Section: Radiation Oncology

Original Research Article

COMPARATIVE STUDY OF USE OF DAILY CISPLATIN VERSUS WEEKLY CISPLATIN CONCURRENTLY WITH RADIATION THERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

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ABSTRACT

Background: The aim of this study was to evaluate and compare the use of daily low dose cisplatin versus weekly Cisplatin concurrently with radiation in locally advanced squamous cell carcinoma of head and neck.
Materials and Methods: It is a Double arm prospective study done for 2 years in 50 Patients who have histologically proven head and neck cancers were selected randomly and allotted to each arm. 25 cases in weekly cisplatin arm and 25 cases in low dose daily cisplatin arm. Age 20- 60 years No previous chemotherapy or radiotherapy No other comorbidities in whom Biopsy proven newly diagnosed squamous cell carcinoma of the head & neck ECOG 0-1 with Primary tumor sites oropharynx, oral cavity, larynx, hypopharynx, locally advanced squamous cell carcinoma (stage II, III, IVA) are included in study.
Results: In the trial arm the complete response was seen in 84% and in the control arm the complete response was seen in 80%. partial response was seen in 16% of trial arm while 20% had partial response in control arm. The results are showing enough to infer that daily low dose cisplatin is as efficacious as weekly cisplatin. Toxic effects were less incident in the low dose daily cisplatin over all when compared to weekly cisplatin. P value was also significant to back up that statement. Dermatitis and mucositis was less seen in trail arm.
Conclusion: The low dose daily cisplatin had another advantages in our study. Daily chemotherapy allowed us to see the patients daily and asses for toxicity in early stage and opportunity to talk to the patients allowing us to better implement some precautionary measures in preventing toxicities and maintain the nutritional status of the patient. So there by the overall toxicity was less in low dose daily cisplatin arm while having the same efficacious as weekly cisplatin in terms of tumor.
Keywords: Squamous cell carcinoma, Chemotherapy, low dose cisplatin, radiotherapy.

INTRODUCTION

Concurrent chemoradiation (CCRT) has become the standard treatment option for locally advanced (stage III-IVB) head and neck squamous cell cancer (LA-HNSCC), since several randomized trials reported a significant survival benefit of adding chemotherapy to radiation over radiation therapy alone.[1,2] Also,

CCRT enables preservation of organs in neck and improves functional outcomes and quality of life of survivors without compromising survival outcomes, compared to primary surgical approach.[3,4] The current standard CCRT protocol, based on evidences, includes the use of radiation treatment concurrent with 3 cycles of bolus cisplatin 100 mg/m2 given in every 3 weeks. Despite improved outcomes with such protocol, treatment-related toxicity continues to be a major concern.[5,6] Specifically, adding bolus cisplatin to radiation was associated with increased acute toxicity, including gastrointestinal symptoms (xerostomia, mucositis, and nausea/vomiting), hematologic toxicities, and acute kidney injury.[7,8] In a randomized trial, more than 70 percent of patients receiving CCRT exhibited grade 3 or higher adverse events with the current standard regimen.[2] Unacceptable toxicity frequently results in inevitable delay in the delivery schedule of definitive radiation therapy, which in turn might affects overall therapeutic outcome negatively, especially in medically unfit or elderly patients. 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 chemoradiotherapy 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

It is a Double arm prospective study done from December2020–November 2022 in MNJ institute of oncology, regional cancer centre, Osmania medical college, Hyderabad. 50 Patients who have histologically proven head and neck cancers were selected randomly and allotted to each arm. 25 cases in weekly cisplatin arm and 25 cases in low dose daily cisplatin arm. Approval from the institute ethical committee was obtained on 10/12/2020. All patients enrolled in the study were informed about the merits and demerits of participating in this study and signed an informed consent form in their regional language, which is Telugu and hindi.

Inclusion Criteria: Age 20- 60 years No previous chemotherapy or radiotherapy No other comorbidities in whom Biopsy proven newly diagnosed squamous cell carcinoma of the head & neck ECOG 0-1 with Primary tumor sites oropharynx, oral cavity, larynx, hypopharynx, locally advanced squamous cell carcinoma (stage II, III, IVA).

Exclusion Criteria: Tumor site as nasopharynx, paranasal sinus, nasal cavity Adenocarcinoma, impaired renal and hepatic function test. Inadequate bone marrow reserve Metastatic or recurrent disease, Previously received treatment for any other malignancy.

