A prospective randomized study comparing concurrent chemoradiation with weekly and 3 weekly cisplatin in locally advanced oropharyngeal carcinoma

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Abstract

Introduction: The chemotherapy schedules with cytotoxic dose or weekly regimes are still challenging, weighing the benefits versus toxicities. This prospective randomized study is an attempt to assess the efficacy of two schedules of cisplatin in management of locally advanced HNSCC. **Objectives:** The objectives of this study was to evaluate tolerance, tumour response and toxicities of concurrent chemoradiation with cisplatin in weekly and three weekly regimes. **Methods:** Locally advanced oropharyngeal squamous cell carcinoma patients fit for concurrent chemoradiation with cisplatin 40 mg/m^2 (weekly) and 100 mg/m^2 (3 weekly) were randomized to Arm A and B concurrently with radiotherapy of 70Gy/35frs/7 weeks. **Statistical Analysis:** Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between the groups. The statistical software SPSS 15.0 was used. **Results:** Between December 2010 and January 2013, 60 patients were enrolled. The median cycles of cisplatin in Arm-A was 5 and 2 in Arm-B. The complete response of 80.9% vs 75% and partial response of 14.3% vs 12.5% was observed in both arms respectively. There was no statistical difference in acute radiation and hematological toxicities between the two groups. With median follow up of 28 months, the 2 and 5 years overall survival was 55% and 58%; 41.6% and 32.3% in arms A and B respectively. **Conclusion:** In our study of locally advanced oropharyngeal carcinoma treated with radical radiotherapy comparing concurrent chemotherapy with cisplatin weekly vs 3 weekly had no significant difference in overall response, complete response and acute toxicities.

Key words: Advanced oropharyngeal carcinoma, concurrent chemoradiation, survival, 3 weekly and weekly cisplatin, toxicities

Introduction

Head-and-neck squamous cell carcinoma (HNSCC) is the fifth most common cancer and the sixth leading cause of cancer mortality worldwide. About two-thirds of patients with HNSCC present with advanced stage disease, most commonly involving regional lymph nodes.[1-3] The treatment of locally advanced HNSCC is extremely challenging, and an aggressive treatment approach is necessary to achieve cure. A combination of radiotherapy and concomitant chemotherapy showed an improved response rate and allowed for organ preservation.[4,5] The evidence recommends platinum-based concurrent chemoradiotherapy as standard of care for locally advanced head-and-neck cancer from rigorously conducted randomized trials and meta-analysis using mortality as outcome of interest.[6-8] Despite compelling evidence regarding the benefit of adding chemotherapy, there exists considerable difficulty in choosing the optimal chemotherapy schedule due to the heterogeneity of study design and different combinations of radiotherapy and chemotherapy.[9] Hence, this study was conducted. The objectives of this study were to evaluate the tolerance, tumor response, and toxicities of concurrent chemoradiation with cisplatin in weekly and 3 weekly regimens.

Materials and Methods

Patient selection

This study was conducted in a regional cancer center between August 2011 and September 2013 to compare the response and outcome of two different cisplatin schedules concurrently with radical radiotherapy.

Inclusion criteria

Histologically proven newly diagnosed oropharyngeal SCC Stage III–IV patients attending the radiotherapy department of our institute were enrolled for the study after taking written informed consent. Patients aged 20–70 years and those who had karnofsky performance scale >70, well-controlled medical comorbidities, and normal baseline hematological, hepatic, and renal functions were included. Institutional Scientific Review Board and ethical committee approval was obtained.

Exclusion criteria

Patients who had active tuberculosis, retroviral infection, and cardiac abnormalities with ejection fraction <60 and those who had received neoadjuvant chemotherapy or undergone surgery were excluded.

Methodology

All patients underwent detailed clinical examination and investigations including direct laryngoscopy and biopsy from primary lesion. Hematological parameters, glomerular filtration rate, chest X-ray, two-dimensional echocardiography, audiometry, computed tomography scans of the head and neck, and dental prophylaxis were done.

