Section: Radiation Oncology

Original Research Article

A PROSPECTIVE STUDY COMPARING CONCURRENT CHEMO-RADIATION WITH WEEKLY GEMCITABINE VS CONCURRENT CHEMO-RADIATION WITH WEEKLY CISPLATIN IN ORAL AND OROPHARYNGEAL CANCERS AT TERTIARY CANCER CENTRE

Vemugadda Satish Kumar[1], Velishetty Srinivas[2], Nanuvala Prathyusha[3], Aarathi Ardha[4], Kuppa Prakash[5]

[1]*Senior Resident, Department of Radiation Oncology, M.N.J Institute of Oncology and Regional Cancer Centre/Osmania Medical College, Koti, Hyderabad, Telangana, India.*
[2]*Associate Professor, Department of Radiation Oncology, Gandhi medical college, Secunderabad, Telangana, India.*
[3]*Associate Professor, Department of Radiation Oncology, M.N.J Institute of Oncology and Regional Cancer Centre/Osmania Medical College, Koti, Hyderabad, Telangana, India.*
[4]*Assistant Professor, Department of Radiation Oncology, M.N.J Institute of Oncology and Regional Cancer Centre/Osmania Medical College, Koti, Hyderabad, Telangana, India.*
[5]*Professor and HOD, Department of Radiation Oncology, M.N.J Institute of Oncology and Regional Cancer Centre/Osmania Medical College, Koti, Hyderabad, Telangana, India.*

Received *: 29/03/2025*
Received in revised form *: 20/05/2025*
Accepted *: 05/06/2025*

Corresponding Author:
Dr. Vemugadda Satish Kumar,
Senior Resident, Department of Radiation Oncology, M.N.J Institute of Oncology and Regional Cancer centre/Osmania medical college, Koti, Hyderabad, Telangana, India.
Email: drvenugaddasatishkumar@gmail.com

DOI: 10.70034/ijmedph.2025.2.374

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

Int J Med Pub Health
2025; 15 (2); 2075-2083

ABSTRACT

Background: Aims: The aim of study is to compare the effect of concurrent chemo-radiation with weekly Gemcitabine versus concurrent chemo-radiation with weekly cisplatin in oral and oropharyngeal cancers in terms of tumor response, acute toxicity, and quality of life.

Materials and Methods: A prospective comparative study done from August 2022 To June 2024 in Department of Radiation oncology, 60 patients presented to the OPD with early and locally advanced oral and oropharyngeal carcinoma. Patients who fulfilled the inclusion criteria were recruited for the study and randomly assigned into two groups, consisting of 30 patients per group. Group A (Gemcitabine + concurrent RT) – 30 patients, Group B (Cisplatin + concurrent RT) – 30 patients

Results: There is no statistical significant difference between the two groups in terms of Tumor response rates. Quality of life Questionnaire before treatment (Baseline) and Post treatment 3 months. In terms of quality of life, Both groups of patients has shown similar changes in terms of domains like pain, swallowing, teeth, opening of mouth, Dry mouth, senses, social eating, social contact. Cisplastin showed statistically significant difference between both the groups post treatment in quality of life due to pain, senses, felt ill, social eating, social contact when compared to gemcibine. Toxicity in patients of gemcitabine arm had early incidence of mucositis, compared to cisplatin arm but this was not statistically significant, and the other toxicities were also manageable.

Conclusion: cisplatin has showed better efficacy in achieving complete response, gemcitabine shows lower efficacy with minimal tolerable side effects compared to cisplatin.

Keywords: Concurrent Chemo-Radiation (CCRT), cisplatin, gemcitabine, Quality of life Questionnaire Head & Neck.

INTRODUCTION

From the base of the skull to the thoracic inlet, head and neck cancers (HNC) are a heterogeneous group of malignancies with unique etiological and epidemiological characteristics. Head and neck cancers affect both men and women and account for 1100,000 cases globally. The prevalence is growing in developing nations. According to ICMR data, it is the most common cancer among Indian men,

presumably as a result of rising smoking and chewing tobacco use. As per the International Journal of Head and Neck Surgery, the head and neck cancer burden in India is as follows: out of all head and neck cancers worldwide (except from cervical esophageal cancers), Asia, particularly India, accounts for 57.5% of cases, affecting both genders. In India, they represent 11–16% of all cancer cases in women and 30% of all cancer cases in men.[1]

India reports over 200,000 cases of head and neck cancer annually, and our nation also reports about 80,000 cases of mouth cancer. The gingivo buccal sulcus, where the betel quid is stored in the oral cavity for extended periods of time, is the site of nearly two-thirds of oral malignancies. About 29,000 cases of laryngeal cancer (18% of all cases worldwide) and over 40,000 cases of pharyngeal cancer (excluding nasopharyngeal cancer, which accounts for 31% of all cases worldwide) are reported from India annually.[2]

