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Concurrent Chemoradiotherapy with Weekly Versus Three-Weekly Cisplatin In Locally Advanced Head And Neck Squamous Cell Carcinoma- A Comparative Study

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Abstract:
Background*: Chemo-radiation consisting of 3 weekly Cisplatin is the standard of care for locally advanced head and neck cancer, but numerous toxicities accompany treatment. Hence several centres have adopted weekly administration of Cisplatin for a favourable toxicity profile. Currently, no prospective data is comparing three-weekly and weekly Cisplatin in the treatment of head and neck cancers. We want to conduct this study to compare the efficacy and toxicity profile of two different chemotherapy regimens.*
Materials and Methods*: Between August 2015 to March 2017, 40 patients with locally advanced head and neck cancers were included in the study. Patients were divided into two arms each consisting of 20 patients. All participants received Intensity Modulated Radiotherapy Technique (IMRT) on Linear Accelerator to a total dose of 70 Gy, 2Gy per fraction over 35 fractions. Patients in Arm A received concurrent chemotherapy with Cisplatin 100mg/m^2 given on day 1, day 22 and day 43 whereas patients in Arm B received Cisplatin 40mg/m^2 weekly for 7 weeks. Toxicity grade was noted during radiotherapy (RT) and at one and two months following completion of treatment using the CTCAE v4. WHO criteria were used for the assessment of clinical and radiological responses.*
Results*: All participants completed the planned radiotherapy. 80% in Arm A and 90% in Arm B received the planned dose of chemotherapy. Mean cumulative Cisplatin dose was 364 mg/m^2 and 356 mg/m^2 in Arm A and Arm B, respectively. At 1st-month follow-up, complete response (CR) rates in Arm A and Arm B were 55% and 60% and partial response (PR) rates were 45% and 40% respectively. At 2nd-month follow-up CR rates in Arm A and Arm B were 75% and 70% and partial response (PR) rates were 20% and 30% respectively. One patient (5%) in Arm A showed progressive disease at 2nd-month follow-up. Acute toxicities were more in Arm A compared to Arm B: grade 3-4 skin reaction (25% Vs 15%), grade 3-4 dysphagia (60% Vs 50%), grade 3-4 nausea (50% Vs 30%), grade 3-4 vomiting (60% Vs 40%).*
Conclusion: *Concurrent chemo-radiation using weekly Cisplatin has a better toxicity profile, improved compliance, and comparable treatment response and may serve as an alternative for the conventional three weekly Cisplatin regimen.*
Key Word*: Locally advanced head and neck cancer; Chemoradiation; Toxicity; Compare chemo regimen; Cisplatin.*

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I. Introduction

Head and neck tumours represent a heterogeneous group of neoplasms. Worldwide, nearly 690,000 new cases and 340,000 deaths are reported annually. (1) A major sub-group of the head and neck carcinomas is the one referred to as "oral cancers" (arising in the mucous membranes of the mouth, i.e. lip, tongue, buccal mucosa, gums, the floor of the mouth and hard palate), and pharynx (comprising the oropharynx, hypopharynx and nasopharynx). (2)

At presentation, the majority of patients have locally advanced disease, for which multimodality treatment is required to improve locoregional control and survival. Concurrent chemoradiation has become a standard modality for this disease. (3,4) Many chemotherapeutic agents have been used with radiotherapy, including cisplatin, fluorouracil, methotrexate, bleomycin and mitomycin. (3–5) However, concurrent

chemoradiotherapy with cisplatin offered the best survival advantage, as shown in a meta-analysis, which proved that the addition of chemotherapy to radiotherapy yielded 6.5% absolute benefit of overall survival compared with radiotherapy alone over 5 years. (4) Single-agent cisplatin given every three weeks at a dose of 100 milligrams per square meter is accepted as the standard reference regimen in case of definitive chemo-radiation. (6) This regimen is, however, usually associated with a significant increase in acute toxicities such as a higher rate of mucositis, haematological complications, and renal complications. The occurrence of these side effects resulted in early treatment termination or a decrease in treatment compliance, 70 to 85 % of patients only were treated with the intended cisplatin dose. (6,7) Therefore, splitting full dose three-weekly cisplatin as a weekly cisplatin schedule might decrease toxicities and increase compliance while maintaining the same dose intensity.

