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Efficacy and safety of low-dose celecoxib with chemoradiation in locally advanced head-and-neck squamous cell carcinoma

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ABSTRACT

Background: Head-and-neck squamous cell carcinoma (HNSCC) is a major cancer in India with a poor prognosis. Novel antineoplastic agents, such as selective cyclooxygenase-2 inhibitors such as celecoxib, have shown antitumor, anti-angiogenesis, and radiosensitizing effects, improving radiotherapy response in many cancers. **Aims and Objectives:** This study aimed to determine the efficacy and safety of low-dose celecoxib combined with concurrent chemoradiation in Locally Advanced HNSCC. **Materials and Methods:** A double-arm prospective randomized control study was conducted, in which 103 eligible locally advanced HNSCC patients were randomized to concurrent chemoradiotherapy 66 Gy/2 Gy/33 fractions/6[1/2] weeks along with Inj Cisplatin 40 mg/m^2 weekly either with celecoxib 100 mg twice daily (Study Arm – 62) or placebo (Control Arm – 41). Tumor response was evaluated using response evaluation criteria in solid tumors criteria 1.1 and acute toxicities based on the radiation therapy oncology group and common terminology criteria for adverse events criteria 5.0. **Results:** On analysis using the Chi-square test, the complete response rate was 65.6% in the study arm compared to 44.7% in the control arm, with P = 0.0441 (significant at P < 0.05). The incidence of acute dermatitis and mucositis (grade ≥3) in the study and control arms was 29.3% versus 23.6%, with P = 0.544 and 40% versus 37% with a P = 0.782 (insignificant at P < 0.05), respectively. The patients in both arms were followed up to assess late toxicities, locoregional control rate, disease-free survival, and overall survival. **Conclusion:** Adding low-dose daily celecoxib to concurrent chemoradiation with weekly cisplatin in locally advanced HNSCC significantly improved the clinical response rates with acceptable treatment-related toxicities.

Key words: Celecoxib; Cyclooxygenase-2 inhibitors; Head-and-neck cancers; Chemoradiation; Cisplatin

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INTRODUCTION

Head-and-neck squamous cell carcinoma (HNSCC) constitutes a substantial proportion of cancer cases in India, and most of them present at a locally advanced stage. The poor prognosis of locally advanced disease has led to an increasing interest in exploring the use of novel antineoplastic agents.[1] Cyclooxygenase-2 (COX-2) is one interesting potential target.[1] COX-2 enzyme is overexpressed in many malignant tumors.[2] Several preclinical studies on selective COX-2 inhibitors (Celecoxib) have shown that these agents have antitumor, anti-angiogenesis, decreasing distant metastasis, inducing apoptosis, and radiosensitizing effects.[3] Celecoxib has been progressively used in clinical studies to improve the radiotherapy response in many cancers.[4-9]

Aim and objectives

The aim of the study is to evaluate the efficacy and safety of adding low-dose celecoxib to concurrent chemoradiation in locally advanced head-and-neck squamous cell carcinoma.

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The objectives include comparing response rates, assessing safety, evaluating tumor growth and angiogenesis effects, and analyzing survival outcomes.

MATERIALS AND METHODS

This double-arm prospective randomized control study was conducted for 1 year, from November 2018 to October 2019. One hundred and three newly diagnosed, histopathologically proven, locally advanced HNSCC patients were recruited based on the inclusion and exclusion criteria. Eligible patients were randomized to receive concurrent chemoradiotherapy with celecoxib 100 mg twice daily (Study Arm 62) or with a placebo (Control Arm 41). This study was approved by the Institutional Ethical Committee as per the recommendations of the World Medical Association Declaration of Helsinki. Written informed consent in the local language was obtained from all participants before the study. The location, size, and extent of the primary tumor and cervical lymph nodes were assessed using computed tomography (CT). Staging was performed according to the 8th edition of the American Joint Committee on Cancer TNM 2018 staging system.

Inclusion criteria

The inclusion criteria were biopsy-proven newly diagnosed locally advanced (Stage III, IVA, and IVB) HNSCC patients in the age group of 18–80 years, Karnofsky's performance score of >70, primary tumor sites of the oral cavity, oropharynx, hypopharynx, and larynx, normal blood parameters (hemoglobin >10 g%, total count >4000/mm^3, platelets >1,00,000 cells/mm^3), and no major life-threatening comorbidities with normal or acceptable kidney, liver, and cardiovascular functions.

Exclusion criteria

Exclusion criteria included non-squamous histopathology, other head-and-neck tumor sites, metastatic (Stage IV C) or recurrent disease, deranged hepatic and renal functions (>twice the upper limit), reduced bone marrow reserve, patients not cooperating at any point during treatment, pregnant and lactating women, history of allergic reaction to non-steroidal anti-inflammatory drugs, uncontrolled hypertension, gastrointestinal bleeding, gastrointestinal ulcer, any previous malignancies diagnosed or treated, inability to receive celecoxib or chemotherapy for any reason, presence of severe inflammatory bowel disease, or coagulation disorders, and patient's refusal to participate in the trial or sign the consent form.