The 5-year survival rate for patients with malignancies of the oral cavity is approximately 50% in the United States, 45–49% in Europe, and 30% in India, based on demographic data. Overall 5-year survival rates have not improved significantly over the last three decades; in the US, 5-year survival rates for localized tumors were over 80%, but in several developing countries, they were only over 60%.[3]

Surgery and radiotherapy are the most common modalities of treatment for Head and neck cancers in various prominent cities in India and radiotherapy being main treatment modality in advanced Head and neck cancers. Squamous cell carcinoma of the head and neck (SCCHN) represents approximately 90% of all cancer arising in the head and neck area.

Treatment choices for Head and neck cancers mainly based on the primary tumour site, TNM staging, and performance status. Locally advanced disease often requires multimodal treatment, consisting of surgery, radiotherapy and chemotherapy. Radical RT with concurrent chemotherapy with cisplatin (CDDP) remains the present-day standard management in the non-surgical management of patients with locally advanced HNSCC (2).

When combined with Radiotherapy, Systemic chemotherapy is most frequently based on platinum compounds, which have shown to yield good benefits in combined treatment strategies.[3] The other radiation sensitive chemo-therapeutic drugs include Gemcitabine, Paclitaxel, 5-FU, Carboplatin, Docetaxel. There are many trails regarding the efficacy of other chemo-sensitive drugs like paclitaxel, docetaxel, carboplatin. There were fewer trails on chemo-sensitive efficacy of gemcitabine in Indian population in head and cancers. Therefore the present study was intended to test the efficacy of Gemcitabine in comparasion to cisplatin with concurrent chemo-radiation in locally advanced oral and oropharyngeal cancers at tertiary cancer centre

MATERIALS AND METHODS

A prospective comparative study done from August 2022 To June 2024 in Department of Radiation oncology, MNJ Institute of oncology & Regional Cancer Centre, Osmania Medical College, Hyderabad.

60 patients presented to the OPD department of Radiation Oncology, MNJIO & RCC with early and locally advanced oral and oropharyngeal carcinoma. Patients who fulfilled the inclusion criteria were recruited for the study and randomly assigned into two groups, consisting of 30 patients per group.

Group A (Gemcitabine + concurrent RT) – 30 patients

Group B (Cisplatin + concurrent RT) – 30 patients

All of the study participants were thoroughly informed about the study, the type of treatment, and the benefits and drawbacks of the therapy. Patients have given their informed consent after addressing their questions, and agreed to participate in the study.

Inclusion Criteria: Age > 18 years to <80 years, ECOG score 0-2, TNM stage I to IVB, with Radical treatment intent, Histologically proven squamous cell carcinoma of oral cavity and oropharynx.

Exclusion Criteria: All histological types other than squamous cell carcinoma, Prior therapy including chemotherapy/radiotherapy, any synchronous or meta-chronous malignancy, Metastatic disease, Medical co-morbidities which preclude the use of concurrent chemo-radiation, Poor ECOG Score 3-4

Procedure

Patients were selected for the study in OPD department as per inclusion criteria, after taking proper informed consent will undergo: Complete history of patient and clinical examination. All routine workup includes CBP, RFT, LFT, RBS, serum electrolytes, viral markers such as HIV, HBsAG.

All histologically proven squamous cell carcinoma of oral cavity and oropharynx patients will undergo necessary radiological investigations, required for staging of disease.

Patients will be randomly assigned into two groups—A & B.

In Group A – patients will receive treatment with radiotherapy and concurrent chemotherapy with weekly Gemcitabine.

In Group B – patients will receive treatment with radiotherapy and concurrent chemotherapy with weekly Cisplatin.

All patients were evaluated for tumor response after 3 months of completion of concurrent chemo-radiation according to RECIST CRITERIA. Toxicities were evaluated during and after completion of radiotherapy. Patient's quality of life will be assessed before treatment (baseline), and during follow-up at post treatment 3 months.

All parameters assessed such as tumor response, acute toxicities and quality of life will be compared among both the groups.

General Preparation of the Patient

The required procedures were explained to the patients once they had been recruited in the study. All participants will undergo Pre RT dental evaluation. Dental procedures and tooth extractions were done as needed. A minimum of 10 to 14 days, enough time for healing, given between the final dental extraction and the initiation of radiation and chemotherapy.