II. Material And Methods

This prospective comparative study was carried out on patients of the Department of Radiation Oncology at Yashoda hospital, Somajiguda, Hyderabad, Andhra Pradesh from June 2014 to June 2016. A total of 40 adult subjects (both male and females) aged ≥ 18 years were incorporated in this study.
Study Design: Prospective open-label comparative study

Study Duration: June 2014 to June 2016.
Sample size: 40 patients.
Subjects & selection method: The study population was drawn from consecutive head and neck cancer patients who presented to Yashoda Hospital for treatment between June 2014 and June 2016. Patients were divided into two groups (each group had 20 patients). The prescribed doses of chemotherapy were as follows:
Group A (N=20 patients) - concurrent chemotherapy with Cisplatin 100mg/m^2 given on day 1, day 22, and day 43.
Group B (N=20 patients) - concurrent chemotherapy with Cisplatin 40 mg/m2 given weekly for 6-7 weeks.

Inclusion criteria:
1. Histo-pathologically confirmed locally advanced non-metastatic Squamous cell carcinomas of head and neck
2. Age less than 75 years
3. ECOG performance status of 0-2
4. Haematological parameters with total leukocyte count of >4000cells/mm^3, platelet counts of >1.5 lakh/mm^3
5. Renal parameters with Serum creatinine <1.5 mg/dL.
6. Any co-morbid condition or acute infection where treatment is contraindicated.

Exclusion criteria:
1. Tumours of non-squamous histology.
2. Age greater than 75 years.
3. ECOG Performance status >2.
4. Any prior treatment received for the tumour.
5. Patients having abnormal renal, cardiac, and haematological parameters.
6. Patients who were unwilling to participate.
7. Patient not likely to be available for follow-up.

Procedure methodology
Initial evaluation and enrolment

On presentation, a full medical history was obtained followed by a physical examination including an endoscopic assessment for initial clinical assessment of tumour site, stage, nature, and extent. Laboratory and radiological investigations included complete blood picture, renal and liver function tests, chest X-ray and a CT scan with intravenous contrast of head and neck. Eligible patients were enrolled and assigned to either arm.

Treatment planning and delivery

All the patients were treated in a supine position and properly immobilized by a thermoplastic cast (orfit cast). Patients underwent a pre-treatment CT simulation with the immobilizing thermoplastic cast. Serial axial images with a slice thickness of 3mm were obtained and these images were transferred to the ECLIPSE™ planning system, where following image acquisition, the target volume, and critical organs were contoured.

The gross target volume (GTV) was defined as the initial extent of the gross tumour and involved gross lymph nodes, based on clinical examination and imaging at presentation. CTV70 was a 5mm margin around GTV. CTV59.5 additionally encompassed potential microscopic spread around primary and nodes while CTV56

covered uninvolved nodal drainage at risk. PTV margin was 5mm. intensity-modulated radiotherapy (IMRT) plan was generated to cover at least 95% of PTV with at least 95% of the dose. Organs at risk were delineated and the dose delivered was evaluated. Patient setup was verified during treatment with the electronic portal imaging device. Patients received a dose of 70 Gy in 35 fractions at 2 Gy per fraction PTV 1, 62.7 Gy at 1.9 Gy per fraction to PTV 2, and 56.7 Gy at 1.7 Gy per fraction to PTV 3. All patients were assessed after every 5 fractions for treatment-related acute toxicity and graded using Common terminology criteria for adverse events (CTCAEv4)(8)

The chemotherapy regimens were as follows:
Group A- concurrent chemotherapy with Cisplatin 100mg/m2 given on the day, day 22, and day 43
Group B - concurrent chemotherapy with Cisplatin 40 mg/m2 given weekly for 6-7 weeks

Follow up
After completion of treatment, patients in both arms were followed up on the date of completion of treatment, at 4 weeks, 8 weeks from the completion of treatment.

At the follow-up visit, patients were assessed for acute toxicity, tumour response based on symptoms and toxicity was graded using CTCAEv4. They underwent a physical examination and indirect laryngoscopy to assess mucosal integrity, skin integrity, tumour and nodal status including bi-dimensional measurement of the tumour and the nodal site. A CT scan was done at the second follow-up visit to know tumour and nodal response. Patients were encouraged to visit earlier if new or progressive symptoms developed. All patients were encouraged to adhere to the prescribed regimen for good oral hygiene and abstain from any form of tobacco. Locoregional tumour response evaluation was done at 4 weeks and 8 weeks using the WHO criteria. (9)

Statistical analysis
Data were analysed using SPSS version 20 (SPSS Inc., Chicago, IL).
The two arms were compared using the chi-square test to check whether they were balanced in terms of patient and disease-related characters like the stage, sex, tumour site, performance status, age, and histology.
Response to treatment was assessed based on WHO criteria and analysis were done using descriptive statistics and compared between the arms using the Chi-square test.
Toxicity was assessed using common toxicity criteria (CTCAE.V4) and analysis was done using descriptive statistics by using the available charts. The maximum grade of toxicity was compared between the two arms with the chi-square test.

