Section: Radiation Oncology

Original Research Article

COMPARISON OF LOW-DOSE DAILY CISPLATIN VERSUS WEEKLY CISPLATIN ALONG WITH CONCURRENT ACCELERATED RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Abstract

Background: The sixth most common cancer worldwide is head and neck cancer. This study aimed to comprehensively analyse clinical outcomes, toxicities, and treatment responses in two treatment arms, ARM 1 (low dose daily cisplatin) and ARM 2 (weekly dose of cisplatin), for head and neck cancer patients. **Materials and Methods:** The chemotherapy schedule was divided into Arm 1 low dose daily cisplatin 6 mg/m2 and Arm 2-weekly cisplatin 40 mg/m2. A total of 30 consecutive patients were enrolled in each arm, all having received a histopathological confirmation of their condition. Patient demographics, tumour characteristics, treatment-related adverse effects, and treatment responses were assessed in a cohort of patients. Data were analysed to understand the implications of these factors on treatment outcomes. **Results:** The demographic distribution highlighted varied age groups and a male predominance. ECOG performance status and patient habits were recorded, adding context to patient profiles. Tumour characteristics revealed differences in tumour nodal stages and histological differentiation, contributing to understanding disease progression and tumour biology. Staging grouping reflected variations in cancer stages between the arms, potentially impacting treatment responses. Treatment responses indicated a higher number of complete responses in ARM 1. Systematic toxicity analysis identified prevalent adverse effects, such as nausea and vomiting, with distinct patterns between the treatment arms. **Conclusion:** Despite slightly higher toxicity, a daily low-dose cisplatin regimen is comparable in effectiveness to the weekly approach. While the study lacks long-term follow-up, it highlights the potential of the daily cisplatin method to achieve strong local control as an out-patient set-up in overburdened institutions.

INTRODUCTION

Cancer remains a formidable global health concern, escalating prevalence as life expectancy rises. This trend is particularly pronounced in developing nations, including India. The prevalence of head and neck cancers in India is particularly alarming due to the widespread use of smokeless and smoked tobacco products, contributing to substantial morbidity and mortality.[1] Globally, head and neck cancers are the 6th most common form of cancer. However, in India, their occurrence is even more prevalent, constituting around 30% of all cancers among males and 11 to 16% among females. The country witnesses over 200,000 new cases of head and neck cancers annually, with oral cancers alone accounting for approximately 80,000 diagnoses yearly.[2] Notably, a Lancet study from March 2012 revealed that tobacco-related cancers accounted for about 42% of male and 18% of female cancer-related deaths in India. The most prevalent fatal cancers among men were oral (including lip and pharynx) and lung.[3]

Many patients present with locally advanced stage head and neck cancers, where surgical resection is often unfeasible or associated with substantial morbidity. Historically, treatment involved localised radiotherapy (RT), resulting in local control rates ranging from 50-70% and 5-year survival rates of 10-20%. To address this, combining chemotherapy and

radiation emerged as a rational strategy for locally advanced head and neck cancer.[4] Chemotherapy plays a crucial role in sensitising tumours to radiotherapy. It achieves this by impeding tumour repopulation, targeting hypoxic cells, hindering the repair of radiation-induced sublethal damage, eradicating micrometastatic disease beyond radiation fields, and reducing tumour mass. This reduction enhances blood supply and reoxygenation, amplifying radiation's efficacy.

Numerous trials have examined combining chemotherapy and radiation's viability and enhanced outcomes. Cisplatin often forms the cornerstone of chemotherapy as a sole agent or in combination with other compounds. These trials consistently showcased the anticipated benefits of supplementing radiation with chemotherapy, a finding corroborated by various meta-analyses. Numerous such analyses have explored whether the combination of chemo-radiotherapy surpasses radiotherapy alone regarding locoregional control and survival.[5]

The challenge of head and neck cancers in India underscores the necessity for comprehensive strategies, merging chemotherapy and radiation, to combat the locally advanced cases. This approach holds promise as it combines the unique advantages of both treatments, potentially improving patient outcomes and quality of life. This study aimed to evaluate and compare daily low-dose cisplatin versus weekly Cisplatin concurrently with accelerated radiation in locally advanced squamous cell carcinoma of the head and neck.