Patients were prospectively randomized to two arms using randomization table. Concurrent cisplatin was planned for 40 mg/m^2 weekly, for a minimum of four cycles and maximum of six cycles, and for 100 mg/m^2 once in 3 weeks for maximum two cycles in Arm A and Arm B, respectively to achieve targeted cumulative dose of 200 mg/m^2. Radical radiotherapy was delivered with cobalt-60 teletherapy machine.

Radiotherapy

The radiation treatment volume included the primary tumor site and the neck nodes. All patients were treated with three-field technique initially followed by off-cord boost with two parallel-opposed lateral portals. Total dose to primary and draining lymph node was 70 Gy in 35 fractions, with 2 Gy/fraction/5 days a week. The lower neck with no disease was treated up to 50 Gy

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at a 3-cm depth. Spinal cord sparing was done after 46 Gy. Electron boost was planned for patients with significant nodes in level IIb or V to a dose of 24 Gy in ten fractions. Treatment breaks if necessary were allowed during radiation only for healing of severe (≥Grade 3) normal tissue reactions.

Chemotherapy

All patients received prechemotherapy hydration 24 h prior. Premedication with antiemetics, ondansetron 8 mg and dexamethasone 16 mg were given before chemotherapy, and 20-mmol potassium chloride and a vial of magnesium sulfate (1000 mg) diluted with saline were infused over 1 h each. In weekly arm, cisplatin of 40 mg/m^2 was given along with saline over 3 h. In 3 weekly arm, cisplatin dose of 100 mg/m^2 was given in divided doses over 2–3 days. Postchemotherapy hydration was given and antiemetics continued for the following 2 days. Following our institutional policy, the weekly arm received no more than six cycles of concurrent chemotherapy, and the per-day dose limit of cisplatin was restricted to maximum of 70 mgs in both the arms.

Chemotherapy was administered with minimum levels of hemoglobin >12 gm/dl, leukocyte count >4.0 × 10^9/L, absolute neutrophil count > 2.0 × 10^9/L, platelet count >100 × 10^9/L, and normal renal functions. Further chemotherapy was deferred if required criteria were not met. Growth factors granulocyte macrophage colony stimulating factor (GM-CSF) were not used in the study.

Toxicity assessment

Severe dysphagia and continuous weight loss during therapy were the indications for nasogastric intubation. Complete blood counts and biochemistry (renal function tests, liver function tests, and serum electrolytes) profiles were done weekly. All patients were assessed weekly using the Radiation Therapy Oncology Group criteria for radiotherapy-induced acute toxicities, common toxicity criteria for chemotherapy-induced toxicity, and tumor response according to the WHO criteria. Radiotherapy treatment gap was considered to be an interruption exceeding 5 consecutive days.

Follow-up

Post treatment patients were followed up regularly every 2 weeks for a period of 6 weeks, every 6 weeks up to 3 months and once every 2 months thereafter. Clinical response was assessed at 6 weeks and was confirmed radiologically (contrast-enhanced computed tomography scan) at 3 months after completion of radiotherapy.

Statistical analysis

This study is a descriptive and analytical study. The sample size was calculated by the statistician based on 80% power with 5% level of significance using the formula. The results on continuous measurements are presented on mean ± standard deviation (minimum–maximum) and the results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. $P < 0.05$ was considered to be statistically significant.

Chi-square/Fisher's exact test has been used to find the significance of study parameters on categorical scale between the groups. The survival analysis is carried out using Kaplan–Meir methods. The statistical software SPSS version 15.0 was used for the analysis of the data.

Results

Sixty patients were enrolled in the study between December 2010 and January 2013. Twenty-nine and thirty-one patients were randomized to Arm A and Arm B, respectively. The patient characteristics are shown in Table 1. The base of the tongue was the most common subsite in both the groups (48.3% and 54%, respectively). Majority of them were habituated to tobacco use (93.1% and 93.5%) and alcohol (75% and 67%). Most of the patients presented with T3 tumors 18 in Arm A and 17 in Arm B (67.8% and 58%, respectively). T4 tumors were 9 (31.1%) and 13 (42%) in respective arms. The nodal disease observed at presentation was N0 (17.2% and 22.6%), N1 (31.1% and 32.2%), N2 (44.8% and 35.5%), and N3 (6.9% and 9.7%), respectively in both the arms.

