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Comparison of daily low dose cisplatin versus weekly cisplatin concurrently with radiotherapy during head and neck cancer

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ABSTRACT

Introduction : Head and neck cancers can arise in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands and include a variety of histopathologic tumours. Squamous cell cancer (SCC) is the most common pathological type of head and neck cancer.
Materials and Methods: This is prospective, Observational and comparative study. The diagnosis of untreated squamous cell carcinoma of the head and neck region, i.e., oral cavity, oropharynx, hypopharynx, or larynx in advanced stage III, IVA or IVB SCCHN was confirmed by a radiation oncologist prior to the initiation of the treatment.
Results : Patients were considered to comply with radiation treatment if they completed 70 Gy within 45 days. Chemotherapy compliance (six cycles in weekly or 28–30 cycles in daily cisplatin) were 63% and 73%, respectively. The primary reason for noncompliance toward chemotherapy (37% vs. 27% in weekly vs. daily Cisplatin studies, respectively) was due to the development of excessive toxicity. This also included those who left treatment midway (due to any reason) or died during therapy.
Conclusions : Therefore, if an intensified treatment protocol has to be used, i.e. modest acceleration along with either "weekly" or "daily" cisplatin, both can be used, provided patients are selected properly and due attention is paid to timely and adequate supportive care.

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1. Introduction

Head and neck cancers account for more than 550,000 cases and 380,000 deaths annually worldwide and are the 6^{th} most common cancer type.[1] Head and neck cancers can arise in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands and include a variety of histopathologic tumours. Squamous cell cancer (SCC) is the most common pathological type of head and neck cancer.[2] Prognosis of patients with squamous cell carcinoma of the head and neck (SCCHN) has improved in the last decades.[3] For numerous tumours, concurrent chemo radiotherapy (CCRT) has a vital role in the management of loco regional disease. The usage of CCRT in head & neck cancer is significant because loco regional control is pivotal here.[4]

The primary and chief method includes definitive surgery; which is followed by adjuvant concurrent chemo radiotherapy (CCRT) or Radiotherapy (RT) alone, which ensures precise pathologic staging and exact identification and documentation of high-risk characters that guide the adjuvant therapy.[5]The alternative method comprises definitive concurrent chemo radiotherapy (CCRT) with salvage surgery as an optional backup management plan. This management approach lacks the pathologic data, a setback which is equalised by superior organ protection. This advantage is previously recognised for laryngeal cancer but is progressively documented for other anatomic locations; however, this method remains controversial for oral cavity tumours.[6]

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The third method usages of neoadjuvant chemotherapy followed by definitive surgery or radiation with curative intent. Major benefits comprise a fast decrease in tumour bulk in responders and the possibility to reduce the risk of distant failure. Frequently times response to induction predicts responsiveness to following definitive chemo radiotherapy. Though, this can lead to lengthy treatment time and extra chemotherapy-related lethal effects from complete doses.[7] This method remnants controversial for valid reasons, and is presently under analysis in numerous huge, multicentre, randomized trials to determine important advantages over CCRT.[8] Owing to the prominent incidence of acute toxic effects, management should preferentially be done at experienced centres, in which superior outcomes are seen.[9]

Cisplatin is an effective radio sensitizer and the most usually used for concurrent chemo radiotherapy (CCRT) in head & neck cancer. A meta-analysis investigative numerous chemo radiotherapy regimens suggested that platinum comprising regimens might offer an existence benefit equated with non-cisplatin comprising regimens.[10] Presently, the most extensively used standard regimen is 100 mg/m^2 cisplatin every 3 weeks, combined with ~70 Gy radiation delivered in 1.8–2.0 Gy daily fractions. This regimen causes severe lethal outcomes, such as ototoxicity, nephrotoxicity and neurotoxic effects, nausea and vomiting, as well as severe mucositis, which make the treatment appropriate only for patients with normal creatinine clearance and good performance status. Moreover, loco regional failure rates are 35–65%, depending on tumour location, stage, and respectability.[11] To limit toxic effects, other management schedules are likewise being used, but equal effectiveness has not been done. For example, with once-weekly 30 mg/m^2 cisplatin regimens, no nephrotoxic effects were stated, but mucositis and neutropenia were prominent.[12]

The present study is a comparison of two successive prospective safety and efficacy, i.e. use of concurrent cisplatin either a daily schedule or weekly. Both chemotherapy schedules were used along with a moderately accelerated radiotherapy (RT) schedule.

2. Materials and Methods

2.1. Study design

This is prospective, Observational and comparative study

2.2. Study population

The diagnosis of untreated squamous cell carcinoma of the head and neck region, i.e., oropharynx, oral cavity, hypopharynx, or larynx in advanced stage III, IVA or IVB SCCHN was established by a radiation oncologist before to start the treatment.