Additionally, the side effects of head and neck chemoradiotherapy and the necessity of maintaining good dental hygiene were discussed with the patients. Patients were instructed to frequently use a mouthwash made of salt and soda bicarbonate that had been dissolved in water to rinse their mouth at least ten times daily. In order to prevent further damage to the mucosa, patients were advised to refrain from brushing their teeth with tooth brushes with harsh bristles. Additionally, they were told to stay away from foods that were extremely hot and gritty because these foods could further damage the mucosa.

Since dysphagia is a common initial symptom in patients, insertion of nasogastric tube was recommended. The chances of getting dysphagia owing to mucositis and the requirement for a nasogastric insertion were discussed with individuals who did not yet have dysphagia. The patients were advised to have a healthy diet which are high in nutrients, such as fruits, eggs, dairy and other items. The insertion of a nasogastric tube is done on willingness of patients.

Participants were suggested to drink at least 1.5 to 2 litres of water per day at regular intervals. Protein supplements which were accessible in the department were provided to all of the patients. Intravenous fluids with multivitamin support were given to patients if necessary. Weights of the patients were assessed weekly for any significant weight changes. The significance of adhering to the treatment plan and the need to prevent treatment pauses unless specifically advised otherwise owing to the emergence of adverse effects were explained to patients and patient attenders.

60 patients with early and locally advanced squamous cell carcinoma of the oral cavity and oropharynx enrolled in the study underwent the full pre-treatment work up and preparation. All the participants were assigned randomly into two Groups - A & B.

Radiation Therapy

All the Participants were treated with CT based conformal IMRT planning technique, using Varian Linac machine. Tumor volumes were given according to ICRU 50, such as

Gross tumor volume (GTV) includes primary tumor and primary node.

Clinical target volume (CTV) includes 37 High risk CTV in which 5mm margin given around the GTV. Intermediate risk CTV includes subsequent neck nodal levels at risk of microscopic spread and 5mm margin to CTV high risk volume. Low risk CTV includes low risk neck nodal levels and intermediate risk volume.

Planning target volume (PTV) include PTV High risk in which 5mm margin to high risk clinical target volume.

PTV intermediate risk includes 5mm margin to intermediate risk CTV.

PTV low risk includes 5 mm to low risk CTV.

The patients received a tumoricidal dose to various volumes such as: 66GY to PTV high risk. 60Gy to PTV intermediate risk. 54Gy to PTV Low risk.

Treatment duration is over six and half weeks, with 2Gy per fraction, of total 30 to 33 fractions in either sequential technique or simultaneous integrated boost technique.

Chemotherapy

Group A: Chemotherapy was started for every patient of group A on day 1of radiation. Following pre-medications with injection ondansetron 8mg, injection dexamethasone 8mg and injection pantop 40mg, injection Gemcitabine 40mg/m2 diluted in 500ml of Normal Saline was given over a period of two hours. Advised the participants to take the radiation after completion of respective chemotherapy cycle. The successive chemotherapy cycles were administered to participants at intervals of one week.

Group B: Chemotherapy was started for every patient of group B on day 1of radiation. Following pre-medications with injection ondansetron 8mg, injection dexamethasone 8mg and injection Pantop 40mg, injection of kcl+mgso4 1 amp each added to 500 ml to normal saline over 2hours. Then injection cisplatin 40mg/m2 diluted in 500ml of normal saline was given over a period of two hours. Advised the participants to take the radiation after completion of respective chemotherapy cycle. The successive chemotherapy cycles were administered to participants at intervals of one week.

Assessment during chemoradiation: Toxicity Assessment

All the patients were assessed every week to see for any toxicities like Radiation Dermatitis, Mucositis, Dysphagia, Pain, Nausea, Vomiting, Hyponatraemia, Hypokalaemia, Neutropenia, Anemia, Elevated Alanine Transaminase (ALT), Elevated Bilirubin, Elevated Creatinine. Documentation of above findings and grading done according to the CTCAE Version 5.0 toxicity criteria. Routine blood tests were done every week before initiation of chemotherapy and if any abnormality like anemia, neutropenia, any electrolyte imbalances were corrected. If required G-CSF injections were considered for any Grade 3 or 4 neutropenia patients.

Response Evaluation

Three months after the completion of treatment, a clinical evaluation and contrast enhanced CT imaging were conducted to evaluate the patient's response. Based on the Response Evaluation Criteria in Solid Tumors Criteria (RECIST 1.1 version),[4] the response to treatment was described.