Proper history of patients illness with Complete physical examination was done. ideolayngscopy and rhinoscopy if needed to visualize the primary tumor. Trucut biopsy from the primary and the neck nodes with Complete blood count, Renal function test, Liver function test and Blood grouping and RH Typing, Chest X ray, CT head and neck plain and contrast, Cardiac evaluation, naso-gastric tube insertion if indicated. Dental prophylaxis including scaling, dental filling and extraction if required. A gap of two weeks was given after dental prophylaxis for proper healing of gums if extraction is done. Tumor stage, performance status and weight were recorded. Staging was done based on the American Joint Committee staging manual 8 th edition (for head and neck cancers). Weekly CBP, RFT, LFT before each cycle of chemotherapy.

Patient preparation during treatment: The patients was advised to quit tobacco chewing and smoking and alcohol habits before initiating the treatment. Patients were advised to wears of t tshirts instead of shirt. Patients were advised to maintain a proper oral hygiene by gargling water mixed with salt and baking soda.

Dysphagia is one of the most common symptom in head and neck cancers. This may lead to nutritional deprivation in patients. Nasogastric tube was placed in patients with severe dysphagia. Patients were advised to take more protein rich foods like dal. Patient was advised to maintain proper hydration. Protein powders were given in some patients to maintain the nutritional status.

Treatment protocol: 50 patients randomly selected locally advanced head and neck cancer were randomized to Arm 1- low dose daily cisplatin 6 mg/m2 with radiation. Arm2- weekly cisplatin 40mg/m2 with radiation.

Radiation Therapy: All patients were treated with an dose schedule of 2Gy perfraction Five days per week total 33

Patients were made to lie in a supine position with neck slightly extended and hands pulled downward with traction. Patient was immobilized with head and neck raycast. Ct simulation was done with 3mm slice thickness with IV contrast 1ml per kg and patient was scanned from vertex to carina. Images are transferred and imported. After image registration alloars and target volumes were delineated GTV, CTV 66, CTV

60 GY and PTV were created as per contouring guidelines. IMRT planning was done to give adose of 66 gy 2GY /#I N33 # for high risk areas. 60gy 2GY/# 30# to cover the intermediate risk area.

After approval of suitable plan, image guided verification was done using kv imaging.

Table 1: TNM staging and treatment adopted

Tumor site	Stage	Clinical treatment volume
Oral tongue, floor of the mouth	T1–T4N0	Include the tumor bed, the entire oral tongue and the base of the tongue. For floor of the mouth lesions, consider including the alveolar ridge, due to its proximity to the floor of the mouth. Both sides of the neck should be treated with radiotherapy (even for well-lateralized T1–T2N0 lesions, if the depth of invasion is >4 mm), although physician discretion can be usedtodetermineiftheseshouldbeinthelow-orhigh-riskCTV.Consideripsilateraland/or contralateral levels I–IV
	T1–T4N1–3	Include the tumor bed, the entire oral tongue and the base of the tongue. For floor of the mouth lesions, consider including the alveolar ridge, due to its proximity to the floor of the mouth. Both sides of the neck should be treated with radiotherapy, although physician discretioncanbeusedtodetermineiftheseshouldbeinthelow-orhigh-riskCTV.Consider ipsilateral and/or contralateral levels I–V
Buccal mucosa	T1–T4N0	Itisimportanttobegenerouswithtargetvolumeswhentreatingtheinnercheek.Includethe tumor bed and the entire buccal mucosa. Posteriorly, this should extend to retromolar trigone. Superiorly, this should extend to near the inferior orbital rim. If the tumor is well lateralized, ipsilateral levels I-IV alone can be treated. Otherwise, consider treating bilateral cervical lymph nodes
	T1–T4N1–3	Itisimportanttobegenerouswithtargetvolumeswhentreatingtheinnercheek.Includethe tumor bed and the entire buccal mucosa. Posteriorly, this should extend to retromolar trigone. Superiorly, this should extend to near the inferior orbital rim. Ipsilateral levels I-IV should be treated within the neck. Depending on pathologic findings and discussions with the surgeon, consideration can be given to treating the contralateral neck as well
Retromolar trigone, hard palate, gingiva	T1–T4N0	Include the preoperative tumor volume and postoperative tumor bed. Consider covering ipsilaterallevelsI–IVforallcases.Treatmentofthecontralateralneckisatthephysician's discretion. Hard palate tumors are generally minor salivary gland tumors, and treatment guidelines from "Chapter 8: Major Salivary Glands" should be used to guide treatment of lymph node regions
	T1–T4N1–3	Include the preoperative tumor volume and postoperative tumor bed. Treat the ipsilateral levelsI–IVforallcasesandconsidertreatmentofthecontralateralneck.Hardpalatetumors are generally minor salivary gland tumors, and treatment guidelines from "Chapter 8: Major Salivary Glands" should be used to guide treatment of lymph node regions