Physical examination, panendoscopy, CT scan of neck & face as well as chest radiograph and ultrasound of abdomen were done to determine the degree of disease and to exclude distant metastases. The patients are staged according to the tumour-node-metastasis (TNM) classification.

2.3. Inclusion criteria

1. Age: 18 to 75.
2. SCCHN proved by histopathology.
3. American Joint Committee on Cancer (AJCC stage-III, IVA and IVB.
4. Eastern Cooperative Oncology Group (ECOG performance status ≤ 2.
5. 5. Laboratory Values: WBC $\geq$4000/mm^3, Platelets count 1.4 lakh/ mm^3, haemoglobin $\geq$9 gm/dl, alanine aminotransferase (ALT), Aspartate aminotransferase (AST) level of less than twice the upper limit of the normal range and total bilirubin 2.0 mg/dl, Serum Creatinine 1.5 mg/dl, and creatinine clearance $\geq$60 ml/min
6. Informed written consent signed before enrolment.

2.4. Exclusion criteria

1. Earlier chemotherapy or head and neck radiation
2. Patients having a second primary neoplasm
3. Lactating or Pregnant female
4. Sever diseases of vital organs
5. Carcinoma of the nasopharynx and paranasal sinuses
6. Other malignancies
7. Active uncontrolled infection

2.5. Treatment protocol

Subsequent build-up and dental prophylaxis, patients were planned for a moderately accelerated RT schedule delivering 70 Gy in 35 fractions over 6 weeks (instead of 7 weeks) at 2 Gy per fraction, in both the studies. The RT was delivered in a phased manner using conventional three field techniques. Three‑dimensional conformation or intensity-modulated RT (IMRT) was not practised in the department at that time. In a daily group, Cisplatin was given at 6 mg/m^2 (capped at 10 mg) in 500 ml normal saline (NS) solution for all 6 weeks of treatment. And Cisplatin (35 mg/m^2) weekly (maximum 50 mg) along with 3 L of fluids and mannitol was given.

2.6. Radiotherapy technique

In both the studies, patients were simulated with a thermoplastic head and neck immobilization device. Phase I was planned to include the primary and the draining lymph node regions and a dose of 44 Gy/22 fractions/4.5 weeks was delivered 5 days in a week at 2 Gy/fraction (Monday to Friday). In phase, II-off‑cord reduction was done,

and a dose of 16 Gy/8 fractions/1.5 weeks at 2 Gy/fraction was delivered 5 days in a week (Monday to Friday). Phase III was delivered as a boost on Saturday, as limited volume portal including original GTV with a margin of 2 cm. A dose of 10 Gy/five fractions/ over five Saturdays at 2 Gy/fraction was delivered. Scheduled overall treatment time was 40 days. Treatment was delivered using a telecobalt machine (Theratron 780-C, AECL).

2.7. Chemotherapy delivery

Patients who received weekly Cisplatin schedule received prophylactic antiemetic cover (i.e., oral dexamethasone and ondansetron for 3 days). Chemotherapy was administered as "patient" since daycare facility was unavailable. Patients who received a daily dose of Cisplatin were administered chemotherapy on an outpatient basis, with hydration with one unit of NS over 120 minutes. A single shot of injection ondansetron was given just before chemotherapy. Cisplatin was delivered as a bolus in 50 ml NS over 10 min. No planned hospitalization or round the clock antiemetic cover was given in this group. RT was synchronized with Cisplatin therapy in both the groups and delivered within an hour of administration of Cisplatin. Chemotherapy was withdrawn if total leukocyte count dropped <4000/cumm.

Patients were monitored frequently throughout RT and subsequent completion of treatment. Compliance, acute and severe toxicity containing cisplatin-induced ototoxicity and nephro were verified based on European Organization for Research and Treatment of Cancer/ Radiation Therapy Oncology Group (EORTC /RTOG) grading system and equated to both procedures. The two-principal toxicity-xerostomia and dysphagia were recognised by the handling oncologist. Aspiration was studied using serial video fluorography analyses. Hearing valuation, to study cisplatin-induced hearing loss, was done by serial pure tone audiometry assessment. Likewise, nephrotoxicity was studied using GFR estimation, as a baseline and during follow-up. Existence outcome measures (LRS and overall survival [OS]) were also calculated and equated.

2.8. Primary outcome measure

The Primary endpoint of this study is a treatment response. Treatment response was measured 6 weeks subsequent accomplishment of management according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 as complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD) using the data of panendoscopic assessment and CT scans of neck & face obtained 6 weeks after therapy. Pathologic validation will be essential for patients supposed to have a medical indication of residual disease at the primary site 6 weeks after therapy.