Quality Of Life Assessment: Head & Neck 35 Quality of Life questionnaire (QLQ H&N35)

Quality of life questionnaire-H&N35 is meant for a wide range of patients with head & neck malignancy, varying in disease stage and treatment modality (i.e., surgery, Radiation Oncology, and chemotherapy). The questionnaire consists of 35 questions assessing symptoms and side effects of treatment, social function, and body image. The questionnaire has been designed according to the guidelines and pretested on patients from Sweden, Denmark, Norway, the UK, and Belgium. It has been field-tested in The Netherlands, Norway, Sweden, and in a large cross-cultural study consisting of more than ten countries (EORTC Protocol 15941). We obtained QOL H&N 35 questionnaire from EORTC by requesting through their official website. Questionnaire obtained in English, Telugu and Hindi languages. Then Quality of Life assessment had done by filling the questionnaire by patient himself before start of treatment and Post treatment 3 months.

Scoring system of the head & neck cancer questionnaire:

Analysis and scoring of questionnaire has done according to scoring manual provided by the EORTC. The QOL H&N35 questionnaire has seven multi-item scales that assess pain, swallowing, senses of taste and smell, social eating, social contact, speech, and sexuality. There are eleven single items. For all of the scales and questions, high scores indicate more problems.[5]

The principle for scoring of H&N 35 module:

1. Estimation of the mean of the items that contribute to the scale, which is the raw score.
2. Using a linear transformation to standardize the raw score, so that the scores range from 0 to 100. A higher score implies a worse level of symptoms.

Technical Summary:

In practical terms, if items i1, i2,.... in are included in the scale, the procedure is as follows:

Raw score:

Raw Score = RS = (i1 +i2 + i3 + i4... in)/n

Linear transformation:

Symptom scale "S" = {(RS – 1)/ range} * 100.

The range is the difference between the maximum value possible of raw score and the minimum possible value. The range of raw scores equals the range of the item values. Items are scored 1 to 4, giving a range of 3.

QOL outcomes were assessed using the EORTC Head-Neck module (H&N- 35) at baseline (pre-treatment) and three months post-treatment. All scores were linearly transformed, such that all scales ranged from 0 to 100 according to the recommendations of EORTC scoring manual. High score for the Symptom scale on H&N 35 module represents the presence of a symptom or problems.

Folllow Up:

After the treatment completion, patients were instructed to follow up every 3 monthly as per our institution protocol. For every follow-up complete clinical examination, toxicities and Quality of Life is done. Radiological investigations were done, if necessary.

- Participants were advised complete abstinence from the use of tobacco in any forms and alcohol, to keep good oral hygiene.
- Other complaints and symptoms were treated.

Statistical Analysis: Statistical analysis done between two groups in terms of Tumor Response, Acute toxicities and quality of life by Chi Square Test using analytical EPI INFO software tool.

RESULTS

Total 60 patients were included in the study. These 60 patients were assigned randomly into two Groups A & B, where 30 Patients were allocated to each group.

Male participants were more as compared to the females.

Table 1: Distribution of study population

Sex	Gemcitabine + RT	Cisplatin + RT	Total
Male	27	27	54
Female	3	3	6
Total	30	30	60
Site			
Oral cavity	24	27	51
Oropharynx	6	3	9
Subsite			
Tongue	15	15	30
Buccal mucosa	2	4	6
Soft palate	3	3	6
Base of tongue	3	1	4
Retro molar trigone	2	3	5
Hard palate	2	2	4
Alveolus	2	2	4
Floor of mouth	1	0	1

All patients had an ECOG performance status of 1-2 at the time of presentation. Oral cavity is the most common primary site in both study population compared to oropharynx. On comparing the various subsites, the most common cancers were in the Tongue followed by the Buccal mucosa, base of tongue and soft palate.

Table 2: Staging of cancer in present study

Stage	Gemcitabine + RT	Cisplatin + RT	Total
III	9	12	21
IVA	16	14	30
IVB	5	4	9
TOTAL	30	30	60
Histological Grade			
Well differentiated grade 1	23	22	45
Moderately differentiated grade 2	5	8	13
Poorly differentiated Grade 3	2	0	2

The most common histological grades in the groups were grade 1 well differentiated followed by grade 2 moderately differentiated, grade 3 poorly differentiated. Out of total 60 patients, 55 patients completed their treatment as advised.

All the patients who have completed the treatment were assessed clinically and radio-logically by CECT scan after 3 months of treatment for response evaluation, and then described as per the Revised RECIST criteria (version 1.1). All the patients who are included in the study are included in analysis as intention to treat (ITT) analysis.

Table 3: Tumor responses after 3 months of treatment

Tumor response after 3 months	Gemcitabine + RT	Cisplatin + RT
Complete	12 (40.0%)	18 (60.0%)
Partial	13 (43.3%)	10 (33.3%)
Progressive	2 (6.7%)	0 (0.00%)
Overall response	25 (83.3%)	28 (93.3%)

Overall response rate was 83.3% in Group A and 93.3% in Group B. Complete response is 40.0% and 60.0% in Group A & B respectively. Partial response is 43.3% and 33.3% in Group A & B respectively. Disease progression is 6.7% and 0.0% in Group A & B respectively.