III. Result

40 patients were divided into two arms Arm A and Arm B, each arm consisting of 20 patients. The median age in Arm A was 45 years, age ranging from 22-68 years. The median age in Arm B was 48 years, age ranging from 27 -69 years.

Table no 1: Patient demographic data

Parameter	Arm A	Arm B
No of patients	20	20
Median age (years)	45	48
Age range (years)	22-68	27-69
Male: female	16:4	17:3
ECOG PS 1	19	18
ECOG PS 2	1	2
Stage III	11	10
Stage IVA/IVB	9	10
Grade 1	12	11
Grade 2	4	6

Grade 3	4	3
Tongue	4	4
Buccal mucosa	2	2
Floor of mouth	1	0
Retro molar trigone	1	1
Pyriform sinus	2	3
Post cricoid	2	2
Tonsil	1	2
Supraglottic	2	2
Nasopharynx	5	4

Chemotherapy dose

The mean cumulative dose of Cisplatin was 364 mg/m^2 in Arm A and 356 mg/m^2 in Arm B. Percentage of patients who received planned chemotherapy in Arm A was 80% whereas in Arm B it was 90%.

Table no 2: Shows cumulative doses of Cisplatin in Arm A and Arm B.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Arm A	450	450	300	280	450	390	480	480	300	480	300	450	420	540	510	540	390	480	340	450
Arm B	420	360	350	360	360	280	420	315	350	300	360	455	360	420	420	300	350	200	390	350

Response

Complete response (CR) in Arm A at 1 month and 2 months follow-up visits were 55% and 75% respectively whereas CR in Arm B at 1 month and 2 months were 60% and 70% respectively. Partial response (PR) in Arm A at 1 month at 2 months were 45% and 20% respectively whereas PR in Arm B at 1 month and 2 months were 40% and 30% respectively. One patient in Arm A developed cervical nodal disease two months after treatment.

Table no 3: Response to treatment

	Arm A	Arm B	Arm A	Arm B
	1 month follow up	1 month follow up	2 months follow up	2 months follow up
Complete response	55%	60%	75%	70%
Partial response	45%	40%	20%	30%
Stable disease	0%	0%	0%	0%
Progressive disease	0%	0%	5%	0%

