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Original Research Article

A comparative study of radical radiotherapy with weekly paclitaxel versus radical radiotherapy with weekly cisplatin in the management of locally advanced squamous cell carcinomas of head and neck

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ABSTRACT

Background: Concurrent chemo radiation is standard of care in locally advanced squamous cell carcinomas of head and neck. Single agent Cisplatin either weekly or three weekly is commonly used concurrently with radiation. The present study aims to evaluate the response rate and toxicity of radical radiotherapy with weekly paclitaxel and cisplatin in head and neck cancers.
Methods: This is a prospective double arm study in which sixty patients with histologically proved squamous cell carcinomas registered in our department were accrued into the study with thirty patients in each arm. All patients were treated using Theratron phoenix 780 cobalt unit with a dose of 66 Gy in 33 fractions. The patients were randomized to receive 40 mg/m^2 of weekly cisplatin or 40 mg/m^2 of weekly Paclitaxel concurrently with radiation. The response to the therapy was assessed six weeks after completion of treatment. The statistical analysis was done using SPSS software.
Results: In cisplatin group 18 patients achieved complete response and 12 patients achieved partial response whereas in Paclitaxel group 21 patients achieved complete response and 9 patients achieved partial response. However in paclitaxel arm the incidence of radiation dermatitis, mucositis, dysphagia and laryngitis are slightly higher compared to cisplatin group.
Conclusions: The weekly paclitaxel concurrent with radiation is a feasible alternative to weekly cisplatin in locally advanced squamous cell carcinomas of head and neck.

Keywords: Cisplatin, Paclitaxel, Radiation therapy

INTRODUCTION

The treatment of locally advanced head and neck carcinomas include multiple modalities like surgery, radiotherapy and chemotherapy.[1] The proper sequencing of these modalities are individualised depending on the site of the tumour, histology and patient preferences. The functional outcome of the treatment, resectability of the tumour and the general condition of the patient should also be considered before taking any treatment decisions.[2,3]

However the use of concurrent chemo radiation is associated with improved loco regional control and overall survival rate. The use of single or multiple chemotherapeutic agents will potentiate the effect of

radiation therapy. Single agent cisplatin given concurrently with radiation is the standard of care for squamous cell carcinomas of head and neck.[4,5] Newer agents like docetaxel and paclitaxel are most important because of their single agent activity in head and neck cancers and their ability to act as potent radio sensitizers. The purpose of this study is to explore the possibility of using weekly paclitaxel as an alternative to weekly cisplatin concurrent with conventional radiotherapy and to compare the response rate and toxicity of radical radiotherapy with weekly paclitaxel and cisplatin in head and neck cancers.

METHODS

This study is a prospective double arm study involving previously untreated patients with locally advanced squamous cell carcinomas of head and neck. Sixty patients with histologically proved squamous cell carcinomas registered in our department were accrued into the study with thirty patients in each arm. The accrual of the patients was started after obtaining consent from the ethical committee for conducting this study in our institute. The informed consent was obtained from all the patients included in the study.

The study period was from February 2012 to October 2012. The inclusion criteria was age <70 years, Eastern Cooperative Oncology Group performance status I & II, histological proof of squamous cell carcinoma, absolute Neutrophil count ≥2000/µL, Platelet count ≥100,000/µL, Haemoglobin ≥10 g/dL, Total bilirubin ≤1.5 mg/dL, Serum Creatinine ≤1.2 mg/dL and patients who have given informed consent prior to study.

The patients with metastatic disease, Nasopharyngeal, Para nasal sinus and salivary gland carcinoma, Prior surgical treatment excluding diagnostic biopsy of the primary site or neck, patients with history of prior radiotherapy, patients with history of prior chemotherapy for any reason to the head and neck region and patients with recurrent head and neck cancers were excluded from the study.

The pre-treatment workup include detailed history, complete physical examination, biopsy from the primary or metastatic node, blood grouping, complete blood count, Renal function test, Liver function test, Computed tomography scan of Head and neck, Chest X ray and cardiology evaluation and fitness.

