Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Response Rate, Toxicity, and Compliance in Head-and-neck Cancer Patients Treated with Concurrent Chemoradiation – A Retrospective Analysis

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Abstract

Introduction: Head-and-neck cancer (HNC) is heterogeneous group of cancers and as a whole, they are the fifth most common cancer worldwide with an estimated annual global incidence of over half a million. Treatment approaches vary depending on the location of the tumor, staging, and individual patient's characteristics.

Aim: The aim of the study is to retrospectively assess the acute toxicity profile, response rates, and compliance with treatment in locally advanced squamous cell carcinoma of head and neck (SCCHN) treated with concurrent chemoradiation.

Materials and Methods: We analyzed retrospectively 85 patients with histologically proven SCCHN (nasopharynx, oropharynx, larynx, hypopharynx, and oral cavity) treated with definitive chemoradiation. All patients received 60–66 Gy in 30 daily fractions with concomitant weekly cisplatin 40 mg/m^2. We assessed treatment toxicities and patient compliance.

Results: The radiation therapy oncology group acute Grade 3 or worse mucositis was seen in 29 (34.1%) patients. Grade 3 or more skin reaction was seen in 14 (16.4%) patients. Common toxicity criteria Grade 3 or worse emesis occurred in 4 (4.7%) patients, mostly toward the end of chemoradiotherapy. Acute hematologic toxicity in the form of leukopenia and thrombocytopenia was mild and acceptable. Toxicity of treatment leading to interruption or compromise in the planned dose of radiotherapy was seen in 21 (24.7%) patients and chemotherapy break occurred in 39 (45.8%) patients. Of 100% (n = 85), 65.8% (56) had complete clinical response while 27.05% (23) had partial clinical response. Nodal response to treatment was analyzed separately. 19/27 (70.3%) patients in N1 stage, 22/33 (66.66%) patients in N2 stage, and 1/2 (50%) patients in N3 stage had complete clinical response whereas partial response was observed in remaining patients.

Conclusion: Concurrent chemoradiotherapy using cisplatin 40 mg/m^2 weekly is well tolerated by locally advanced HNC patients. Acute toxicities were reversible with supportive management and were not severe enough to cause discontinuation of treatment. The clinical complete response rates obtained in this study (65.8%) are comparable to the results in published literature (65–70%) and the results confirmed the importance of the stage of the disease as the most significant predictor of outcome. Survival benefits and late normal tissue complications were not predictable due to short period of follow-up. Carefully designed prospective randomized studies are needed to address these issues.

Key words: Chemoradiotherapy, Cisplatin, Head and neck neoplasms

INTRODUCTION

Head-and-neck cancer (HNC) is a major form of cancer in India, accounting for 23% of all cancer in males and 6% in females.[1] The 5-year survival rate varies from 20% to 90% depending on the subsite of origin and the clinical extent of the disease. India has the dubious distinction of having the world's highest reported incidence of HNC in women.[2] The disproportionately higher prevalence of HNC in relation to other malignancies in India may be due to the use of tobacco in various forms, consumption of alcohol, and low socioeconomic condition related to poor hygiene, poor diet, or infections of viral origin.[3]

The baseline risk of developing cancer is acted on throughout life as the genome of different cells interacts

Access this article online

www.ijss-sn.com

Month of Submission : 09-2019
Month of Peer Review : 10-2019
Month of Acceptance : 11-2019
Month of Publishing : 11-2019

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with environment in the form of exposures (e.g., toxins and infections). As genetic damage is incurred throughout a lifetime (directly to DNA sequences or to the epigenome), events are set in motion to progressively disrupt normal cellular pathways toward tumorigenesis.[4]

Strong epidemiologic and molecular data now support the conclusion that human papillomavirus infection is responsible for a distinct form of squamous cell carcinoma of head and neck (SCCHN). HNC is best managed in a multidisciplinary setting. Surgery, radiation therapy (RT), chemotherapy, and more recently biologic therapy are often employed in various combinations in an attempt to eradicate both clinically apparent and occult diseases. The goals of treatment include maximizing tumor control while maintaining function and quality of life. Long-term survival is improving with advances in therapy but remains suboptimal. Approximately 50–60% of patients develop local disease recurrence within 2 years.[5]

Patients with resectable locally advanced SCCHN (LASCCHN) are managed with surgical resection followed by adjuvant RT. The addition of concurrent chemotherapy to adjuvant RT has resulted in significant improvement in survival. For patients with unresectable LASCCHN, concurrent chemoradiotherapy has produced a survival benefit compared to RT alone. With respect to targeted therapy, the epidermal growth factor receptor (EGFR) is overexpressed in many head and neck tumors. EGFR inhibition through anti-EGFR antibody therapy or small molecule inhibitors of EGFR may act in a synergistic fashion with RT through inhibition of cellular proliferation, tumor angiogenesis, and DNA repair.[6]

Aim

The aim of the study is to retrospectively assess the acute toxicity profile, response rates, and compliance with treatment in LASCCHN treated with concurrent chemoradiation.