MATERIALS AND METHODS

This study was designed as a prospective double-arm investigation with a Phase II structure conducted at the Department of Radiotherapy within the Barnard Institute of Radiology & Oncology at Madras Medical College in Chennai from October 2016 to August 2017.

The study focused on patients afflicted with squamous cell carcinoma of the head and neck. A total of 30 consecutive patients were enrolled in each arm, all having received a histopathological confirmation of their condition. The recruitment occurred within the outpatient department of the medical facility. The primary objective of the treatment was curative, tailored to the patient's disease stage, performance status, and any co-existing medical conditions. The study received approval from the institute's ethical committee on October 4, 2016. Patients who participated in the study were extensively informed about their involvement's potential advantages and drawbacks. Each patient then provided informed consent in their local language, Tamil.

Inclusion criteria were established to identify eligible participants

Biopsy-proven cases of newly diagnosed squamous cell carcinoma in the head and neck region. The primary tumour sites were limited to the oral cavity, oropharynx, hypopharynx, and larynx. The age of participants ranged from 20 to 60 years, and patients exhibited locally advanced squamous cell carcinoma, specifically Stage III or IV A. Individuals had not previously undergone chemotherapy or radiotherapy. Performance status on the Eastern Cooperative Oncology Group (ECOG) scale was 0-1. No major, life-threatening comorbidities were present.

Exclusion criteria were defined to exclude certain cases from the study

Cases with histopathology other than squamous cell carcinoma. Tumours in the nasal cavity, paranasal sinuses, and nasopharynx. Patients with inadequate hepatic and renal function and limited bone marrow reserves. Participants who declined chemotherapy treatment at any stage. Individuals with a history of prior treatment for a different malignancy and patients with metastatic or recurrent disease were excluded.

Chemotherapy schedule

Arm 1-low dose daily cisplatin 6 mg/m2:

CDDP was given at 6 mg/m2 (capped at 10 mg) in 50 ml normal saline (NS) solution infused over ten minutes on all radiation treatment days after hydration with 500 ml of normal saline. Injection of ondansetron 8 mg as antiemetics was given just before chemotherapy. This was given on all RT days one hour before radiation. Renal and hematologic parameters were assessed every week. Daily chemotherapy was given on an outpatient basis.

Arm 2-weekly cisplatin 40 mg/m2

Inj. Cisplatin 40mg/m2 diluted in 500 ml normal saline, infused over 2 hours, every week on Mondays, during radiation to 5-6 cycles. Renal and hematologic parameters were assessed before each cycle of chemotherapy.

All the data were entered into MS Excel, and frequency and percentage were expressed.

RESULTS

The study examined two treatment arms, ARM 1 and ARM 2, within specific age groups. In ARM 1, the age distribution was as follows: 17% of participants were aged 31-40, 30% were aged 41-50, and 53% were aged 51-60. In ARM 2, the respective age distributions were 20%, 37%, and 43%. The gender distribution showed that ARM 1 comprised 24 males and six females, while ARM 2 had 25 males and five females.

Regarding performance status, based on the ECOG scale, ARM 1 had 63% of participants with an ECOG score of 0 and 37% with a score of 1. In ARM 2, these percentages were 60% and 40% respectively. Habits such as tobacco use and alcohol consumption were also recorded. In both arms, 27% used tobacco (smoking) and the same percentage used smokeless tobacco. Alcohol consumption was reported by 20% and 16% in ARM 1 and ARM 2, respectively, while a small portion engaged in tobacco and alcohol use.

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Participants with no such habits accounted for 13% in ARM 1 and 10% in ARM 2.

The study evaluated various symptoms and signs in the participants. The most common symptoms included ulcer growth (60% in ARM 1, 53.3% in ARM 2), pain (43.3% in ARM 1, 46.6% in ARM 2), and dysphagia (40% in ARM 1, 43.3% in ARM 2). Other symptoms, such as odynophagia, neck swelling, and voice changes, were also observed, albeit with varying frequencies between the two arms.

The distribution of primary tumour sites indicated that ARM 1 had 20% of cases in the oral cavity, 33.3% in the oropharynx, 30% in the hypopharynx, 16.7% in the larynx, and smaller percentages in other locations. ARM 2 had similar distributions, with 23.3% in the oral cavity, 30% in the oropharynx, 26.7% in the hypopharynx, and 20% in the larynx.