Table 2: Oarconstraints Followed Were

Critical structures	Constraints
Brainstem	Max< 50 Gy
Optic nerves	Max< 54 Gy
Optic chiasm	Max< 54 Gy
Spinal cord	Max<45Gyor 1cc of the PTVcannotexceed50 Gy
Mandible	Max<70GyoutsidehighdosePTV,avoidhotspots
Brachial plexus	Max< 65Gy outside high dose PTV
Other normal structures	Constraints
Parotid gland	(a)Mean ≤26 Gyin one gland
	(b)Oratleast20ccofthecombinedvolumeofbothparotidglandswillreceive<20 Gy
	(c)Or atleast50 % of one gland will receive <30 Gy
Submandibular gland	Mean dose<39Gy
Cochlea	Max<50GyorD05<55Gy
Lens	Max<5Gy
Glottic larynx	Mean< 45 Gy

Chemotherapy Schedule

Arm 1: Cisplatin was given daily 6mg /m2 in 100ml NSIV over 20 mins 30 mins before radiation. 500 ml of normal saline was daily to maintain the hydration. Antiemetics ondansetron 8mg was given daily. renal function test liver function test and complete blood picture, serum electrolytes was monitored weekly.

Arm 2: Inj. Cisplatin 40mg/m2 in 500ml normal saline is given iv over 90minutes.Premedication involves

Inj. Dexamethasone 8mg IV, Inj. Ondansetron 8mgIV, Injection pantoprazole diluted in 100ml of normal saline given IV over 20 minutes on BID basis. Hydration was given with 500ml of normal saline Injections mannitol 20%100ml was given over 20 minutes intravenously after cisplatin transfusion. This was given weekly once after monitoring of renal and haematological parameters

Toxicity Assessment: Patients were examined for toxicities daily before chemotherapy. RTOG grading criteria was used to grade toxicities like mucosities, dermatitis. Treatment was suspended if the patients develop higher toxicities more than grade 3. Renal function test, liver function test, serum electrolytes, complete blood picture was done weekly. Packed red cell transfusion was done if HB was less than10mg/dl. WBC count was monitored weekly and fil gastrin was given subcutaneously if absolute neutrophil count dropped less than 1000. Platelet count was also monitored and platelet transfusion was done if patient was symptomatic.

Response Evaluation: All patients were reassessed by clinical examination and with a CT Neck,4-6 weeks after completion of treatment. Response to treatment was described based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria.

Complete Response: Disappearance of all target lesions; malignant nodes<10 mm.

Partial Response: Atleast 30% reduction in the sum of the longest diameter of target lesions, confirmed at 4 weeks.

Stable Disease: Neither partial response non progressive disease criteria are met, in a minimum time set by the protocol.

Progressive Disease: At least 20% increase in the sum of the diameter, with a minimum absolute increase of 5mm, taking as reference the smallest sum in the study or appearance of new lesions.

Follow up: Patients after completion of concurrent chemoradiation were discharged from the hospital. Post RT instruction were given and discharged from Hospital. Response evaluation was done based on RECIST criteria after 4-6 weeks.

Follow up is done 1-2 months for the first 1 year and the every 3 months for year 2-3 then every 6 month for 4-5 year and then annually. At each visit all the complication were addressed and residual and recurrence were evaluated and further treatment were given.

RESULTS

A total of 50 patients have been taken under the study after prior consent from the patients and 25 patients were kept under trail arm and 25 patients have been kept under control arm.

On analysis of both arms 21 subject were under age 45 it is 42% and 12%were above 61.

Table 3: Age distribution in present study

Age(Years)	Group		Total
	Cases	Controls	
<= 45	6	15	21
46 -60	16	7	23
61 &Above	3	3	6
Total	25	25	50

P Value-0.025 (Chi-SquareTest)

Table 4: Tumour Subsite and its distribution

Diagnosis	No. of Subjects	Percentage
CA Floor of Mouth	2	4.0%
CA Glottis	5	10.0%
CA Hard Palate	2	4.0%
CA Hypopharynx	4	8.0%
CA Larynx	3	6.0%
CA Left Buccal Mucosa	8	16.0%
CA Left Gingivobuccal Sulcus	1	2.0%
CA Left Lateral Border of Tongue	1	2.0%
CA Left Lateral of Tongue	2	4.0%
CA Left RMT	1	2.0%
CA Right Buccal Mucosa	11	22.0%
CA Right Gingivobuccal Sulcus	1	2.0%
CA Right Lateral ofTongue	2	4.0%
CA Right RMT	1	2.0%
CA Supraglottis	2	4.0%
CA Tongue	4	8.0%