Below are the treatment related toxicities of both groups. For every toxicity mean, median and standard deviation are calculated and compared among two groups. Quality of life of patients in both groups before start of treatment (Baseline), post treatment 3 months table listed below. There is statistically significant difference in quality of life between both the groups post treatment due to pain, senses, felt ill, social eating, social contact.

Table 4: Toxicities comparison during treatment in between two groups of study population

Toxicity	Gemcitabine + RT			Cisplatin + RT			P Value
	Mean	Median	Standard deviation	Mean	Median	Standard deviation	
Mucositis	2.6	3	0.5	2.5	3	0.51	0.799
Radiation dermatitis	1.8	2	0.66	1.5	1	0.51	0.033
Anemia	0.8	1	0.68	0.7	1	0.65	0.699
Neutropenia	0.6	0	0.93	0.4	0	0.57	0.407
Nausea	0.5	1	0.51	0.9	1	0.25	<0.001
Vomiting	0.7	0	.084	1.9	2	0.63	<0.001
Elevated creatinine	0.4	0	0.57	0.8	1	0.46	0,004
Elevated total bilirubin	0.1	0	0.35	0.1	0	0.25	0.398
Elevated ALT	0.07	0	0.25	0.03	0	0.18	0.561
Dysphagia	2.2	2	0.75	2.2	2	0.59	1
Hyponatremia	0.3	0	0.48	0.7	1	0.48	0.009
Hypokalemia	0.1	0	0.35	0.1	0	0.35	1

Table 5: Quality of life comparison between two groups over time before and post treatment 3 months

Domains (QOL H&N 35)	Time Period	Group A (Test arm) Gemcitabine + RT	Group B (control arm) Cisplatin + RT	P value
Pain	**Baseline**	68.93 ± 23.122	73.87 ± 20.519	0.386
	3 months post treatment	38.85 ± 16.968	58.64 ± 25.973	0.002
Swallowing	**Baseline**	60.23 ± 19.156	59.17 ± 19.341	0.831
	3 months post treatment	34.52 ± 22.32	41.36 ± 29.812	0.341
Teeth	**Baseline**	37.77 ± 31.35	49.93 ± 34.84	0.16
	3 months post treatment	30.74 ± 26.082	35.25 ± 28.697	0.545
Mouth Opening	**Baseline**	21.1 ± 36.62	31.1 ± 35.008	0.284
	3 months post treatment	50.59 ± 23.556	50.82 ± 26.849	0.973

Dry Mouth	**Baseline**	0±0	5.5 ± 12.509	0.019
	3 months post treatment	58.19 ± 15.184	60.14 ± 26.852	0.742
Sticky Saliva	**Baseline**	75.73 ± 22.996	40.03 ± 34.458	<0.001
	3 months post treatment	18.44 ± 23.273	8.04 ± 16.274	0.059
Senses	**Baseline**	0±0	4.47 ± 15.177	0.112
	3 months post treatment	68.04 ± 21.22	42.64 ± 32.729	0.001
Coughing	**Baseline**	53.33 ± 20.975	46.63 ± 19.065	0.201
	3 months post treatment	43.19 ± 22.517	40.61 ± 25.685	0.694
Felt Ill	**Baseline**	38.8 ± 21.775	51.17 ± 26.053	0.051
	3 months post treatment	14.74 ± 21.325	38.32 ± 40.423	0.01
Speech	**Baseline**	69.03 ± 19.968	66.77 ± 22.38	0.68
	3 months post treatment	41.07 ± 21.035	44.21 ± 28.034	0.641
Social Eating	**Baseline**	76.1 ± 19.836	88.53 ± 15.186	0.008
	3 months post treatment	43.26 ± 20.152	61.71 ± 31.446	0.013
Social Contact	**Baseline**	72.63 ± 17.399	83.97 ± 10.788	0.004
	3 months post treatment	42.74 ± 24.302	69.04 ± 31.627	0.001
Sexuality	**Baseline**	77.9 ± 23.312	93.93 ± 17.667	0.004
Feeding Tube	**3 months post treatment**	66.67 ± 48.038	65.18 ± 47.794	0.909
Weight Loss	**Baseline**	96.67 ± 18.257	100 ± 0	0.321
	3 months post treatment	7.41 ± 26.688	50.89 ± 50.223	<0.001
Weight Gain	**Baseline**	3.33 ± 18.257	0±0	0.321
	3 months post treatment	51.85 ± 50.918	33.04 ± 47.167	0.161