The median number of chemotherapy cycles in Arm A was 5 and 2 in Arm B. The median total cumulative dose of cisplatin in Arm A is 271.8 mgs (range: 120–320 mgs) and Arm B is 303 mgs (range: 180–350 mgs) ($P = 0.02$). Twenty-five (89%) in Arm A and thirty (96.8%) in Arm B received cisplatin >200 mg/m^2. Both the groups of patients received radiation dose of 70 Gy in 35 fractions over 7 weeks. There was no difference in the overall treatment time (OTT) in both the arms (Arm A: 53.4 days [±5.2] and Arm B: 53.8 days [±7.7]).

All patients completed the planned radiation dose of 70 Gy. We observed a median gap of 6 days (range: 5–18 days) during radiation due to reactions (Grade II–III mucositis and candidiasis) in nine patients – four in weekly and five in 3 weekly.

Eighteen patients in weekly arm discontinued chemotherapy (fourth cycle [three patients], fifth cycle [nine patients], and sixth cycle [six patients]) due to candidiasis (one patient), diarrhea (two patients), neutropenia Grade II

Table 1: Patient characteristics

Characteristics	Arm A (%)	Arm B (%)	*P*
Gender			
Male	27 (93.1)	30 (96.8)	4.49
Female	2 (6.9)	1 (3.2)	
Median age (years)	54.4±7.9	55.0±6.5	0.14
Habits			
Tobacco	27 (93.1)	29 (93.5)	0.82
Alcohol	21 (75)	21 (67)	
Site			
BOT	14 (48.3)	17 (54)	0.83
Tonsil	10 (34.5)	7 (22.6)	
Soft palate	3 (10.3)	5 (16.1)	
PPW	2 (6.9)	2 (6.5)	
T status			
2	2 (6.9)	1 (3.2)	0.67
3	18 (62)	17 (54.8)	
4	9 (31.1)	13 (42)	
N status			
0	5 (17.2)	7 (22.6)	0.35
1	9 (31.1)	10 (32.2)	
2	13 (44.8)	11 (35.5)	
3	2 (6.9)	3 (9.7)	
Stage			
III	10 (34.5)	11 (35.5)	0.91
IV	19 (65.5)	20 (64.5)	

BOT=Base of tongue, PPW=Posterior pharyngeal wall

(two patients), leukopenia Grade II–III (eight patients), hyponatremia (two patients), pneumonia (one patient), and social reasons (two patients). The treatment discontinuation rate was 53.5% beyond four cycles of chemotherapy in weekly arm.

The delays within the weekly cycles ranged from 5 to 13 days (median: 7 days) during the third, fourth, and fifth cycles in 12 patients. Seventeen patients in 3 weekly arm had delayed the second cycle ranging between 5 and 20 days (median: 12 days) due to oropharyngeal infection (two patients), pneumonia (one patient), mucositis and candidiasis (five patients), leukopenia Grade II–III (five patients), and neutropenia Grade II–III (four patients).

Toxicities

There was no statistical difference in acute radiation toxicities and hematological toxicities between the two groups [Tables 2 and 3]. Acute hematological toxicities such as ≥Grade 3 leukopenia and neutropenia were higher in Arm A. Two patients of Arm B died due to neutropenic sepsis and one in Arm A due to aspiration pneumonia.

The nutrition of patients was maintained by nasogastric feeding tube placement at the end of the 3rd week and parenteral nutrition fortnightly throughout the duration of chemoradiation. None of our patients had renal toxicities.

Outcomes

The complete response and partial response were seen in 80.9% versus 75% and 14.3% versus 12.5% in weekly and 3 weekly, respectively. Stable disease was 4.8% in Arm A and 4.2% in Arm B at 8 weeks after completion of the treatment.