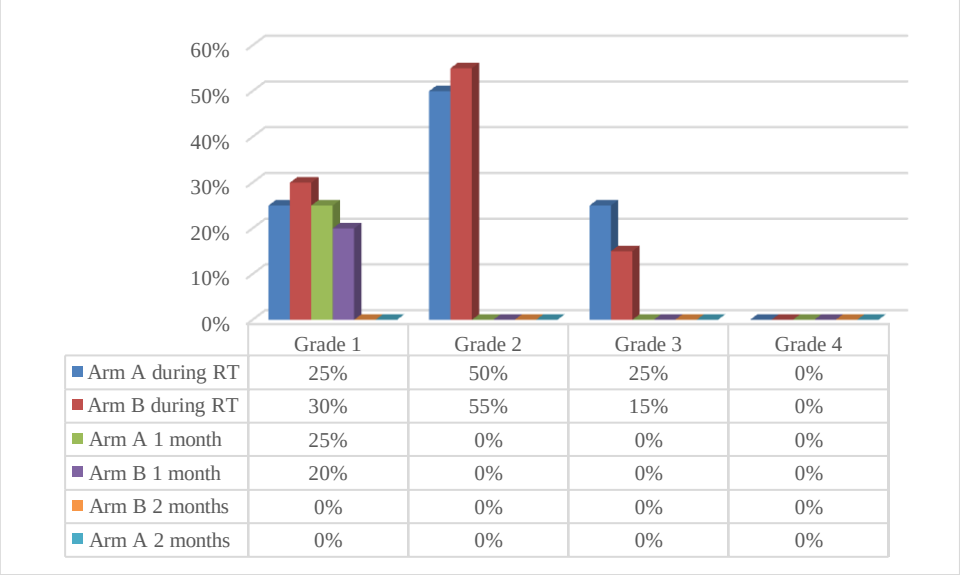
Skin reaction

Skin reactions during radiotherapy (RT) (Arm A Vs Arm B): Grade 1 (25% Vs 30%), Grade 2 (50% Vs 55%) and Grade 3 (25% Vs 15%, p=0.42). At 1-month follow-up patients in Arm A had more Grade I skin reaction (25% Vs 20%, p=0.7) but the difference was not statistically significant. At a follow-up of 2 months, skin reaction was absent in all patients.

Table no 4: Grade of skin reactions

	Arm A RT	Arm B RT	Arm A 1 month	Arm B 1 month	Arm A 2 months	Arm B 2 months
Grade 1	25%	30%	25%	20%	0%	0%

Grade 2	50%	55%	0%	0%	0%	0%
Grade 3	25%	15%	0%	0%	0%	0%
Grade 4	0%	0%	0%	0%	0%	0%

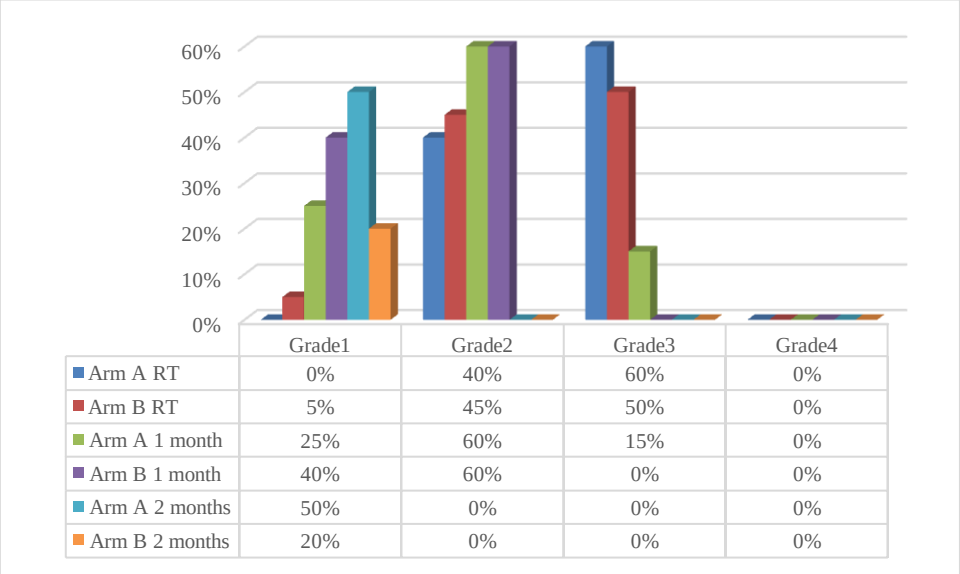


Dysphagia

Patients in both the arms had comparable grade 1 and 2 dysphagia during RT, Grade 1 (0% Vs 5%), Grade 2 (40% Vs 45%), whereas grade 3 dysphagia was more in Arm A. At one month follow-up, patients in Arm A had more Grade 3 dysphagia (15% Vs 0%). At two months follow-up, grade 1 dysphagia was more in Arm A (50% Vs 20%).

Table no 5: Grade of Dysphagia

	Arm A RT	Arm B RT	Arm A 1 month	Arm B 1 month	Arm A 2 months	Arm B 2 months
Grade1	0%	5%	25%	40%	50%	20%
Grade2	40%	45%	60%	60%	0%	0%
Grade3	60%	50%	15%	0%	0%	0%
Grade4	0%	0%	0%	0%	0%	0%



Dry mouth

During RT, Grade I dryness of mouth was comparable between the two arms (92% Vs 93%). No patient had grade 3,4 dryness of the mouth. At one month follow up the two arms had comparable toxicity of grade 1 (66.6% Vs 60%) and grade 2 (33.3% Vs 40%). At two-month follow-up, the two arms had comparable toxicity of Grade 1(40%Vs 40%) and Grade 2 (60% Vs 53.3%).