DISCUSSION

Most of the patients will be presenting at an advanced stage due to lack of awareness, illiteracy and poor socioeconomic status which makes surgical resection either impossible or very morbidly associated. Previously, local RT was given to these patients who had poor 5-year survival rates of 10-20% and local control rates between 50 and 70%. Many trials have been published in different radiation and chemotherapy combinations in head and neck cancer. Chemotherapy sensitizes tumours to radiation by inhibiting tumour repopulation, preferentially killing hypoxic cells, inhibiting the repair of sub lethal radiation damage, sterilizing micro metastatic disease outside radiation fields, and decreasing tumour mass, which leads to improved blood supply and re-oxygenation, thus amplifying the effect of radiation. Fractionated radiotherapy sensitizes tumors to chemotherapy by inhibiting the repair of cells. It also reduces tumour size, which improves blood supply to the tumour and allows the chemotherapy to reach the tumour cells more easily, resulting in a more cytotoxic effect.

There have been several trials conducted to investigate the feasibility as well as the improvement of outcomes by combining chemotherapy and radiation. In majority of trials, Cisplatin was the mainstay of chemotherapy either alone or in combination with other agents. A number of meta-analysis trails have confirmed the theoretical benefit by addition of another cytotoxic agent to radiation in the form of chemotherapy. The most well-known and significant of these meta-analyses is the Meta-Analysis on chemotherapy for Head and Neck Cancer (MACH-NC).[11] MACH-NC study demonstrated that combining chemotherapy with radiation had the following benefits in patients with locally advanced head and neck cancer:

The absolute benefit of using concurrent chemotherapy and radiation improved overall survival by 6.5% and 3.6% over 5 and 10 years, respectively. The use of chemotherapy has increased overall survival at 5 years by 5%, regardless of the timing of the association. The use of neo-adjuvant chemotherapy followed by radiation alone is less effective, when compared to concurrent chemo-radiation. Concurrent chemotherapy with cisplatin is beneficial. As the patient's age approaches 70, the benefit of adding chemotherapy becomes less clear.

The standard of care is proved to be concurrent chemo-radiation with radiation 66-70 Gy in 33 – 35 fractions in 2 Gy per fraction 5 days a week along with chemotherapy Inj. Cisplatin 100mg /m2 in D1, 22 and 43. The drawback in this regimen is Cisplatin in high doses is not tolerated by most of the people and toxicity is high. MACH-NC literature review states that the minimum cumulative dose of weekly cisplatin should be 200mg/m2 in order to be as effective as three weekly course. Weekly cisplatin regimen has less toxicity compared to three weekly. Concurrent chemo-radiation in locally advanced stages of head and neck cancers is now the global standard of care. Platinum-based CCRT, in particular, is considered standard for patients with un-resectable LA-SCCHN.

In MACH-NC analysis, only platinum based drugs have been compared either individually or in combination chemotherapy.

There have been many trails on the other chemotherapeutic drugs like gemcitabine, paclitaxel, 5-FU etc., with radiation sensitizing effect, to know whether these drugs can be used along with radiation and prove to be as effective as cisplatin with minimal tolerable toxicities.

J.L. Aguilar-Ponce,[6] Phase II trial conducted a study to assess gemcitabine efficacy and toxicity with concurrent radiation in patients with advanced HNSCC. No difference was observed in response or toxicity with gemcitabine dose of 50 or 100 mg/m2. The concurrent use of radiotherapy and gemcitabine is effective but produces manageable severe mucositis in a high percentage of patients in 100mg/m2 arm compared to 50mg/m2. When compared with our institute study, grade 3-4 mucositis is 53.3%, which is less than rates of grade 3-4 mucositis (74%) observed in aguilar trial. The referenced study reported an overall response rate of 88%, when compared with our study which is 83.3%; the difference could be due to more number of locally advanced stage in our study and might be due to higher dose of 100mg/m2 in referenced study.

Elsayed M Ali et al,[7] study showed an overall response rates 88.45% with grade 3-4 mucositis rates of 76%, grade 3 dysphagia rates of 42% and grade3-4 dermatitis rates of 4% with gemcitabine dose of <50mg/m2. Our institutional study demonstrated overall response rates of 83.3%, with lesser grade 3-4 mucositis rates of 53.3%, grade 3 dysphagia rates of 33.3% and grade 3-4 dermatitis rates of 6.66% The variation might be due to different patient population, treatment protocols, differences in supportive care practices or patient tolerance.

Halim et al,[8] reported an mild hematological toxicity. Grade 3 neutropenia was reported in 2 pts where as in our study only one pt developed grade 3 neutropenia. Similar incidence of grade 3 anemia noted in both the studies. Both the studies have an similar overall response rates.