Tumour staging revealed differences between the arms. In ARM 1, the majority of cases were at the T3 stage (46.6%), followed by T2 (26.7%) and T4a (26.7%). ARM 2 showed a similar pattern, with 46.7% at T3, 30% at T2, and 23.3% at T4a. Nodal staging indicated that the prevalence of the N1 stage was 43.3% in both arms, followed by the N2 stage (36.7%). [Table 1]

Evaluating tumour nodal stages within ARM 1 demonstrated varying distributions across primary sites. The findings highlighted the prevalence or absence of specific stages within each site, shedding light on the distribution and composition of cases regarding tumour size and nodal involvement [Table 2].

The analysis of staging grouping, histological differentiation, and treatment response in ARM 1 and 2 revealed distinct patterns and trends. ARM 1 had 43.3% of cases in Stage 3 and 56.7% in Stage 4a. ARM 2 had an even distribution of 50% in both Stage 3 and Stage 4a. Histological differentiation showed variations in well-differentiated (20-23.33%), moderately differentiated (56-60%), and poorly differentiated (20%) tumours in both arms. ARM 1 exhibited 24 cases of complete response and 6 cases of partial response. ARM 2 showed 22 cases of complete response and 8 cases of partial response [Table 3].

The study's assessment of acute toxicity revealed varying degrees of adverse reactions in different categories. Skin reactions were predominantly mild, with a minority experiencing moderate or severe symptoms. Mucositis, salivary gland reactions, and pharyngitis/dysphagia displayed similar trends, while laryngitis demonstrated a unique distribution of toxicity grades. Importantly, the most severe grades (Grade 4 and Grade 5) were not observed in any of the recorded adverse reactions [Table 4].

In ARM 1, nausea was common, with most cases (86.7%) having mild (Grade 1) symptoms. Vomiting was prevalent, too, with 93.3% having mild symptoms. Diarrhoea occurred in 6.66% of cases with Grade 1 symptoms. In ARM 2, similar patterns were seen: nausea affected 66.7% (Grade 1), and vomiting 80% (Grade 1). Diarrhoea affected 6.66% with Grade 1 symptoms, and the rarity of Grade 3 and Grade 4 toxicities suggests tolerability of treatments. The findings emphasise the need for supportive care to manage adverse effects during cancer treatment [Table 5].

The study assessed anaemia and white blood cell (WBC) count in two treatment arms, ARM 1 and ARM 2. In ARM 1, anaemia grades were as follows: Grade 0 (Hb > 11 gm) - 66.7%, Grade 1 (9.5-11 gm) - 23.3%, Grade 2 (7.5-9.5 gm) - 10%, and Grades 3 and 4 had no cases. ARM 2 had similar results: Grade 0 - 60%, Grade 1 - 26.7%, Grade 2 - 13.3%, and Grades 3 and 4 had no cases. WBC counts in ARM 1 were Grade 0 (>4000) - 86.7%, Grade 1 (3000-4000) - 10%, Grade 2 (2000-3000) - 3.3%, and Grades 3 and 4 had no cases. ARM 2's WBC counts were Grade 0 - 80%, Grade 1 - 13.3%, Grade 2 - 6.7%, and Grades 3 and 4 had no cases. These findings highlight anaemia and WBC count variations between the arms, suggesting potential differences in treatment response and patient tolerability [Table 6].

Table 1: Demographic data between the arms

Age group	ARM 1 NUMBER (%)	ARM 2 NUMBER %
31-40	5 (17%)	6 (20%)
41-50	9 (30%)	11(37%)
51-60	16 (53%)	13 (43%)
Sex		
Male	24	25
Female	6	5
ECOG		
ECOG 0	19 (63%)	18 (60%)
ECOG 1	11 (37%)	12 (40%)
Habits		
Tobacco (smoking)	8(27%)	8(27%)
Tobacco (smokeless)	7(23%)	8(27%)
Alcohol	6(20%)	5(16%)
Both tobacco & Alcohol	5(17%)	6(20%)
None	4(13%)	3(10%)
Symptoms/Signs		
Pain	13(43.3%)	14(46.6%)
Ulcer Growth	18(60%)	16(53.3%)
Dysphasia	12(40%)	13(43.3%)
Odynophagia	8(26.6%)	7(23.3%)