TABLE no 6: Shows grade of dry mouth

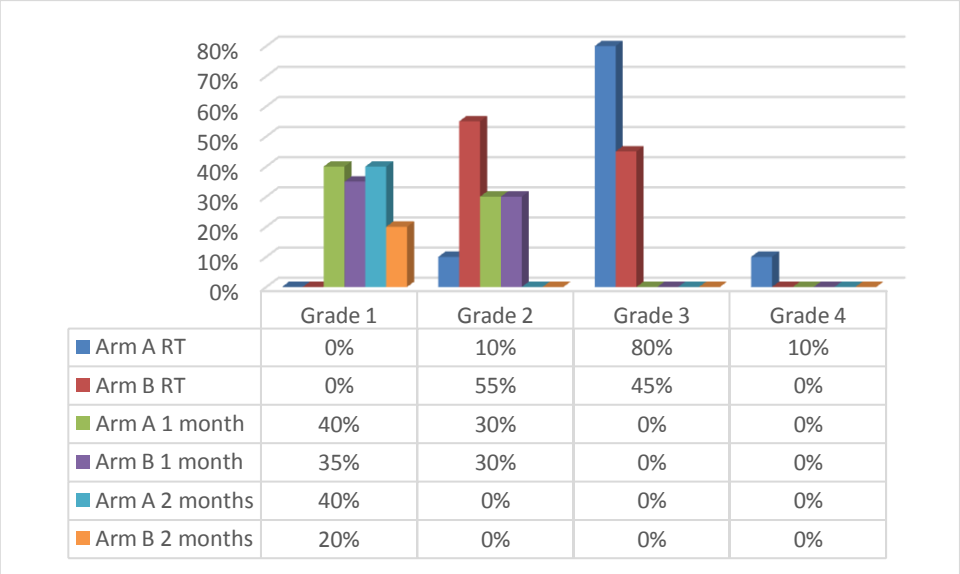
	Arm A RT	Arm B RT	Arm A 1 month	Arm B 1 month	Arm A 2months	Arm B 2 months
Grade 1	90 %	90%	50 %	40 %	30%	40%
Grade 2	0 %	0%	40 %	40%	60%	40%
Grade 3	0 %	0%	0 %	0%	0%	0%
Grade 4	0 %	0%	0 %	0%	0%	0%

Mucositis

All patients developed mucositis during RT, grade 2 Mucositis was lesser in Arm A (10% vs 55%), but higher-grade mucositis Grade 3 (80% Vs 45%), Grade 4 (10% Vs 0%) in Arm A compared to Arm B. At one month follow-up, Arm A patients had more mucositis Grade 1 (40% Vs 35%). At two-month follow-up, Arm A patients had more mucositis Grade 1 (40% Vs 20%).

Table no 7: Shows grade of mucositis

	Arm A RT	Arm B RT	Arm A 1 month	Arm B 1 month	Arm A 2 months	Arm B 2 months
Grade 1	0%	0%	40%	35%	40%	20%
Grade 2	10%	55%	30%	30%	0%	0%
Grade 3	80%	45%	0%	0%	0%	0%
Grade 4	10%	0%	0%	0%	0%	0%



Nausea

The rate of nausea during RT were Grade 1 (10% Vs 10%), Grade 2 (35% Vs 60%) and Grade 3 (55% Vs 30%). At one-month follow-up lower grade nausea was more in Arm B whereas higher grade nausea was more in Arm A, Grade 1 (15% Vs 20%), Grade 2 (40% Vs 45%), Grade 3 (35% Vas 20%). At two months follow-up, grade 1 nausea was more in Arm B (15% Vs 30%) and grade 2 nausea was more in Arm A (30% Vs 10%).

Table no 8: Shows grade of nausea

	Arm A RT	Arm B RT	Arm A 1 month	Arm B 1 month	Arm A 2 months	Arm B 2 months
Grade 1	10%	10%	15%	20%	15%	30%
Grad e2	35%	60%	40%	45%	30%	10%
Grade 3	55%	30%	35%	20%	0%	0%
Grade 4	0%	0%	0%	0%	0%	0%

Vomiting

During RT Grade 1 vomiting was less in Arm A, Grade 1 (0% Vs 20%), whereas Grade 2 is similar in both arms (40% Vs 40 %) and Grade 3 was more in Arm A (60% Vs 40%). At one-month follow-up Grade 1,2 vomiting were higher in Arm A: grade 1 (60% Vs 55%) and Grade 2 (10% Vs 5%). At two-month follow-up Arm A had higher grade 1 vomiting (35% Vs 15%).