Table 5: Tumor stage and Histopathology distribution in groups

T Stage	Group		Total
	Cases	Controls	
T2	2	6	8
T3	14	9	23
T4	9	10	19
P Value 0.208(Chi-SquareTest)			
Histopathology			
Moderately Differentiated	5	11	16
Well Differentiated	20	14	34
P Value 0.069 (Chi-Square Test)			

Table 6: Adverse events in present study

Vomiting	Group		Total
	Cases	Controls	
Nil	23	5	28
Grade1	2	10	12
Grade2	0	10	10

P Value<0.001 (Chi-Square Test			
Mucositis			
Nil	6	1	7
Grade1	14	6	20
Grade2	5	18	23
P Value 0.001 (Chi-Square Test)			
Dermatitis			
Nil	5	0	5
Grade1	10	6	16
Grade2	8	14	22
Grade3	2	5	7
P Value 0.03 (Chi-Square Test)			
Leucopenia			
Nil	22	23	45
Grade1	1	1	2
Grade2	2	1	3
P Value 0.837			
Hypokaelemia			
Nil	25	24	49
Mild	0	1	1
P Value 0.31			
Dysphagia			
Nil	3	2	5
Grade1	2	2	4
Grade2	11	13	24
Grade3	9	8	17
P Value 0.935 (Chi-Square Test)			

Vomiting was seen more in weekly cisplatin arm. 40% of patient in weekly cisplatin arm developed grade 2 vomiting

Mucositis:72% patient in weekly cisplatin arm developed grade 2 mucositis while it was seen only in 20% of patient daily cisplatin arm.

Dermatitis: Grade 3 dermatitis was seen in 20% of patients in weekly cisplatin arm while it was seen only in 8% of patients in low dose daily cisplatin arm

Hypolkaelemia was seen in only patient in control arm and It was manageable and asymptomatic.

Dysphagia: Dysphagia grade 2 was seen in 44% of the patients in low dose daily cisplatin arm while it was seen in 52% of patients in weekly cisplatin arm.

Table 7: Mean weight loss in present study

Group	Weight Loss (Kg's)		P Value (t-test)
	Mean	Std. Deviation	
Cases	6.04	1.513	0.232
Controls	6.48	1.005	

Weight loss: The mean weight loss in weekly cisplatin arm was 6.48 while it 6.04 on low dose daily cisplatin arm.

DISCUSSION

Head and neck cancer is one of the most common cancer seen in our OPD, the major cause of incidence of oral cavity is the use of oral tobacco. Even after drastic measures by government to promote the carcinogenic effects of oral tobacco the use of oral tobacco has increased amoung they oungerage. Majority of patients present in locally advanced stage where surgical resection is not possible or associated with lot of morbidity. So Radiotherapy has played a major role in managing the head and neck cancer local control rates were 50%-70%. There was a definite rationale in using the use of concurrent chemotherapy. Chemotherapy inhibits tumor repopulation and there by sensitizes the tumor to radiotherapy. It also sterilizes the micrometastatic disease outside the radiation fields.

Many meta-analysis have been done to prove the efficacy of concurrent chemotherapy. MACHNC Metaanalysis showed the following benefits in head and neck cancer. The use of chemotherapy increased the overall survival at 5years by 5% irrespective of the timing of association. The concurrent use of chemotherapy with radiation improved the overall survival by 8%. The use of neoadjuvant chemotherapy followed by radiation alone is less effective as compared to concurrent chemoradiation. The use of cisplatin as the chemotherapy has evident benefit. The use of combination chemotherapy does not seem to provide added advantage over the use of single agent and as the age of the patient increase over 70, the benefit of adding chemotherapy is less evident. As of now the standard treatment is concurrent chemoradiation with 40mg/m2. Theoretically daily administration of low dose cisplatin may be superior owing it to the fractionated administration of concurrent chemoradiation.[9] The choice of daily cisplatin instead of weekly schedule was based on the experience reported by Jeremic et al,[10] and Bartelink et al.[11] Jeremic et al,[10] have reported superior outcomes with concurrent use of

daily cisplatin as compared to RT alone. There are some practical benefits in daily low dose cisplatin: No need for elective hospitalization as it is low dose the patient can take chemo in day care setup daily without the need of hospitalization. No need for excess hydration. We could monitor the patient daily, assessing the toxic effects.