MATERIALS AND METHODS

This is a retrospective study which assessed the acute toxicities and response rates in LASCCHN treated with concurrent chemoradiation. Patients included in the study were registered in the Department of Radiotherapy, Medical College Thiruvananthapuram, between June 2008 and June 2010.

Patients were given radiotherapy by Cobalt 60 external beam to a total dose of 60–66 Gy, 1.8–2 Gy per fraction, and 5 days a week. Injection cisplatin was administered intravenously once a week as 40 mg/m^2 during the whole course of radiotherapy.

Inclusion Criteria

The following criteria were included in the study:

- Patients having LASCCHN
- Patients with histological evidence of malignancy
- Hemoglobin of more than or equal to 10 g%
- Total white blood cell count of more than or equal to 4000/mm^3
- Eastern Cooperative Oncology Group performance status of 0–2.

Exclusion Criteria

The following patients were excluded from the study:

- Patients with carcinoma of nasopharynx
- Patients with no evidence of distant metastasis
- Patients with prior history of radiation to head and neck region.

Pretreatment Evaluation

Patients were evaluated by physical examination, ear, nose, throat examination, and necessary laboratory and radiological evaluation. Routine blood counts, liver function test, renal function test, chest X-ray, and indirect and direct laryngoscopy were carried out to determine the extent of the tumor and staging. Biopsy of the tumor was done in all cases for confirmation and fine-needle aspiration cytology of the lymph nodes was done when indicated. Computed tomography scan and magnetic resonance imaging were considered optional. The clinical staging was confirmed by the principal investigator. All patients had a routine dental checkup, scaling, and extraction of teeth as indicated before radiation. The patients were advised to stop smoking, advised proper oral care, and encouraged to drink plenty of water. All patients were introduced Ryle's tube before starting the treatment.

Weekly Assessment

All patients were monitored closely every week during the course of concurrent chemoradiation for assessing the toxicity of therapy. Toxicity grading was done according to the RT oncology group (RTOG) and common toxicity criteria (CTC) grading systems for radiation-related and chemotherapy-related toxicities, respectively. The patients were required to follow-up at 4–6 weeks from completion of therapy to assess response and disease status. Subsequent follow-up visits were scheduled at 3–6 monthly intervals for the first 2 years and annually thereafter. All patients were personally seen at least 2 times a week. They were monitored and recorded every week with the following parameters.

1. Mucosal reaction (grade of mucositis) and skin reaction (grade of skin reaction) were recorded according to the RTOG scale
2. Acute treatment-related side effects such as dysphagia, dryness of mouth, hoarseness of voice, and pain on swallowing were also measured.

Patients who developed Grade 3 reaction were given a break in treatment and were admitted in the ward and treated with supportive medication which included vitamins, hydration, analgesics, mouth wash, antibiotics, and antifungal treatment if required.

Outcome Measurement

Patients were evaluated for response to treatment both primary and lymph nodes at 3 weeks and 6 weeks of completion of treatment.

- Complete response (CR) is complete disappearance of all measurable disease
- Partial response (PR) is regression of more than 50% measurable disease
- No response is regression of <50% of measurable disease
- Progressive disease is progression of the initial disease.

Follow-up of Patients

All patients were assessed at 3 weeks and 6 weeks after treatment for residual disease at the primary site or at the neck. No adjuvant chemotherapy was administered to the patients.

Statistical Analysis

The acute reactions and the response of the tumor were carried out using Fisher's exact test and Chi-square test. The statistical analysis was performed with SPSS software.

RESULTS

A total of 85 patients satisfied the eligibility criteria and form the dataset for this analysis. The sociodemographic and clinicopathologic characteristics of all the analyzable 85 patients with LASCCHN receiving radical RT with concurrent weekly cisplatin were consistent with previously published head and neck literature. Although medical comorbidities consistent with the age-pyramid were prevalent, they were not significant enough in the large majority (such as active tuberculosis, uncontrolled hypertension or diabetes mellitus, or nephropathy) precluding systemic chemotherapy.