Table 2: Radiation toxicities

Toxicities	Arm A (*n*=28), *n* (%)	Arm B (*n*=31), *n* (%)	*P*
Mucositis			1.00
Grade ≤2	19 (67.85)	22 (70.96)	
Grade ≥3	9 (32.14)	9 (29.03)	
Dysphagia			0.27
Grade ≤2	15 (53.6)	21 (67.7)	
Grade ≥3	13 (46.4)	10 (32.3)	
Dermatitis			0.73
Grade ≤2	24 (85.72)	25 (80.65)	
Grade ≥3	4 (14.28)	6 (19.35)	
Larynx			1.00
Grade ≤2	25 (89.3)	28 (90.3)	
Grade ≥3	3 (10.7)	3 (9.7)	
Nausea/vomiting			0.22
Grade ≤2	26 (92.86)	31 (100)	
Grade ≥3	2 (7.1)	0	

Table 3: Hematological toxicities

Toxicities	Arm A (*n*=28), *n* (%)	Arm B (*n*=31), *n* (%)	*P*
Anemia			1.00
Grade ≤2	28 (100)	30 (96.7)	
Grade ≥3	0	1 (3.3)	
Leukopenia			0.32
Grade ≤2	21 (75)	27 (87.1)	
Grade ≥3	7 (25)	4 (12.9)	
Neutropenia			0.24
Grade ≤2	23 (82.1)	29 (93.5)	
Grade ≥3	5 (17.9)	2 (6.6)	
Thrombocytopenia			1.00
Grade ≤2	28 (100)	30 (96.7)	
Grade ≥3	0	1 (3.3)	

Locoregional control

The median follow-up was for 28 months (range: 2.8–66.9 months). A number of patients who developed locoregional relapses were 4 (14.2%) in Arm A and 2 (6.4%) in Arm B at 13 and 16 months, respectively. Stable or progressive disease was seen in 8 (28.5%) and 13 (41.9%) patients, respectively, assessed at 3 months posttreatment. Nondisease-related deaths were two in weekly arm and five in 3 weekly arm. Median disease-free survival (26.4 and 27.4 months) and overall survival (35.4 and 32.9 months) at 2 years were similar in both the arms. OS and disease-free survival at 5 years were not significant [Figures 1 and 2].

Discussion

Radiotherapy and surgery have played a primary role in the management of locally advanced head-and-neck cancers. Addition of chemotherapy has improved locoregional control or organ preservation. Many chemotherapeutic agents such as cisplatin, 5-fluorouracil, methotrexate and mitomycin with radiation therapy have been used either in definitive treatment or adjuvant treatment.[10-17] Strong evidence recommending platinum-based concurrent chemoradiation as the standard of care for locally advanced head-and-neck cancers comes from rigorously conducted randomized trials and meta-analysis.[6-8]

High-dose 100 mg/m^2 cisplatin once in 3 weeks is the most widely used regimen as it has systemic cytotoxic effect seen by decrease in the rate of distant metastasis and also radiosensitizing effect as denoted by enhanced locoregional control but is associated with increased toxicity.[5,12,18] A smaller individual dose may lead to less chemotherapy-induced morbidity without compromising on the efficacy. The frequent administration of smaller doses would ensure sustained radiosensitization of the administered radiotherapy dose.[9,19,20]

The uncertainty regarding the optimal scheduling of cisplatin with radiation in head-and-neck carcinoma has led to a comparison of various dose schedules. We have compared patients receiving cisplatin 100 mg/m^2 once in 3 weeks and 40 mg/m^2 weekly with definitive radiotherapy. There was no dose reduction of cisplatin done in our study, as our aim was to assess the toxicity profile and tolerance of two schedules of concurrent cisplatin. The incidence of mucositis, dysphagia, and skin and hematological toxicities was slightly higher in the 3 weekly arm in literature; hence, only two cycles of cisplatin were aimed in our study.[21-25]

Toxicities were manageable with Grade III mucositis in 32.14% and 29.03%, Grade III dysphagia in 46.4% and