Complete pretreatment evaluation with biopsy from a tumor, weekly complete blood count, liver function tests, renal function tests, and serum electrolytes before every cycle of chemotherapy, viral markers, contrast-enhanced CT (CECT) scan neck (from base of skull to Root of Neck), chest X-ray - PA view, electrocardiogram, bleeding time, CT and international normalized ratio, cardiology evaluation with fitness, and dental evaluation with prophylaxis was performed.

Patients in both arms were immobilized using thermoplastic molds with suitable headrests and treated with radiotherapy in the form of Phase I to include the primary and draining lymph node regions to a dose of 40 Gy in 20 fractions over 4 weeks, followed by Phase II with offcord reduction, to a dose of 26 Gy in 13 fractions over 2 weeks and 3 days at 2 Gy/fraction was delivered 5 days in a week (Monday to Friday) using two parallel opposing fields to a total dose of 66 Gy along with chemotherapy, Inj. Cisplatin 40 mg/m^2 every week from day 1 of radiotherapy with proper pre-medications for a total of six cycles. Care was taken to maintain adequate hydration, nutrition, and analgesia before, during, and after treatment completion.

The patients in the study arm received Cap. Celecoxib 100 mg twice daily orally from day 1 of radiotherapy until the end of the treatment course. In contrast, patients in the control arm received a placebo on all days of radiotherapy. Complete blood counts, renal and liver function tests, and Sr electrolytes were performed weekly. Acute toxicities were assessed from the start of chemoradiation based on (radiation therapy oncology group acute morbidity criteria and common terminology criteria for adverse events) version 5.0.

In case of deranged blood parameters or any severe Grade 3 or 4 toxicities, treatment was interrupted until recovery and then restarted. Patients were carefully monitored for these symptoms, and supportive care was provided. All patients in both arms were assessed with a CECT scan 2 months after completing chemoradiation with or without celecoxib to evaluate the locoregional response and were categorized according to the response evaluation criteria in solid tumors criteria (version 1.1).

RESULTS

Of the 103 recruited patients (Study Arm – 62: Control Arm – 41), seven patients were excluded (in study arm, four patients [two defaulters, one expired during treatment, and one refused chemotherapy] and in control arm, three patients [three defaulters]) with attrition values of 6.4% and 7.3%, respectively, and the remaining 96 patients (study arm – 58; control arm – 38) were analyzed. The variables analyzed are shown in Table 1.

Table 1: Comparative analysis of study and control arm variables

Variables	(Number of patients)	
	Study arm	Control arm
Recruited	62	41
Attrition	4	3
Eligible	58	38
Sex		
Male	43	29
Female	15	9
Age (in years)		
<40	6	3
40–60	33	20
>60	19	15
Primary tumor site		
Oral cavity	20	14
Oropharynx	13	7
Hypopharynx	13	9
Larynx	12	8
Stage		
III	18	11
IV A	29	21
IV B	11	6
Clinical response		
Complete	38	17
Partial	16	19
Progressive	Nil	Nil
Static	4	2
Acute toxicity		
Dermatitis		
Grade 1 and 2	41	29
Grade 3 and 4	17	9
Mucositis		
Grade 1 and 2	35	24
Grade 3 and 4	23	14

In the study arm, 43 patients (74%) were male, and 15 patients (26%) were female compared to the control arm, and 29 patients (76%) were male and 9 (24%) were female, with a male: female sex ratio of 3:1 in both arms. The mean ages in the study and control arms were 49 (37–76 years) and 53 years (42–74), respectively. The proportion of patients in varying age groups of <40, 40–60, and >60 years in both the study and control arms was 10%, 57%, and 33% and 8%, 53%, and 39%, respectively, with the majority in the age group of 40–60 years in both arms.

The proportion of patients with primary tumor sites in the oral cavity, oropharynx, hypopharynx, and larynx in both the study and control arms was 35%, 22%, 22%, and 21%, and 37%, 18%, 24%, and 21%, respectively. The stages at presentation (Stage III, IVA, and IVB) in the study were 31%, 50%, and 19%, and in the control arm was 29%, 55%, and 16% with the majority being Stage IVA disease in both arms.

In the study arm, out of 58 patients, 38 (65.6%) achieved complete response (CR), 16 (27.5%) achieved partial response (PR), and 4 (6.9%) had stable disease (SD) compared with the control arm, where out of 38 patients, 17 (44.7%), 19 (50%), and 2 (5.3%) had CR, PR, and SD, respectively. No patients with disease progression were observed in either arm of the study. Using the Chi-square test, comparing the CR to other than the CR in both arms, there was a significant increase in the CR rate in the study arm compared to the control arm with a P=0.044 (significant at P<0.05).