A Meta analysis study by Vanderveken, Szturz, Specenier et al,[9] done to assess the efficacy and tolerance of gemcitabine used together with radiation as single agent and as a part of multi-agent based chemoradiotherapy, in combination with other cytotoxic agents in treatment of patients with locally advanced head and neck cancer. For schedules using a gemcitabine dose intensity (DI) below 50mg/m2 per week, the complete response rate was 86%(95%CI, 74%–93%) with grade 3-4 acute mucositis rate of 38% (95% CI, 27%–50%) and acceptable late toxicity. Compared with DI of > 50mg/m2 per week, there was no difference in the complete response rate but a significantly higher (p<001) grade 3–4 acute mucositis rate of 74% (95% CI, 62%–83%), often leading to treatment interruptions. In the referenced study, gemcitabine treatment at dose intensity (DI) below 50 mg/m2 per week demonstrated a overall response rate of 86% (95% CI, 74%–93%). This high rate of complete responses suggests favorable treatment efficacy in achieving tumor control and regression. In contrast, our institute's study reported a slightly lower overall response rate of 83.3%. While this difference is marginal, variations may be due to different patient populations, treatment protocols, or institutional practices. Acute mucositis, a common side effect of chemotherapy, was notably reported in both studies. The referenced study reported a grade 3-4 acute mucositis rate of 38% (95% CI, 27%–50%), indicating a significant incidence requiring management and supportive care during treatment. Comparatively, our institute's study reported a higher grade 3-4 mucositis rate of 53.3%. This difference suggests potential variations in treatment tolerability and supportive care practices between the two settings. This highlights the radio-sensitizing potential of gemcitabine and suggests that even very low dosages (less than 50mg/m2 per week) provide a sufficient therapeutic ratio and therefore should be further investigated.[10]

In this study the overall response rate (CR+PR) was 83.3% in Group A and 93.3% in Group B. Complete Response is 40.0% and 60.0% in Group A & B respectively. Partial Response is 43.3% and 33.3% in Group A & B respectively. Disease progression is 6.7% and 0.00% in Group A & B respectively. But there is no statistical significant difference between the two groups in terms of Tumor response rates.

Almost all the patients developed some form of acute toxicity during treatment. Toxicities like Radiation Dermatitis and Mucositis, an increased incidence of Grade 3 or 4 reactions in Group A is noted. In Group A 6.66% of patients developed Grade 3 or 4 dermatitis, where as in Group B none of the patients developed Grade 3 or 4 dermatitis. For mucositis, 53.3% in Group A and 53.3%

percent in Group B developed Grade 3 or 4 reactions. Even though there is an equal incidence of mucositis in both groups, early incidence of mucositis noted in group A compared to group B. Other side effects like Neutropenia, 6.6% developed grade 3 neutropenia from Group A, where as in group B none had developed grade 3 neutropenia. There were no severe abnormality seen in liver function test and electrolytes in both groups and no statistically significant difference. Patients also had other systemic toxicities such as nausea, vomiting, although they were all manageable. While group A has none of the patients with grade 3 vomiting, group B has 13.3 % of patients has grade 3 vomiting.

The hematological toxicity like Anemia there was incidence of grade 3 toxicity in one patient in group A, where as in group B none of the patients developed grade 3 toxicity. These were corrected by blood transfusion. There was incidence of Grade 3 neutropenia in 6.6 % of patients in Group A, there was no incidence of Grade 3 neutropenia in Group B. There was an incidence of 33.3 % of grade 3 dysphagia in group A, while group B has an incidence of 26.6 % of grade 3 dysphagia. There was

no severe renal toxicity, liver toxicity and electrolyte imbalance observed in any of the patients in both groups.

Quality of Life of patients was recorded through H&N 35 QLQ – Quality of life Questionnaire before treatment (Baseline) and Post treatment 3 months. In terms of quality of life, Both groups of patients has shown similar changes in terms of domains like pain, swallowing, teeth, opening of mouth, Dry mouth, senses, social eating, social contact. There is statistically significant difference between both the groups post treatment in quality of life due to pain, senses, felt ill, social eating, social contact.

Concurrent chemo-radiation with injection gemcitabine was found to be tolerated by the majority of patients in this study with manageable high grade mucositis reactions. When compared to Group A of Concurrent Chemo-radiation with injection gemcitabine, Group B has a higher percentage of patients who achieved complete response. The regimen also had a good rate of compliance, with a large proportion of patients having completed the treatment without or with a short break. However, the sample size is small, and is also not statistically significant.

