Research Article

Concurrent chemoradiation with paclitaxel versus cisplatin in locally advanced head and neck cancer patients – A prospective comparative study

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ABSTRACT

Background: External beam radiotherapy with concurrent chemotherapy has become the mainstay of treatment for locally advanced head and neck cancers. **Objective:** The objective of this study was to compare paclitaxel to cisplatin as an agent for concurrent chemoradiation in locally advanced squamous cell carcinoma of head neck region in terms of toxicities and response to treatment. **Materials and Methods:** Biopsy-proven Stage III and Stage IVA head and neck squamous cell cancer patients were included in the study. The study arm patients received concurrent dose of paclitaxel 20 mg/m^2 I/V 1 h infusion 4 h before radiation, repeated weekly for 6 cycles. Patients in the control arm received concurrent dose of cisplatin 30 mg/m^2 I/V 1 h infusion 4 h before radiation, repeated weekly for 6 cycles. Patients of both arms received a total dose of 66 Gy external beam radiation, 200 cGy/day, 5 fractions in a week in 6.5 weeks treated on a Theratron 780E Cobalt-60 teletherapy unit. **Results:** Acute Grades III and IV renal toxicity and nausea were reported significantly more number of cases in cisplatin arm in comparison to paclitaxel arm. There was no statistically significant difference observed in the groups in terms of treatment response and failure pattern ($\chi^2 = 3.63$, df = 1, level of significance 0.05). On follow-up, up to 6 months, 51.85% of cases are disease free in the control arm and 50.66% of cases in the study arm. **Conclusion:** Low-dose weekly paclitaxel concurrent with external beam radiation therapy given in conventional fractionation is comparable to concurrent cisplatin in locally advanced head and neck squamous cell carcinoma in terms of efficacy. There is lower incidence of severe renal toxicity and vomiting with concurrent paclitaxel than with cisplatin.

KEY WORDS: External Beam Radiotherapy; Concurrent Chemotherapy; Head and Neck Cancer

INTRODUCTION

Head and neck cancer is imposing a great threat to mankind worldwide. It is the fifth most common malignancy globally among adults.[1] It is among the most common malignancy in India. Overall 57.5% of global head and neck cancer occur in Asia, especially in India.[2] Over 200,000 cases of head and neck cancers occur each year in India.[3] It accounted for 30% of all cancer in males and 11–16% of all cancer in females in India. Among them, oral cancer is the most common head and neck cancer for both sexes.[4] In India, the incidence among males is 12.48 and females is 5.52/1,00,000 population.[5] The mortality rates due to this cancer among males and females are 3.48 and 1.34/1,00,000 population, respectively.[5] The exceptionally high incidence of head and neck cancer in India compared to western and other developed countries are attributed to certain habits and risk factors such as smoking, oral intake of tobacco, betel nut chewing, and poor oral hygiene. Due to difficult surgical approach and devastating functional morbidities associated with surgery, radiotherapy

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and concurrent chemotherapy have become the mainstay of treatment for locally advanced head and neck cancers.[6] In most of the trials on concurrent chemoradiotherapy, cisplatin has been used as the chemotherapeutic agent with good locoregional control in comparison to radiotherapy alone.[7-9] However, cisplatin often results in significant toxicities most importantly nausea, renal dysfunction resulting in treatment interruption.[10] The 3 weekly or weekly schedule of cisplatin may not be tolerable to elderly subjects.[11] Hence, there has been a search for alternative agent.

In the present study, we tried to compare cisplatin with paclitaxel as chemotherapeutic agent in concurrent setting in locally advanced squamous cell carcinoma of head and neck. Paclitaxel, a microtubule stabilizer[12,13] blocks the cell cycle at the G2 phase to mitosis transition,[14] the most radiosensitive phase of the cell cycle,[15] resulting in a radiation sensitizing effect.[16] In addition, paclitaxel seems to improve tissue oxygenation in tumor cells.[17]

Aims and Objectives

The objective of this study was to compare paclitaxel to cisplatin as an agent for concurrent chemoradiation in locally advanced squamous cell carcinoma of head and neck region in terms of toxicities and response to treatment.