Table no 9: Shows grade of vomiting

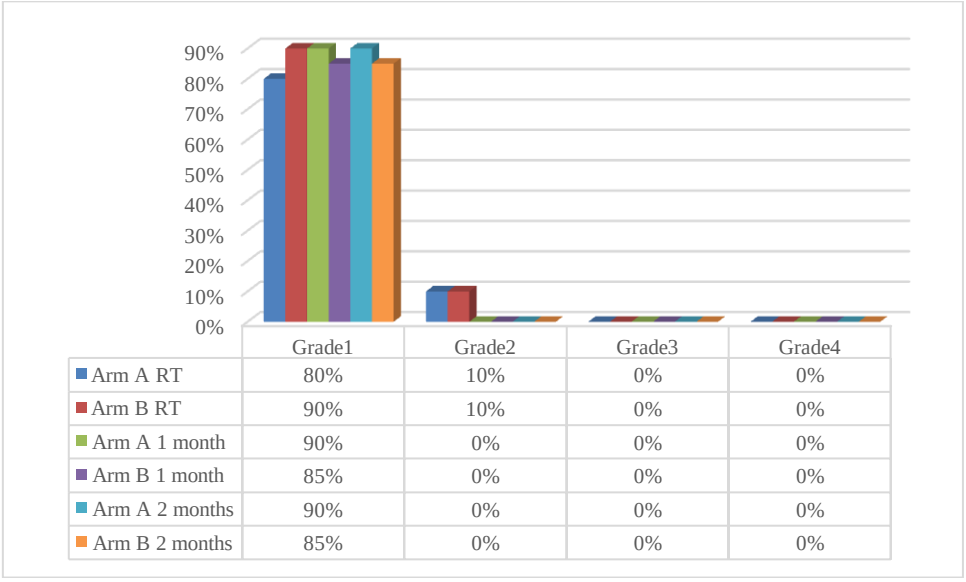
	Arm A RT	Arm B RT	Arm A 1month	Arm B 1month	Arm A 2 months	Arm B 2 months
Grade l	0%	20%	60%	55%	35%	15%
Grade 2	40%	40%	10%	5%	0%	0%
Grade 3	60%	40%	0%	0%	0%	0%
Grade 4	0%	0%	0%	0%	0%	0%

Haemoglobin

Haematological toxicity in the form of decreased haemoglobin levels was more common in Arm B during RT Grade 1 (80% Vs 90%), Grade 2 (10% Vs 10%). Grade 1 toxicity was comparable between the two arms during 1st and 2nd-month follow-up (90% Vs 85%).

Table no 10: Shows grade of decreased haemoglobin level.

	Arm A RT	Arm B RT	Arm A 1 month	Arm B 1 month	Arm A 2 months	Arm B 2 months
Grade1	80%	90%	90%	85%	90%	85%
Grade2	10%	10%	0%	0%	0%	0%
Grade3	0%	0%	0%	0%	0%	0%
Grade4	0%	0%	0%	0%	0%	0%