The incidence of acute dermatitis in Grades 1 and 2 and Grades 3 and 4 in the study and control arms was 70.7% versus 76.4% and 29.3% versus 23.6%, respectively, with P=0.544 (insignificant at P<0.05). The incidence of acute mucositis in Grades 1 and 2 and Grades 3 and 4 in the study and control arms was 60% versus 63% and 40% versus 37%, respectively, with P=0.782 (insignificant at P<0.05). Xerostomia, anorexia, nausea, vomiting, diarrhea, and fatigue were other treatment-related toxicities in both groups. The patients in both arms were followed up to assess late toxicities, locoregional control rate, disease-free survival, and overall survival.

DISCUSSION

Locally advanced HNSCC is treated with a combined multimodality treatment. Concurrent chemoradiation with a cisplatin-based regimen is the standard of care for locoregionally advanced HNSCC, although the prognosis remains poor.[10] Few studies have evaluated the efficacy and safety of concurrent chemoradiation with weekly cisplatin in patients with locally advanced HNSCC. They concluded that this treatment approach is safe and effective for most patients, even in elderly patients.[11,12] The prognosis significantly improved with CR after treatment. To achieve this, many novel antineoplastic agents are under investigation, and one of the most promising agents is COX-2 inhibitors.[1]

COX-2 inhibitors, such as celecoxib, may play a role in the treatment of cancers by inhibiting cellular proliferation and angiogenesis, decreasing distant metastases, and inducing apoptosis.[3] Lee et al., showed that the COX-2 enzyme was overexpressed in cultured cells of squamous cell carcinoma of the head and neck compared to normal cells. The authors concluded that COX-2 inhibitors significantly decreased cell growth and increased apoptosis in cultured cells.[2] Soo et al., found celecoxib 400 mg twice daily for 14 days reduced microvessel density and induced changes in gene expression in patients with newly diagnosed, untreated nasopharyngeal carcinoma.[13]

In addition, several studies have found that COX-2 inhibitors significantly enhance the response of tumor cells

to radiotherapy. The exact mechanism(s) responsible for the antiproliferative effect of COX-2 inhibitors remains defined; however, the antiangiogenic effects of COX-2 inhibitors seem mainly responsible for increasing the antitumor effects of ionizing radiation. Therefore, COX-2 inhibitors have a potential role in improving response to radiotherapy.[14-18]

This double-arm prospective randomized controlled trial evaluated the efficacy and safety of low-dose (100 mg twice daily) celecoxib with concurrent chemoradiation in locally advanced HNSCC. The rationale for this lower-dose administration of celecoxib was to evaluate the radiosensitizing effect of a lower dose of celecoxib rather than its antitumor and antiangiogenic effects. Adding celecoxib showed a better clinical CR with a significant $P=0.044$ (significant at $P<0.05$) compared to the control arm. The incidence of treatment-related acute toxicities was higher in the study arm than in the control arm. However, it was not significant, with $P=0.544$ (insignificant at $P<0.05$) and 0.782 (insignificant at $P<0.05$) for dermatitis and mucositis, respectively.

The American Heart Association has recommended celecoxib only at the lowest dose and shortest duration.[19,20] In this study, it was used in low doses only, and all patients received the drug for an average duration of 48 days (Range 45–56 days). None of the patients developed any coronary or cerebrovascular events or deranged renal function despite combining celecoxib and cisplatin, both nephrotoxic drugs, possibly due to the reduced dosage of both drugs and reduced duration of celecoxib intake. The addition of Tab. Celecoxib adds to the expenditure of rupees from approximately 700 to 800 (Approximately) per patient with a significant cost-benefit ratio. Another benefit was the reduced use of Tab. Morphine in the study arm patients. In addition, there is evidence that COX-2 inhibitors have been associated with a significant reduction in vascular permeability and a decrease in acute and chronic inflammation.[21,22] This may explain the non-significant increase in acute toxicities such as dermatitis and mucositis.

Patients with a CR were under regular follow-up, but those with PR or SD were evaluated further and referred to a surgical or medical oncologist for further management. This study principally assessed the tumor response rate and acute toxicity alone. All patients in both arms were treated with a telecobalt machine using conventional techniques. If advanced techniques in intensity-modulated radiotherapy or Rapid Arc using LINAC are used, a better toxicity profile, especially xerostomia, can still be achieved in both arms. Further, a longer follow-up period is needed to assess the patients' locoregional control, disease-free survival, recurrence rate, metastatic rate, overall survival rate, and late toxicities.

Limitations of the study

The study acknowledges limitations including a short follow-up period, limited analysis of side effects, use of older radiotherapy techniques, and a relatively small sample size.

CONCLUSION

The addition of low-dose daily celecoxib to concurrent chemoradiation with weekly cisplatin in locally advanced HNSCC has significantly improved the clinical response rates with acceptable treatment-related toxicities. Furthermore, a large-scale analysis is required.

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