Regarding the optimal dose of low dose cisplatin many studies have used 6 mg/m upto the maximum of 10 mg daily. Homma et al used low dose daily cisplatin at 4 mg/m2and compared it with weekly cisplatin and found results to be inferior. This could have been due to use of ineffectively low dose schedule of cisplatin daily. So in this study we went ahead with 6mg/m2. The primary objective of this study is to see the tumor response compared to low dose cisplatin vs weekly cisplatin.

The overall response in both arms were similar. The effects of low dose daily cisplatin was as efficacious as weekly cisplatin in achieving the tumour control. The results were similar in this study. In the trial arm the complete response was seen in 84% and in the control arm the complete response was seen in 80%. partial response was seen in 16% of trial arm while 20% had partial response in control arm. though the p value doesn't allow to infer that daily cisplatin is superior to weekly cisplatin in terms of tumor response. The results are showing enough to infer that daily low dose cisplatin is as efficacious as weekly cisplatin.

The secondary objective of this study is to compare the toxic effects of the low dose daily cisplatin versus weekly cisplatin. In weekly cisplatin arm 40% patients had grade 2 vomiting and needed the use of antimemetics. The incidence of vomiting in low dose daily cisplatin was very low only 8% had grade 1 vomiting and was significant. Mucositis grade 2 was seen in 72% of patients receiving weekly cisplatin and only 20% had grade 2 mucositis in low dose arm was significant. 20% of patients in weekly cisplatin arm developed grade 3 dermatitis while 8% of patients in low dose daily cisplatin developed grade 3 dermatitis and was significant. Hypokaelemia was seen only in one patient in control arm.

Grade 3 dysphagia was seen in 32% of the patients in control arm while it was seen in 36% of patients in low dose daily cisplatin arm. 52%ofpatientin control arm developed grade 2 dysphagia while it was seen in 44% in trial arm it was not significant.

Toxic effects were less incident in the low dose daily cisplatin over all when compared to weekly cisplatin. P value was also significant to back up that statement. dermatitis and mucositis was less seen in trail arm. The low dose daily cisplatin had another advantages in our study. Daily chemotherapy allowed us to see the patients daily and asses for toxicity in early stage and opportunity to talk to the patients allowing us to better implement some precautionary measures in preventing toxicities and maintain the nutritional status of the patient. So there by the overall toxicity was less in low dose daily cisplatin arm while having the same efficacious as weekly cisplatin in terms of tumor.

The results are comparable to the other done in the same aspect. The study by Frank IP hombres et al,[13] also showed less renal toxicity in low dose daily cisplatin arm when compared to weekly cisplatin and overall response was better in low dose cisplatin 90% compared to 74% in weekly cisplatin arm. PK Gupta et al,[14] study also showed better overall survival in low dose cisplatin arm with insignificant p value. Toxicities like dermatitis and mucositis were also less in low dose daily cisplatin arm compared to weekly cisplatin arm. This studies result are more in parallel with the results of P K Gupta et al,[14] study.

Maximum tumoricidal dose was achieved in all the patients and all the patients were treated by IMRT technique. Optimal dose of weekly cisplatin and daily cisplatin was achieved in all the patients. Toxicities were less in low dose daily cisplatin arm. Tumor response in low dose daily cisplatin was as efficacious as weekly cisplatin. No treatment related deaths were seen. The study requires further long term follow up to report about the long term survival of the patient. The study established that low dose daily cisplatin is non inferior to weekly cisplatin arm and has lesser toxicity and more feasible than weekly cisplatin arm. Randomised trial with larger sample size with the same protocol could be done.

CONCLUSION

Head and neck cancer poses a huge problem in our society. In developed countries like India the patient usually present at locally advanced stage due to lack of proper medical knowledge. Most of our patients are of low socioeconomic status. The primary objective of the study was to evaluate the response of head and cancer to low dose daily cisplatin versus weekly cisplatin. Daily cisplatin had a complete response in 84% and complete response was seen in 80% of patient with weekly cisplatin. P VALUE was 0.713. local toxic effects was seen lesser in low dose daily cisplatin when compared with weekly cisplatin with a significant p value. In a high volume like MNJIO low dose daily cisplatin was feasible and was suitable for giving chemo on opd basis and it removed the need to electively admit the patient for chemotherapy. Future studies with long term followup can shed light about the long term survival of the patient.

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