Based on the primary site of cancer, of 85 patients, 31 (36.4%) had carcinoma oropharynx, 25 (29.4%) had ca larynx, 15 (17.6%) had ca hypopharynx, and 14 (16.4%) had ca oral cavity.

Majority (40%) of the patients 34 were within the age group 50–59 years. Thirty-one patients (36.4%) belonged to age group of 40–49 years. Age groups 60–69 and 30–39 years were 17.6% (15) and 5.8% (5), respectively. Among 85 patients, 71 (83.5%) were male and 14 (16.4%) were female.

T Status, N Status, and Composite Stages

Of 85 patients, 4 patients (4.7%) had T1 tumor, 18 patients (21.1%) had T2 tumor, 51 patients (60.0%) had T3 tumor, and 12 patients (14.1%) had T4 tumor. Among 85 patients, 23 (27.05%) had N0 status, 27 (31.7%) had N1 status, 33 (38.8%) had N2 status, and 2 (2.3%) had N3 status. Of 85 patients, 39 patients (45.8%) had Stage III and 46 patients (54.2%) had Stage IV [Table 1].

Outcome Analysis

This study has tried to analyze the response rates of the primary tumor and the node to concurrent chemoradiation and the acute reactions during the treatment.

Analysis of the Acute Reactions

The RTOG acute Grade 3 or worse mucositis was seen in 29 (34.1%) patients. Grade 3 or more skin reaction was seen in 14 (16.4%) patients. Mild to moderate nausea and vomiting occurred in almost all patients despite antiemetic prophylaxis.

Difficulty in swallowing was seen in almost all patients and around half of the patients had hoarseness [Table 2]. CTC Grade 3 or worse emesis occurred in 4 (4.7%) patients, mostly toward the end of chemoradiotherapy. Acute hematologic toxicity in the form of leukopenia and thrombocytopenia was mild and acceptable. The incidence of CTC Grade 3 leukopenia was 5.7%. No episodes of febrile neutropenia were recorded. No patients experienced CTC Grade 3 thrombocytopenia. Platelet transfusion or growth factor support due to acute hematologic toxicity was not needed in any patient.

There was minimal acute kidney dysfunction, with no episodes of Grade 3 or worse renal toxicity, because the dose of cisplatin was titrated based on indirect EGFR before each cycle of weekly chemotherapy.

Treatment Interruption

Toxicity of treatment leading to interruption or compromise in the planned dose of radiotherapy was seen in 21 (24.7%) patients and chemotherapy break occurred in 39 (45.8%) patients [Table 3]. The most common cause of radiation break was mucositis and chemotherapy break was mostly due to Grade 3 mucositis. The break duration extended from 7 to 14 days. The patients who had Grade 3 mucosal reactions were given 1 week break. During this period, patients were admitted in ward and given hydration and other supportive care. Overall the regimen was well tolerated with acceptable acute toxicity.

Analysis of Control of Disease

Control of the primary at 6th week

Of 100% (n = 85), 65.8 % (56) had complete clinical response while 27.05% (23) had partial clinical response.

Table 1: Patient characteristics – T stage, N stage, and composite stages

	Tumor status				Nodal status				Composite stages	
	T1	T2	T3	T4	N0	N1	N2	N3	Stage III	Stage IV
n (%)	4 (4.7)	18 (21.1)	51 (60.0)	12 (14.1)	23 (27.05)	27 (31.7)	33 (38.8)	2 (2.3)	39 (45.8)	46 (54.2)

Table 2: Outcome analysis – mucositis, skin reaction, and other complications

Mucosal reaction	***n* (%)**
Grade 1 and 2 alone	56 (65.9)
Grade 3 or more	29 (34.1)
Skin reaction	***n* (%)**
Grade 1 and 2 alone	71 (83.5)
Grade 3 or more	14 (16.4)
Other complications	***n* (%)**
Odynophagia	81 (95.2)
Hoarseness	47 (55.2)

Table 3: Outcome analysis – radiation break and chemotherapy break

Radiation break	***n* (%)**
Break present	21 (24.7)
No break	64 (75.3)
Chemotherapy break	***n* (%)**
Break present	39 (45.8)
No break	46 (54.2)

All patients (4/4) in TI stage, 14/18 (77.8%) patients in T2 stage and 38/51 (70.58%) patients in T3 stage had complete clinical response while PR was seen in remaining patients. CR rates were 61.74% (21/31) for primary oropharynx tumor, 60% (9/15) for hypopharynx, 68% (17/25) for larynx, and 64.2% (9/14) for oral cavity.