2.9. Secondary outcome measure

The Secondary endpoint of this study is treatment associated with acute toxicities. Acute toxicities will be stated weekly throughout treatment and 6 weeks after completion of treatment. Acute toxicities of the two regimens will be assessed by determining the frequency of severe ($\geq$ grade 3) toxicities based on RTOG Acute Radiation Morbidity Criteria using the information of the history and physical examinations, ECOG performance status, and blood tests like Complete blood count (CBC), electrolyte, creatinine, ALT and AST.

2.10. Ethical implications

1. Participants were volunteered.
2. All patients were comprised in the study after notifying about the nature of the study. They were clarified about the aim, objective, procedure, risk and benefit of the study in easily own language.
3. Written informed consents were taken from patients.
4. All patients will be coded by a serial number which can be referenced to the chart number only.
5. All members were free to take part or refuse in the study
6. The study was not restricted to patient management or deal with a moral or social issue.

Basic clinic pathologic parameters were recorded, including age, sex, pathologic stage, a primary site of tumour, and pathologic features of the tumour (e.g., differentiation of tumour, extracapsular nodal spread, the status of resection margin, the formation of tumour emboli, regional lymph node involvement, perineural invasion, and lymph vascular invasion).

2.11. Statistical analysis

Differences in patient demographics between Cisplatin treated patients was analysed with chi-squared tests or two-sided student's t-tests. Fisher's exact test or chi-squared test will be used to equate treatment arms concerning toxicity rates and response. Statistical co-relation will be done by SPSS (Statistical Package for the Social Sciences) software. A value of $P < 0.05$ will be considered statistically significant.

3. Results

Comparative outcomes of the two groups analyses that were carried out. The comparative demographic profile is explained in Table 1. All (120) patients had a history of tobacco consumption either in the form of pan masala, paan (betel), bidi, or cigarette smoking. Most of these patients were staged based on computed tomography (CT) imaging and were considered inoperable by the stating ENT surgeon/head and neck oncologist or the patient had

Table 1: Demographic profile

Characteristics	Daily Cisplatin + RT (n=60)	Weekly cisplatin + RT (n=60)	p - value
Age (years) Mean, Range	54 (27-73)	53 (26-73)	0.83
Gender			0.94
Male	56	57	
Female	4	3	
Tumor Location			0.78
Oropharynx	29	28	
Oral cavity	18	16	
Hypopharynx	11	12	
Larynx	2	4	
T stage			0.73
T1	13	14	
T2	19	17	
T3	12	11	
T4	16	18	
N stage			0.53
N0	11	9	
N1	15	18	
N2	28	26	
N3	6	7	
TNM			0.74
III	26	23	
IV	34	37	
KPS			0.63
70	4	5	
80	34	36	
90	22	19	

KPS=Karnofsky performance status

declined surgery.

Patients were considered to fulfil with radiation treatment if they completed 70 Gy within 45 days. Chemotherapy compliance (six cycles in weekly or 28–30 cycles in daily cisplatin) were 63% and 73%, correspondingly. The primary reason for nonfulfillment toward chemotherapy (37% vs. 27% in weekly vs. daily Cisplatin studies, correspondingly) was due to progress of extreme toxicity. This also comprised those who left treatment midway (due to any reason) or died during therapy.

Acute toxicity was documented as per the RTOG/EORTC protocols and is stated in Table 2. Grade III/IV mucositis, i.e., confluent mucosal reactions and ulcerations and dysphagia, both were considerably greater in patients receiving weekly Cisplatin.

During treatment, patients lost weight due to mucositis leading to inadequate oral intake. The enteral/parenteral support was provided either as an outpatient or after hospitalization. On regular, the nasogastric/percutaneous endoscopic gastrostomy (PEG) tube insertion was done out in the 3^{rd} week of RT in both the groups. All patients with Hb <10 g/dl were transfused whole blood as per the policy. The intravenous fluid was given to patients either as daycare or as in-patients, as and when clinical signs and symptoms of dehydration were seen. Antibiotics and growth factors were not used prophylactically.

Hospitalization to take care of treatment-related sickness was measured as an intervention regarding supportive care. This was apart from the regular 1–2 days admission for weekly cisplatin chemotherapy administration. The mean duration of hospitalization for supportive care was 3 days (range: 1–6 days) in both groups.

Late toxicity was noted as per RTOG/EORTC criteria and is cited for both the groups in Table 3. Chemo radiation-related Grade II/III dysphagia, xerostomia, aspiration and nephrotoxicity and chemotherapy-related ototoxicity were reviewed and equated. No significant variance in terms of any of the long-term outcome was found in either group. Chemotherapy-related hearing loss and renal impairment (which was asymptomatic and transient) were also of alike magnitude.