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Neck Swelling	9(30%)	8(26.6%)
Voice Change	4(13.3%)	5(16.6%)
Primary site		
Oral cavity	6 (20%)	7 (23.3%)
Oropharynx	10 (33.3%)	9 (30%)
Hypopharynx	9 (30%)	8 (26.7%)
Larynx	5 (16.7%)	6 (20%)
Subsite		
ANT2/3TONGUE	4 (13.3 %)	5 (16.6 %)
POST 1/3TONGUE	6 (20 %)	4 (13.3 %)
BUCCALMUCOSA	1 (3.3 %)	1 (3.3 %)
RMT	1 (3.3 %)	1 (3.3 %)
TONSIL	4 (13.3 %)	5 (16.6 %)
PYRIFORM SINUS	9 (30 %)	8 (26.6 %)
SUPRAGLOTTIS	5 (16.6 %)	6 (20 %)
Tumour stage		
T 1	0(0)	0(0)
T 2	8(26.7%)	9(30%)
T 3	14(46.6%)	14(46.7%)
T 4a	8(26.7%)	7(23.3%)
Nodal stage		
N 0	6(20%)	6(20%)
N 1	13(43.3%)	13(43.3%)
N 2	11(36.7%)	11(36.7%)

Table 2: Tumour staging revealed differences between the arms

ARM 1 Tumour nodal stage	T2N1	T2N2	T3N0	T3N1	T3N2	T4aN0	T4aN1	T4aN2
Oral cavity	0	0	1	1	1	1	1	1
Oropharynx	2	1	2	2	1	1	1	0
Hypopharynx	1	2	1	1	1	0	1	0
Larynx	1	1	0	1	1	0	1	0
ARM 2 Tumour nodal stage								
Oral cavity	1	1	1	1	0	1	1	1
Oropharynx	1	2	1	1	2	0	1	1
Hypopharynx	1	1	2	2	1	0	1	0
Larynx	1	1	1	1	1	0	1	0

Table 3: The analysis of staging grouping, histological differentiation, and treatment response between the arms

Stage grouping	ARM1 (daily low-dose cisplatin)	ARM 2 (weekly treatment of cisplatin)
Stage 3	13(43.3%)	15(50%)
Stage 4a	17(56.7%)	15(50%)
Histological differentiation		
Well-differentiated	6(20%)	7(23.33%)
Moderately differentiated	18(60%)	17(56.66%)
Poorly differentiated	6(20%)	6(20%)
Response		
Complete response	24	22
Partial response	6	8
Static response	0	0
Progression	0	0

Table 4: Acute toxicity between the arms

Acute toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ARM1 (daily low-dose cisplatin)					
Skin reactions	0	23(76.7%)	5(16.6%)	2 (6.7%)	0
Mucositis	0	11(36.7%)	12(40%)	5(16.7%)	2(6.6%)
Salivary gland	2(6.7	23(76.7%)	5(16.6%)	0	0
Pharyngitis/dysphagia	0	8(26.6%)	11(36.7%)	11(36.7%)	0
Laryngitis	0	8(26.6%)	14(46.7%)	8 (26.7%)	0
ARM 2 (weekly treatment of cisplatin)					
Skin Reactions	0	23(76.7%)	5(16.6%)	2(6.7%)	0
Mucositis	0	11(36.7%)	12(40%)	5(16.7%)	2 (6.6%)
Salivary Gland	2(6.7	23(76.7%)	5(16.6%)	0	0
Pharyngitis/Dysphagia	0	8(26.6%)	11(36.7%)	11(36.7%)	0
Laryngitis	0	8(26.6%)	14(46.7%)	8 (26.7%)	0

Table 5: Systematic toxicity between the arms

Systematic Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ARM 1				
Nausea	26 (86.7%)	3 (10%)	1 (3.3%)	0

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Vomiting	28 (93.3%)	2(6.7%)	0	0
Diarrhoea	2(6.66%)	0	0	0
ARM 2				
Nausea	20 (66.7%)	8(26.7%)	2 (6.6%)	0
Vomiting	24 (80%)	6(20%)	0	0
Diarrhoea	2(6.66%)	0	0	0

Table 6: Anaemia and white blood cell (WBC) count between the arms

Anaemia	ARM1 NUMBER %	ARM2 NUMBER %
Grade 0 Hb >11 gm	20 66.7 %	18 60%
Grade 1 9.5-11 gm	7 23.3 %	8 26.7%
Grade 2 7.5-9.5 gm	3 10 % 4	13.3%
Grade 3 5-7.5 gm	0 0	0 0
Grade 4 < 5 gm	0 0	0 0
WBC count		
Grade 0 >4000	26 (86.7 %)	24 (80 %)
Grade 1 3000-4000	3 (10 %	4 (13.3 %)
Grade 2 2000-3000	1 3.3 %	2 6.7 %
Grade 3 1000-2000	0 0	0 0
Grade 4 <1000	0 0	0 0