In terms of toxicity, patients of gemcitabine arm had early incidence of mucositis, compared to cisplatin arm but this was not statistically significant, and the other toxicities were also manageable. In terms of Quality of life, assessed before the start of treatment and post treatment 3 months are comparable and similar change in quality of life observed in both groups. Although the complete response has achieved in more than half of the cases in two arms. The study shows better complete response in group B patients with injection cisplatin than group A with injection gemcitabine, with statistically insignificant value. However, a large-scale randomised trial must still be conducted in order to evaluate the effect of the addition of gemcitabine on overall survival, disease free survival, progression free survival and local recurrence rates. The study's major drawbacks were its small sample size, short follow-up period. This study is further continued with follow-up of patients in this trial in terms of quality of life.

Merits of the study

- Most of the patients had locally advanced head and neck squamous cell carcinoma, the treatment of choice is concurrent chemo-radiation.
- Optimal tumoricidal dose of 66Gy was administrated.
- Radiation delivery given through conformal ct based imrt planning.
- The chemotherapy in weekly schedule assisted to strict regular monitoring of toxicity reactions.
- Toxicities were manageable. Toxicity was graded with CTCAE version 5.0.
- Response assessment was done after 3 months of completion of concurrent chemo-radiation, REVISED RECIST 1.1 criteria was used for assessment.
- Gemcitabine arm achieved overall good response rates with manageable toxicities with statistically insignificant p value.

Demerits of study

Though Gemcitabine has overall good response rates, but cisplatin has better complete response rates and partial response rate. Most of the patients have experienced early incidence of mucositis reactions in gemcitabine group compared to cisplatin group. There wasn't long term follow up of this study, so locoregional recurrences, progression free survival; overall survival could not be assessed.

CONCLUSION

Both the gemcitabine and cisplatin are radio sensitizing agents which can be given in outpatient clinics. With cisplatin being the standard chemotherapy of choice during chemo-radiation in head and neck cancers, there has been increased incidence of nausea; vomiting, elevated serum creatinine, electrolyte disturbances and other late toxicities such as oto-toxicity.

Though the cisplatin has showed better efficacy in achieving complete response, gemcitabine shows lower efficacy with minimal tolerable side effects compared to cisplatin. Gemcitabine in low doses of < 50 mg/m2 can be considered in patients who are at high risk for nausea, vomiting, renal failure, impaired hearing. The regimen is also well tolerated, with minor systemic side effects, and patient compliance is good. However statistical significance was not achieved. Larger trials are needed to further define gemcitabine efficacy in the treatment of early and locally advanced head and neck cancers.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021 Feb 4;71(3):209–49.
2. Pai P, Tuljapurkar V, Dhar H, Mishra A, Chakraborti S, Chaturvedi P. The Indian scenario of head and neck oncology - Challenging the dogmas. South Asian Journal of Cancer. 2016;5(3):105.
3. Lacas B, Carmel A, Landais C, Wong SJ, Licitra L, Tobias JS, et al. Metaanalysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. Radiation Oncology and Oncology. 2021 Mar; 156:281–93.
4. Nishino M, Jagannathan JP, Ramaiya NH, Van den Abbeele AD. Revised RECIST Guideline Version 1.1: What Oncologists Want to Know and What Radiologists Need to Know. American Journal of Roentgenology. 2010 Aug;195(2):281–9.
5. EORTC QLQ-H&N35 Scoring Manual [Internet]. [cited 2022 Dec 15]. Available from: https://www.eortc.be/qol/ScoringInstructions/HN35%20Summary.pdf
6. .-L. Aguilar-Ponce, M. Granados-García, V. Villavicencio, A. Poitevin- Chacón, D. Green, A. Dueñas-González, Á. Herrera-Gómez, K. Luna-Ortiz, A. Alvarado1, H. Martínez-Said, C. Castillo- Henkel, B. Segura-Pacheco& J. De la Garza; Annals of Oncology 2004:15: 301–306.

7. Ali EM, Abdelraheem AG. Concurrent radiotherapy and chemotherapy for locally advanced squamous cell carcinoma of the head and neck. Head Neck Oncol. 2011 Nov 15; 3:48.
8. Amal Ahmed-Fouad Halim, Hanan Ahmed Wahba, Hend Ahmed El-Hadaad, Ahmed Abo-Elyazeed; Med Oncol (2012) 29:279–284;
9. Vanderveken, Szturz, Specenier et al. The Oncologist 2016; 21:59–71;
10. Homma A, Inamura N, Oridate N, Suzuki S, Hatakeyama H, Mizumachi T, et al. Concomitant weekly cisplatin and Radiation Oncology for head and neck cancer. Japanese Journal of Clinical Oncology [Internet]. 2011 Aug 1 [cited 2022 Nov 27];41(8):980–6.