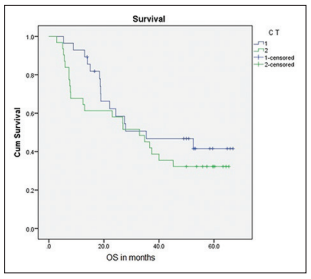

Figure 1: Overall survival. 1 is weekly arm and 2 is 3 weekly arm

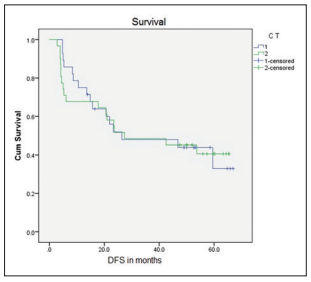

Figure 2: Disease-free survival. 1 is weekly arm and 2 is 3 weekly arm

32.3%, Grade III leukopenia in 25% and 12.9%, and Grade III neutropenia in 17.9% and 6.6%, respectively ($P > 0.05$). Three weekly arm had lesser hematological toxicities but more radiation-induced toxicities compared to the weekly arm. Grade IV laryngeal and hematological toxicities were seen in two patients of Arm B but none in Arm A.

Ho *et al*. compared the differences in dose intensities, delays, and toxicities between concurrent 3 weekly (80–100 mg/m^2) and weekly (40 mg/m^2). Most patients received a higher cumulative dose of at least 240 mgs in weekly arm and 200 mgs in 3 weekly arm.[26] In contrast to other studies, our study had a cumulative dose of 303 mgs in 3 weekly arm compared to 271.8 mg in the weekly arm.[19,27,28] Ang analyzed the different cisplatin schedules and observed that irrespective of the regimens, a cumulative dose of 200 mg/m^2 was sufficient for a beneficial antitumor outcome.[9,29] Majority of our patients received total dose of >250 mg cisplatin in both the arms. Studies also showed that none of the patients who commenced concomitant 3 weekly cisplatin 100 mg/m^2 completed three cycles of chemotherapy, whereas sixty-five percent of patients completed the planned third cycle in 80 mg/m^2.[21,26] In our study, 3 weekly cisplatin dose was fixed at 100 mg/m^2, and 96% of patients completed the planned two cycles in 3 weekly arm. In the weekly arm, 89.34% of patients received four to six cycles of cisplatin.

We observed a median OTT in weekly arm of 53.4 days (range: 47–59 days) and 3 weekly arm 53.8 days (range: 46–68 days), similar to other studies, where the OTT in weekly arm ranged between 43 and 51 days and 3 weekly arm was prolonged and ranged between 44 and 70 days.[19,22,25,30,31] Treatment interruptions in our study were more in weekly arm (19%) compared to 3 weekly arm (12.5%) which was not significant statistically and is comparable with historical data.[31-33]

The overall immediate response was 95.1% in Arm A and 87.5% in Arm B and complete response at 3 months was 80.9% and 75%, respectively ($P > 0.05$). The median OS ($P = 0.303$) and disease-free survival ($P = 0.953$) at 2 years were also comparable between both the arms but were not statistically significant. The 2-year OS survival was 55% and 58% and 5-year OS was 41.6% and 32.3% in Arm A and Arm B, respectively. This has been achieved with acceptable Grade II and III toxicities. Homma *et al*. documented higher 2-year survival of 93% in weekly arm with complete response rate of primary at 98%, whereas Geiger *et al*. showed no significant survival difference between both the treatment schedules.[34,35]

Conclusion

This prospective randomized control study of locally advanced oropharyngeal carcinoma treated with radical radiotherapy comparing concurrent weekly 40 mg/m^2 versus 3 weekly 100 mg/m^2 cisplatin chemotherapy did not find a statistically significant difference in clinical/radiological complete response and acute toxicities. Hence, concurrent weekly cisplatin with radical radiotherapy is an acceptable alternative to high-dose 3 weekly cisplatin in a limited resource setup where a large number of patients are treated on outpatient basis. As our study is not powered enough to comment on OS and disease-free survival, further prospective randomized study is needed with larger number of patients.

The choice of chemotherapy regimen should therefore be based on the individual patient characteristics, available facilities at the treating institute and experience of the treating team.

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Conflicts of interest

There are no conflicts of interest.

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