4. Discussion

This is one of the main potential studies assessing different management regimens for combined radio-chemotherapy in SCCHN patients suffering combined RCT with cisplatin. We examined SCCHN patients treated at three different sites in Arunachal Pradesh. One benefit of this study was, that management allocation was done by the site (based on internal guidelines) and not on patient-based measures, thus

Table 2: Acute morbidity (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring criteria)

Variable	Reactions grade	Daily cisplatin + RT n (%)	Weekly cisplatin + RT n (%)	p – value
Dysphagia	Grade II	16 (26)	4 (6)	<0.0001
	Grade III/IV	35 (58)	53 (88)	
Mucositis	Grade I/II	5 (8)	16 (26)	<0.0001
	Grade III/IV	29 (48)	51 (85)	
Anaemia	Grade I	7 (11)	16 (26)	0.11
	Grade II	3 (5)	7 (11)	
Leukopenia	Grade I/II	9 (15)	18 (30)	0.14
	Grade III	6 (10)	5 (8)	
Weight loss in kg (median)		4 (6)	4 (6)	0.84

Table 3: Late toxicity (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring criteria)

Variable	Daily cisplatin + RT n (%)	Weekly cisplatin + RT n (%)	p – value
Dysphagia and aspiration (Grade II/III)	11 (18)	17 (28)	NS
Xerostomia (Grade II/III)	20 (33)	29 (48)	NS
Nephrotoxicity (>50% fall in GFR)	1 (1.6)	2 (3)	NS
Ototoxicity	2 (3)	3 (5)	NS

without significant selection bias.

Most randomized experiments examining the role of simultaneous cisplatin-based RCT used a three-weekly roster of cisplatin 100 mg/m^2 and this management regimen is measured the standard therapy in LA-SCCHN patients. Though, it is related with considerable toxicity and numerous trials presented suboptimal compliance with cisplatin 100 mg/m^2 possibly negatively influencing the outcome.[13] Consequently, low-dose weekly cisplatin rosters are regularly used in medical tradition despite the deficiency of indication from prospective randomized trials.[14]

Hypothetically, daily administration of low‑dose cisplatin might derive the highest advantage from fractionated administration of both management modalities concurrently. In our study, low dose cisplatin offers a maximum advantage, cisplatin acts as a radiosensitizer.[15] We started a single-arm analysis of using low-dose cisplatin daily, based on the practise reported by Jeremic et al. and Bartelink et al.[16] Low-dose daily cisplatin suggestions ease of administration in the outpatient clinic (avoiding the need for diuresis, hydration, prophylactic hospitalization and antiemesis) along with good acceptability than other regimes and greater consequences in epithelial cancers.[17]

Simultaneous administration of cisplatin at 3 weekly intervals along with RT is the normal of care but is concomitant with severe mucosal and haematological toxicities. Minor and radiosensitizing doses of cisplatin (35–40 mg/m^2) dispensed once every week has been extensively used and revealed alike efficacy and minor toxicity and this was the basis for selecting weekly cisplatin protocol world over.[18]

In our study augmented mucosal toxicity to (65% in the daily group and over 90% in a weekly group). The likely clarifications for superior mucositis in the weekly group could have been (1) more oral cavity tumours (8% Vs 26% vs.) leading to more of oral mucosa included in the RT field (2) with time our awareness and understanding the essential for nutritious support grew; so, enteral support rate increased which could have exposed in slighter mucosal reaction in the analysis that was conceded out using daily cisplatin (3) ultimately, it may well be that daily cisplatin is less toxic than weekly. Our late radiation‑related accepting changes and/or aspiration rate was alike in both the studies and was comparable with other RT series.[19]

In our study, we found considerably advanced renal toxicity with a 3-weekly cisplatin schedule. Numerous studies stated superior toxicity for 3-weekly cisplatin, mostly renal toxicity, but also hematotoxicity and mucositis/dermatitis.[20]In compare, Tsan et al. stated a superior rate of mucositis and overall toxicity in the weekly cisplatin group.[21] Interestingly, consequences from previously examined analyses report conflicting consequences concerning toxicity. Similarly, the current comparative analysis of dissimilar prospective trials presented fewer toxicities with the 3-weekly regimen.[22] We consequently decided to examine oto- and nephrotoxicity as two of the main longstanding toxicities in patients treated with cisplatin.

5. Conclusions

As per this comparative statement of two prospective studies supported out successively, daily cisplatin group seems to be comparable to weekly routine in terms of existence consequences, compliance and toxicity. Hence, if a strengthened management procedure has to be used, i.e. modest acceleration alongside with either "weekly" or "daily" cisplatin, both can be used, provided patients are choosing correctly and due responsiveness is paid to appropriately and adequate supportive care.

6. Source of Funding

None.

7. Conflict of Interest

None.

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