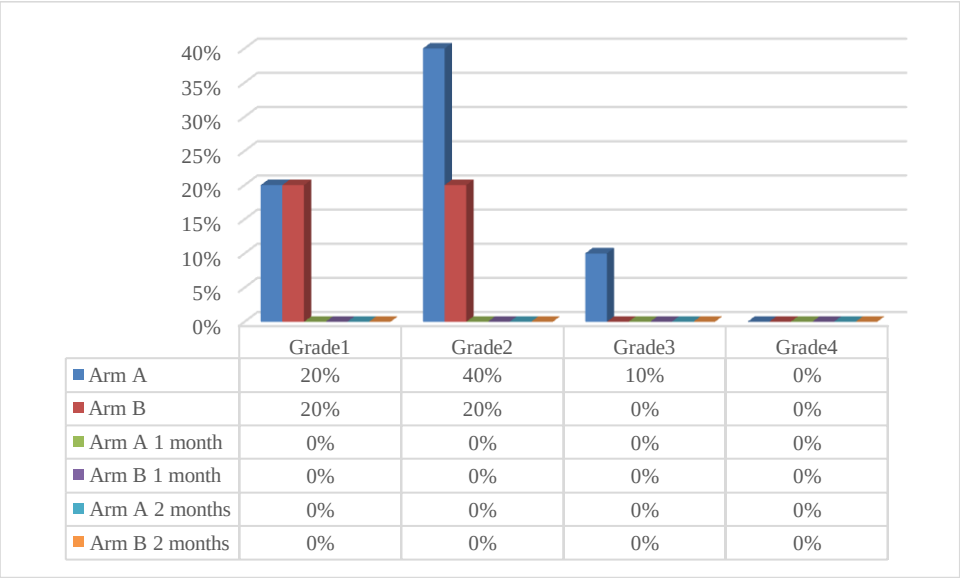


Total leucocyte count

Haematological toxicity in the form of decreased total leucocyte counts was seen only during RT. Grade 1 (20% Vs 20%) and Grade2 (40% Vs 20%), Grade 3 toxicity was seen in Arm A only (10% Vs 0%).

Table no 11: Shows grade of leukocytopenia

	Arm A RT	Arm B RT	Arm A 1 month	Arm B 1 month	Arm A 2 months	Arm B 2 months
Grade1	20%	20%	0%	0%	0%	0%
Grade2	40%	20%	0%	0%	0%	0%
Grade3	10%	0%	0%	0%	0%	0%
Grade4	0%	0%	0%	0%	0%	0%



Platelet count was normal for all patients in both the arms during RT and at follow-up. Renal parameters were normal for all patients in both the arms during RT and at follow-up.

IV. Discussion

The past few decades have seen a transition in the treatment strategies of locoregionally advanced head and neck cancers, from single modality options of either surgery or radiotherapy to multimodality solutions combining surgery, radiation and chemotherapy as needed. The superiority of a combination of radiation and chemotherapy in achieving local control and overall survival has been proven in numerous randomized studies and a meta-analysis. (4) Although adopted as a standard treatment approach in most Western countries, the risk-benefit ratio of concurrent chemo-radiotherapy leaves much to be desired, especially in the context of increased acute toxicities, which may be a significant issue with compliance and treatment tolerability in an undernourished population with inadequate infrastructure and poor support systems. Therefore, unlike standard three-weekly chemotherapy, a more viable schedule is needed which provides similar response rates with a favourable toxicity profile.

The present study was a phase III nonrandomized control trial designed to compare response, toxicity, and quality of life in locally advanced head and neck cancers using three weekly Cisplatin chemotherapy vs weekly Cisplatin chemotherapy. Several phase III trials reported improved loco-regional control when chemotherapy was added to standard radiotherapy practices (5–7,10). Cisplatin (CDDP) was reported to be effective in patients with squamous cell cancers of the head and neck, and an enhanced response was reported when combined with radiation. (3,4) Many investigators refer to 100 mg/m^2 bolus dosing of CDDP on days 1, 22, and 43 of RT as standard. (6) The chemotherapy schedule used in the study arm of this present study was single-agent cisplatin (40 mg/m2) given weekly along with radiotherapy.

Compliance with treatment and treatment interruptions

Compliance with treatment is dependent on total radiation dose, chemotherapy dose intensity, and fractionation. In the present study, the planned radiotherapy treatment was completed in 100% of patients in both arms. Scheduled three cycles of chemotherapy was completed by only 16 of the 20 patients (80%) in Arm A. This was like earlier studies which had a compliance of 61% to 85%. (6,7,11) The most common reason for this was hematologic toxicity followed by a poor general condition. Scheduled weekly cycles of chemotherapy were completed by 18 of the 20 patients (90%) in Arm B. Thus, better compliance to treatment was seen in Arm B. Six patients had RT interruptions, one patient for four days, two patients for three days and three patients for two days in Arm A whereas four patients had interruptions in Arm B, two patients for three days and two patients for two days. Fourteen patients in each arm required nasogastric tube feeding during radiotherapy.

Treatment-related acute morbidity and mortality

In Arm A, 70% of patients had leukopenia, with 10% experiencing grade 3 or above. In Arm B, 40% of patients had leukopenia, with no patient experiencing grade 3 or above. Deranged renal parameters were not seen in both the arms of the present study.