MATERIALS AND METHODS

The study was done in the Department of Radiotherapy, NRS Medical College and Hospital from January 2017 to December 2018 with proper clearance from Ethical Committee. Patients with biopsy-proven head and neck squamous cell carcinoma (HNSCC) Stages III and IVA tumors for all sites were included in the study. Eligibility criteria included the following: Eastern cooperative oncology group performance status <2; age 18–70 years; patients either ineligible for curative resection or unwilling for surgery; no prior radiotherapy or chemotherapy; normal baseline complete blood counts, liver function test, and renal functions test and; no other malignancy and no other serious medical disease.

A total of 200 patients were taken into the study. Ultimately, 176 patients (90 patients in the study arm and 86 patients in the control arm) were able to complete their treatment. The study arm patients received concurrent dose of paclitaxel 20 mg/m^2 I/V 1 h infusion with necessary pre-medications 4 h before radiation, repeated weekly for 6 cycles. Patients in the control arm received concurrent dose of cisplatin 30 mg/m^2 I/V 1 h infusion with full hydration 4 h before radiation, repeated weekly for 6 cycles. Patients of both arms received a total dose of 66 Gy external beam radiation, 200 cGy/day, 5 fractions in a week in 6.5 weeks treated on a Theratron 780E Cobalt-60 teletherapy unit. Patients were assessed weekly for acute toxicities using the common terminology criteria for adverse events version 4.0 during treatment. Response assessment was done at completion of treatment and 6 weekly thereafter up to a period of 6 months by otorhinolaryngological assessment on every occasion and computed tomography scan at 3rd and 6th months.

RESULTS

A total of 200 patients were entered into the study. Of these 86 patients in the control arm and 90 patients in the study arm received complete treatment as per protocol. Of 81 patients in the control arm and 75 patients in the study arm could be followed up to 6 months from treatment completion (a sum of 156 patients) and remained for analysis. Pre-treatment characteristics of patients and tumors are shown in Table 1.

Acute Grades III and IV renal toxicity and nausea were reported significantly more number of cases in cisplatin arm in comparison to paclitaxel arm. There were no significant differences in other toxicities [Table 2]. There was no statistically significant difference observed in the groups in terms of treatment response and failure pattern ($\chi^2 = 3.63$, df = 1, level of significance 0.05). On follow-up, up to 6 months, 51.85% of cases are disease free in the control arm and 50.66% of cases in the study arm [Table 3]. Persistent disease at treatment end is 27.16% in the control arm and 25.33% in the study arm. Recurrence in primary only is 9.87% in the control arm and 8% in the study arm. Only nodal recurrence is 6.17% in the control arm and 12% in the study arm. Locoregional recurrence is 3.70% in the control arm and no locoregional recurrence in the study arm.

Table 1: Pre-treatment characteristics of cases

Characteristics	Control arm		Study arm	
	Number	Percentage	Number	Percentage
Sex				
Male	76	88.37	78	86.66
Female	10	11.62	12	13.33
Eastern cooperative oncology group				
1	47	54.65	55	61.11
2	39	45.34	35	38.88
Primary site				
Oral cavity	26	30.23	27	30
Oropharynx	17	19.76	21	23.33
Hypopharynx	14	16.27	8	8.88
Larynx	29	33.72	34	37.77
Stage				
III	63	73.25	68	75.55
IVA	23	26.74	22	24.44

DISCUSSION

In this study, 88.37% male patients and 11.62% female patients were in control group and 86.66% male and 13.33% female patients were in the study group. Among these cases in the control arm, oral cavity lesion was 30.23%, oropharynx 19.76%, hypopharynx 16.27%, and larynx 33.72%. In the study, arm these were 30%, 23.33%, 8.88, and 37.77%, respectively.

Acute Grades III and IV renal toxicity and nausea were reported significantly higher in cisplatin arm in comparison to paclitaxel arm. There were no significant differences in other toxicities.

On follow-up, up to 6 months, 51.85% of cases are disease free in the control arm and 50.66% of cases in the study arm. Persistent disease at treatment end is 27.16% in the control arm and 25.33% in the study arm. Recurrence in primary only is 9.87% in the control arm and 8% in the study arm. Only nodal recurrence is 6.17% in the control arm and 12% in the study arm. Locoregional recurrence is 3.70% in the control arm and no locoregional recurrence in the study arm.