Control of node at 6th week

Nodal response to treatment was analyzed separately. 19/27 (70.3%) patients in N1 stage, 22/33 (66.66%) patients in N2 stage, and 1/2 (50%) patients in N3 stage had complete clinical response whereas PR was observed in remaining patients.

Control of the disease stage wise

Of 39 patients with Stage III disease, 27 patients (69.2%) had complete clinical response and of 46 patients with Stage IV disease, 29 patients (63.04%) had complete clinical response, whereas the remaining patients had PR.

DISCUSSION

In India, HNCs account for 30–40% of total cancers.[7] SCCHN accounts for approximately 5% of newly diagnosed cancers worldwide each year. The integration of chemotherapy into a combined modality approach involving surgery and/or RT has been investigated in an effort to improve the outcome of LASCCHN based on level I evidence. However, only 60% of patients in clinical trial setting are able to receive all the three planned doses of 3-weekly cisplatin due to unacceptably high systemic and mucosal toxicities,[8] the lack of uniform reporting of side effects and small size of individual studies limits conclusion about the relative tolerability of one regimen over the other. More frequent administration could provide better radiosensitization to a larger proportion of the administered radiotherapy dose.[8] Smaller individual doses of the drug may also result in lesser chemotherapy-induced morbidity without compromising the efficacy.

There are now several reports showing benefit in locoregional control and/or survival with alternative cisplatin regimens. A prospective nonrandomized study[9] compared 3-weekly cisplatin (100 mg/m^2) given to younger patients with good Karnofsky performance status (KPS) (n = 30) with weekly cisplatin (40 mg/m^2) in patients with older age or poor KPS (n = 20) along with radical radiotherapy. The CR rate (50% vs.40%), overall response rate (92% vs. 90%), and Grade 3–4 toxicities (53% vs. 40%) were similar in the two cohorts. The only randomized study comparing daily (6 mg/m^2), weekly (40 mg/m^2), and 3-weekly (100 mg/m^2) schedule of cisplatin with conventionally fractionated radiotherapy[10] did not find any significant difference in the efficacy of the regimens (similar response rates and locoregional control), but reported varying degrees of mucosal, renal, and hematologic toxicity. Overall the available data suggests that a cumulative cisplatin dose of 200–250 mg/m^2 given 3-weekly, weekly, or daily during radiotherapy yields therapeutic benefit. The most popular schedule of concurrent cisplatin for SCCHN outside the context of clinical trials is not the 3-weekly regimen but a weekly schedule of cisplatin in the dose range of 30–40 mg/m^2.

In this setting, the toxicity grading was done according to the RTOG and CTC grading systems for radiation-related and chemotherapy-related toxicities, respectively. Patients were evaluated for response to treatment both primary and lymph nodes at 3 weeks and 6 weeks of completion of treatment. The CR rates obtained in this study are comparable with the data in published literature in which

the clinical CR rate is in the range of 65–70%.[11-13] The difference in response rates did not reach statistically significant value ($P = 0.50$) in terms of T and N stages. The patients who had composite Stage III disease had better response rates and the difference was statistically significant ($P < 0.05$).

CONCLUSION

Concurrent chemoradiotherapy using cisplatin 40 mg/m^2 weekly is well tolerated by LASCCHN patients and all the patients were able to complete the total planned dose of radiation. Acute toxicities, most commonly radiation mucositis were reversible with supportive management and were not severe enough to cause discontinuation of treatment. The clinical CR rates obtained in this study (65.8%) are comparable to the results in published literature (65–70%) and the results confirmed the importance of the stage of the disease as the most significant predictor of outcome. Survival benefits and late normal tissue complications were not predictable due to short period of follow-up. Carefully designed prospective randomized studies are needed to address these issues.

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How to cite this article: Prasanth CC, Harilal P, Jayaraman MB, Binesh P. Response Rate, Toxicity, and Compliance in Head-and-neck Cancer Patients Treated with Concurrent Chemoradiation – A Retrospective Analysis. Int J Sci Stud 2019;7(8):107-111.

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