DISCUSSION

The age distribution observed in the study is consistent with previous reports that demonstrate varying incidence rates of head and neck cancers across different age groups.[6,7] While the study revealed a predominance of males in both treatment arms, this aligns with the well-established male predilection for head and neck malignancies.[8,9] Furthermore, documenting patient habits, such as tobacco and alcohol use, underscores the relevance of lifestyle factors in cancer aetiology and progression.[10] The importance of accurate staging is well-documented in the literature, as it serves as a pivotal prognostic indicator and guides treatment decisions in head and neck cancer.[11] There was no significant association between the response to therapy and the gender of the patient, the age of diagnosis, or the patient's performance status.

In this study, primary tumours in the oropharynx, hypopharynx and larynx had a better response to treatment in both arms than in the oral cavity. This also corroborated the finding that poorly differentiated tumours had better treatment response rates than the well-differentiated histologies.[12] The decision to use daily cisplatin instead of a weekly schedule in this study was influenced by the experiences and findings reported by Jeremic et al.[13] and Bartelink et al.[14] These studies underscored the potential advantages of daily cisplatin administration, particularly in comparison to radiation therapy (RT) alone. Jeremic et al. reported superior outcomes with the concurrent use of daily cisplatin, suggesting that the benefits achieved were comparable to those reported with a 3-weekly schedule. This noteworthy observation supports the notion that daily cisplatin can yield substantial clinical advantages. Furthermore, the practical benefits of using a daily cisplatin regimen were highlighted.

One of the key practical advantages is eliminating the need for excessive hydration during administration due to the low daily doses. This feature is especially relevant in tropical countries where dehydration is common. The reduced hydration requirement can contribute to a smoother treatment process and improved patient comfort. Another significant practical aspect of the daily cisplatin regimen is the absence of the need for elective hospitalisation for chemotherapy administration. This contrasts with some other cisplatin schedules that necessitate hospital stays due to the potential for severe side effects. The convenience of outpatient administration can enhance patient satisfaction and overall treatment compliance. Moreover, the daily cisplatin schedule offers more flexibility and control over chemotherapy delivery or cessation. Adjusting the treatment regimen as needed can be advantageous in managing individual patient responses and minimising unnecessary side effects. This flexibility aligns with personalised medicine principles, tailoring treatment to each patient's needs.

Regarding the optimal dosage of low-dose cisplatin, a range of dosages has been utilised in different studies, typically ranging from 6 mg/m² up to a maximum of 10 mg daily. This variation in dosing can impact treatment outcomes. For example, Homma et al.[15] used a daily cisplatin dosage of 4 mg/m² and compared it to a weekly carboplatin regimen. Their study found inferior results with the lower daily dose of cisplatin, potentially suggesting that the dose might have been too low to achieve significant therapeutic effects.

The study's secondary aim was toxicity assessment. Both treatment groups experienced low rates of severe toxicities (grade 3/4). Skin reactions: arm 1 (6%), arm 2 (3%). Grade 4 mucositis: 3% in both. Pharyngitis: arm 1 (26%), arm 2 (36%). Laryngitis: arm 1 (20%), arm 2 (26%). Systemic toxicities (nausea, vomiting, diarrhoea) were manageable with routine measures; no grade 3 cases. The study suggests manageable toxicities for both daily low dose and weekly cisplatin in stage 3 and 4a head and neck cancer patients.

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CONCLUSION

In India, where head and neck cancer is prevalent, this study compared daily low-dose cisplatin to weekly cisplatin with accelerated radiation. Daily cisplatin (6 mg/m2) achieved 80% complete response and 20% partial response, while weekly cisplatin (40 mg/m2) yielded 73% complete response and 27% partial response, with manageable toxicity. The low-dose approach was non-inferior. In overburdened institutions, low-dose cisplatin with accelerated radiation appears a feasible and logistically suitable outpatient with good locoregional control and manageable toxicity in locally advanced head and neck cancer. Further research is needed for long-term outcomes.

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