Table 2: Comparison of toxicities between two arms

Toxicities	Control arm	Study arm	*P*-value
Neutropenia			
≤Grade2	76	79	0.903
>Grade2	10	11	
Anemia			
≤Grade2	70	81	0.102
>Grade2	16	9	
Oralmucositis			
≤Grade2	58	64	0.27
>Grade2	28	26	
Renaldysfunction			
≤Grade2	63	89	0.00001
>Grade2	23	1	
Nausea			
≤Grade2	61	81	0.001
>Grade2	25	9	
Fatigue			
≤Grade2	61	69	0.38
>Grade2	25	21	

We studied a regimen of concurrently administered injection paclitaxel combined with conventionally fractionated radiation therapy to test the hypothesis that this combination may provide an acceptable disease control with no enhancement of toxicities in comparison to concurrent cisplatin. The rationale for using low-dose weekly paclitaxel is based on preclinical and clinical data that suggest the direct antitumor activity and radiosensitization effect of paclitaxel.[18] In 1995, a prospective study of concurrent infusional paclitaxel administered as a 120-h continuous infusion in combination with radiotherapy for squamous cell carcinoma of head neck was initiated at the National Cancer Institute.[14] Local toxicities including mucositis, dysphagia, and skin reactions were pronounced but tolerable. In view of good tumor control, concurrent paclitaxel seemed to be a feasible and promising treatment for patients with advanced HNSCC. The study by Hoffmann *et al*.[19] shown the effect of dose escalation of concurrent paclitaxel given weekly in combination with conventional radiotherapy in patients with locally advanced HNSCC. Paclitaxel was given at a starting dose of 20 mg/m^2, and subsequently in two higher dose levels of 30 mg/m^2/week and 40 mg/m^2/week. The maximum tolerated dose limited by oropharyngeal mucositis was 30 mg/m^2/week. The study by Milas *et al*.[17] had shown that the radiation sensitizing effect of taxenes on normal tissue is less in comparison to that on neoplastic cells. In another study,[20] on Indian subjects 52 patients were randomly assigned to one of the two concomitant chemoradiation arms: Arm I (n = 26) and Arm II (n = 26) who received injection of paclitaxel 40 mg/m^2 I/V 1-h infusion before radiation, repeated weekly for 6 cycles, and cisplatin 30 mg/m^2 I/V 1-h infusion before radiation, repeated weekly. Paclitaxel-based regimen appeared to be more effective although result was not statistically significant. The study by Lovey *et al*.[21] included 26 patients who were treated with concomitantly 2 mg/m^2 paclitaxel 3 times a week with external beam radiotherapy in conventional fractionation. With an acceptable efficacy (RR: 65%, 2-year overall survival 46%), the treatment was well tolerated and showed a favorable toxicity profile. They concluded that this regimen may be

Table 3: Pattern of failure from treatment completion to 6 months follow-up period

Parameters	Control arm (n=81)		Study arm (n=75)	
	No. of patients	Percentage	No. of patients	Percentage
Persistent disease at treatment end	22	27.16	19	25.33
Recurrence in primary only	8	9.87	6	8
Nodal recurrence only	5	6.17	9	12
Distant metastasis	1	1.23	3	4
Recurrence in primary and node	3	3.70	0	0
Alive without evidence of disease	42	51.85	38	50.66

offered as an alternative for patients in poor performance status with locally advanced head and neck cancers. The study by Tishler *et al*.[22] with paclitaxel every 3 weeks in a dose of 100 mg/m^2 concurrently with external beam radiation on a group of 14 HNSCC patients landed in serious toxicities although with a good tumor control. Another Phase I trial studied the simultaneous treatment of continuous 24 h paclitaxel (75 mg/m^2/d) concomitant with radiotherapy in 24 patients with advanced head and neck cancer.[23] The dose-limiting toxicities in this study were febrile neutropenia and stomatitis. All patients had major response.

CONCLUSION

Low-dose weekly paclitaxel concurrent with external beam radiation therapy given in conventional fractionation is comparable to concurrent cisplatin in locally advanced HNSCC in terms of efficacy. There is lower incidence of severe renal toxicity and emetogenesis with concurrent paclitaxel than with cisplatin. Larger randomized controlled trials are needed in future for further evaluation and also to study the impact on survival.

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