Mucositis is a major complication of any form of radiation therapy in head and neck cancers. It has a significant impact on pain, dysphagia, feeding tube placement, hospitalization, treatment modification or interruptions, weight loss and tumour response. (12) In the current study, grade 3-4 mucositis was encountered in 90% of patients in Arm A during RT. Arm B had decreased incidence of grade 3-4 mucositis of 45% during RT (p=0.22). At one month follow-up, 70% of patients of Arm A had grade 1-2 mucositis compared to 65% in Arm B (p=0.74). At two months follow-up 40% of patients of Arm A had grade 1 mucositis compared to 20% in Arm B (p=0.16). A systematic review of 33 studies on the incidence, severity and effect of mucositis in patients receiving radiotherapy revealed that nearly all patients receiving chemo-radiation (89%) experienced mucositis with 43% experiencing grade 3-4 mucositis. (12) All patients with severe mucositis were managed conservatively. Antimicrobials were prescribed in select patients. The higher-grade mucositis seen in Arm A caused treatment breaks in three patients for a maximum break of three days, whereas only one patient had a treatment break due to mucositis in Arm B.

In our study, severe skin reactions (grade 3- 4) during RT in Arm A vs Arm B were 25% Vs 15%, p=0.42. Severe dysphagia (grade 3-4) during RT in Arm A vs Arm B was 60% Vs 50%, p=0.52; at one-month follow-up it was 15% Vs 0%. Severe nausea (grade 3-4) during RT in Arm A vs Arm B was 55% Vs 30%, p=0.1; at one month follow-up it was 35% Vs 20%, p=0.28. Severe vomiting (grade 3- 4) during RT in Arm A vs Arm B was 60% Vs 40%, p=0.2. Based on our findings, there is a trend towards a higher incidence of grade 3-4 toxicity in Arm A as compared to Arm B.

The complete response rate was similar in both the treatment arms. At 1st-month follow-up, complete response rates in Arm A and Arm B were 55% and 60% and partial response rates were 45% and 40% respectively. At 2nd-month follow-up, complete response rates in Arm A and Arm B were 75% and 70% and partial response rates were 20% and 30% respectively. One patient (5%) in Arm A progressed at the 1st follow-up visit. A much longer follow-up is required to comment on treatment response.

Table no 12: Shows comparison of current outcomes with similar studies

Trial/Study	Number of patients	CT schedule	RT schedule	RT dose	Mucositis (grade3-4)	Hematologic (grade3-4)	anaemia	Skin (grade3-4)	Dysphagia (grade3-4)	Nausea and vomiting (grade3-4)
Adelstein et al(6)	95	100mg/m^2 on day 1,22 & 43	2Gy/day, 5days/week	70 Gy	45%	45%	18 %	7%	-	15.8%
RTOG 9501 Cooper et al(11)	205 (adjuvant)	100mg/m^2 on day 1, 22 & 43	2Gy/day, 5days/week	60-66Gy	62%	78%	6%	14%	50%	40%
Geeta SN et al(13)	Arm A 51	100mg/m^2 on week 1,4 & 7	2 Gy/day, 5 days/week	66 to 70 Gy	4%	8%	4%	8%	51%	-
	Arm B 32	40mg/m^2 weekly, 6 cycles	2 Gy/day, 5 days/week	66 to 70 Gy	28%	16%	12.5%	16%	22%	-
Forastiere et al(7)	172	100mg/m^2 on day 1, 22 & 43	2 Gy/day 5 days/week	70 Gy	43%	47%	-	7%	35%	20%

Al-Sarraf et al (14)	124	100mg/m^2 on day 1, 22 & 43	1.8-2Gy/day, 5 days/ week	66-73.8Gy	31%	9%	7%	2.5%	-	6%
Our study	Arm A 20	100mg/m^2 D1, 22, 43	2 Gy/day, 5 days/week	70 Gy	90%	10%	0%	25%	60%	80%
	Arm B 20	40mg/m^2 weekly	2 Gy/day, 5 days/week	70 Gy	45%	0%	0%	15%	50%	50%

V. Conclusion

The current standard of care in the treatment of locally advanced cancers of the head and neck is concurrent chemoradiotherapy with three weekly Cisplatin given at a dose of 100mg/m^2. Chemoradiotherapy with weekly Cisplatin 40mg/m^2, with its lesser acute toxicity profile, comparable response rates, and better compliance, may serve as an alternative for the conventional arm. Small sample size and shorter duration of follow-up are the limitations of the study and survival outcomes, late toxicity between the study groups cannot be commented upon. A larger trial with longer follow-up is needed to reach a definite conclusion about the better chemotherapy schedule concurrently with radiation in locally advanced head and neck squamous cell carcinoma.

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