity were assessed as per Radiation Therapy Oncology Group (RTOG) scale.

Response evaluation:

Complete response (CR) was defined as complete absence of disease for altleast 6 weeks after complete treatment. Partial response was defined as a reduction of disease by at least 50% in the sum of all measurable products of the longest perpendicular diameter of measurable tumor masses for atleast 6 weeks, with no growth of other lesions or appearance of new lesions. Stable disease (SD) was defined as reduction in lesion by less than 50% or increase by less than 25%. Progressive disease (PD) was defined as an increase by at least 25% of tumor lesions or appearance of new lesions.

RESULTS

Hundred patients with locally advance head and neck cancer (stage III and IV) were irradiated with concurrent chemotherapy, 50 were with concurrent carboplatin and 50 with concurrent cisplatin.

After treatment completion, 60% patients i.e. 30 out of 50 in carboplatin arm (study) and 56% patients i.e. 28 out of 50 in cisplatin arm (control) show complete response of disease, and partial response was equal i.e. 30% (15 out of 50) in both the study and control arm. Disease was stable in 6% (3 out of 50) in study and 10 % (5 out of 50) patients in control arm. Disease was progress in 2 patients in both the arms. Detailed results have been given in table 2.

Table 2: Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) in the patients treated by carboplatin + radiotherapy (study arm) and cisplatin + radiotherapy (control arm)

Response	Complete response	Partial response	Stable Disease	Progressive disease
Study arm	30	15	3	2
Control arm	28	15	5	2

Table 3: Acute toxicities in the patients treated by carboplatin + radiotherapy (study arm) and cisplatin + radiotherapy (control arm)

Toxicity	Grade	Study arm	Control arm
ORAL MUCOSITIS	≤Grade2	35	30
	>Grade2	15	20
HEMATOLOGICAL	≤Grade2	40	45
	>Grade2	10	5
Nausea	≤Grade2	45	33
	>Grade2	5	17
Renal dysfunction	Grade1 OR more	12	33

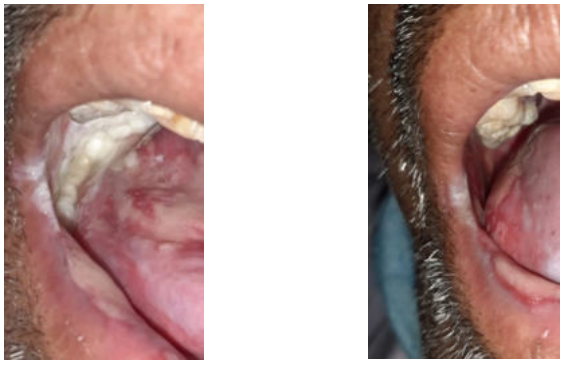
Oral mucositis toxicity ≤ Grade2 in 70% (35 out of 50) and 60% patients (30 out of 50) and > Grade2 toxicity 30% (15 out of 50) and 40% patients (20 out of 50) in study and control arms respectively.

On comparing toxicities in both the arms haematological toxicity ≤ Grade2 was noted in 80% (40 out of 50) and 90% patients (45/50) and > Grade 2 toxicity was noted in 20% (10 out of 50) and 10% patients (5 out of 50) in study and control arms respectively.

Nausea was seen more with cisplatin arm (control). Nausea ≤ Grade2 was noted in 90% (45 out of 50) and 66% patients (33 out of 50) and >Grade2 toxicity was in 10% (5 out of 50) and 34% patients (17 out of 50) in study and control arms respectively.

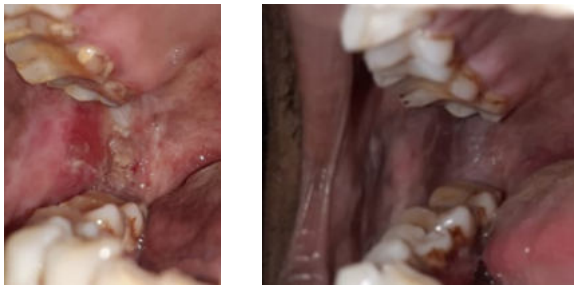
Renal toxicity was also higher with cisplatin arm (control), which is grade1 OR more in 66% (33 out of 50) patients as compared to 24% patients (12 out of 50) in study arm.

Figure 1 and 2 are showing the treatment response of patients before and after the treatment in study and control arms respectively.



(a) (b)

Figure 1: Treatment response in one of the patient with ulcerative fungating lesion (a) before and (b) after treatment in study (carboplatin) arm.



(a) (b)

Figure 2: Treatment response in one of the patient with ulceroproliferative growth in right retromolar region (a) before and (b) after treatment in control (cisplatin) arm.

DISCUSSION

In this study total hundred patients were taken 50 patients in each arm, study arm (carboplatin + radiotherapy) and control arm (cisplatin + radiotherapy) for the comparison of therapeutic outcome of disease. 70% male and 30% female patients in study group and 66% male and 34% female in control group.

On follow-up, results evaluated for disease free survival were better in study arm by 4%, and opposite to it stable disease response are less by 4% in study arm comparison to control arm. Although partial response similar in both arm and progressive disease was also similar in both the arm. These result for response to disease were better than with the result of Dutta *et al.*[11]Better results found in this study may be because of having more number of buccal mucosa cases in this study, they respond better to treatment compare to tongue because these patients having better simulation and target delineation.[12,13]

Carboplatin, the second-generation platinum drug, has all of the radiopotentiation properties of cisplatin but has a different metabolites and side-effect profile.Tolerance of carboplatin better than cisplatin because its less toxic effect like nausea, vomiting and renal toxicity although haematological toxicity more found with carboplatin. So favourable result in toxicity and same mechanism of action make carboplatin attractive than cisplatin.The clinical CR rate reported in phase II studies with concomitant carboplatin and radiation therapy (single daily fraction) is in the range of 65-70%, which is similar to the clinical CR rate reported with cisplatin and radiation therapy.[14]

Similarly in our study also we found the higher grade of haematological toxicity with carboplatin arm (study arm). Haematological toxicity can be managed with hematinics and colony stimulating factors.

Higher grade of gastrointestinal toxicity (nausea and vomiting), renal toxicity and mucositis are found more with cisplatin arm.These toxicity can be managed with hydration and antiemetic agent and mucositis can be managed with hydration, local anaesthetic agent and maintaining oral hygiene.[15,16]

CONCLUSION

Carboplatin is a safer alternative as concurrent chemotherapy agent with radiation without compromising results in locally advanced cancer of H&N cancer. Nephrotoxicity was also lesser with carboplatin arm although there was little increase haematological toxicity, which can be managed very well with hematinics and growth factors.

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