The tumor stage, performance status and weight of all patients were recorded. All patients were persuaded to quit smoking and alcohol because it has been shown that smoking and alcohol intake during radiotherapy has shown poor results. Dental prophylaxis has been done in all required patients in the form of dental filling, scaling and extraction. During radiation, patients were instructed to clean their teeth after each main meals using soft brush. They were also instructed to use soda bicarbonate mouth wash, 5-6 times a day. All the patients involved in the study were encouraged to take adequate nutrition to prevent excessive weight loss. Ingesting food by mouth is the preferred method of feeding; however Nasogastric tube is inserted if required.

A total of 60 patients attending Radiation Oncology OP were recruited to the study. Patients were randomly assigned to two groups, Arm A and Arm B. All patients were treated using Theratron phoenix 780 cobalt unit. Target volume included primary tumor along with 2 cm clearance. Nodal volume included palpable nodes and those nodal levels that have high risk of microscopic disease. Two opposing lateral portals and a Low anterior field are used. Dose per fraction was 200 cGy and five fractions were delivered per week. Anterior field shifting was done after 40 Gy to avoid spinal cord. All patients were assessed after 60 Gy for radiation boost to the primary tumor and palpable nodes. The dose for boost is 6 Gy and there by delivering a total dose of 66 Gy to the gross disease.

In Cisplatin arm patients received 40 mg/m^2 of Cisplatin and in Paclitaxel arm patients received 40 mg/m^2 of Paclitaxel on days 1,8,15,22,29,36 of teletherapy. The toxicities were assessed using RTOG Acute Morbidity Scoring Criteria and Common Toxicity Scoring Criteria. The toxicities were assessed every Monday and recorded. All the toxicities are managed according to the guidelines.

Response to the therapy was assessed six weeks after completion of treatment. Both clinical and radiological assessment was done. Response assessment was done using RECIST criteria version 2.0. Assessment of complete response, partial response, no response or progressive disease was done. All patients with complete response after the protocol were observed on monthly follow up. The patients with residual disease or progressive disease were assessed for salvage surgery. If salvage surgery is not possible the patients were given palliative chemotherapy.

RESULTS

The patient characteristics were given on Table 1. The overall response rate is given in Table 2. The site wise response is given in Table 3 and Table 4.

All patients in the cisplatin and paclitaxel arm experienced grade 1 skin toxicity. In cisplatin arm 24 out of 30 patients progressed to grade 2 toxicity whereas in paclitaxel arm, all the 30 patients progressed to grade 2 skin reactions. None of the patients in the cisplatin group experienced grade 3 or grade 4 complications. However in paclitaxel arm, 3 patients had grade 3 toxicity during sixth week of radiation. None of the patients in the study group experienced grade 4 skin toxicity. All the twenty patients, in whom whole or part of buccal mucosa is irradiated, experienced grade 2 oral mucositis. However

in the paclitaxel arm, 4 patients experienced grade 3 mucositis whereas in cisplatin arm only 2 patients had grade 3 mucositis. Regarding dysphagia all patients in the cisplatin arm and paclitaxel arm experienced grade 3 dysphagia. Six patients in the paclitaxel arm had grade 4 dysphagia (inability to swallow even saliva).

But the patients were given adequate nutrition via nasogastric tube. Regarding laryngitis cisplatin arm had only grade 1 and grade 2 toxicities but paclitaxel arm had two grade 3 toxicities.

Table 1: Patient characteristics.

	Cisplatin arm	Paclitaxel arm
Mean Age	53.5 years	49.5 years
% of male patients	73.3	80
ECOG PS I	19	24
PS II	11	6
Oral cavity	4	4
Oropharynx	15	15
Larynx	7	7
Hypopharynx	4	4
T stage T3	16	12
T4	14	18
N stage N1	8	6
N2a	11	5
N2b	4	8
N2c	6	9
N3	1	2
Grade 1	11	10
2	17	15
3	2	5

Table 2: Overall response to treatment.

Response	Cisplatin group	Paclitaxel group
Complete response	18	21
Partial response	12	9

P value 0.59

Table 3: Site wise response cisplatin arm.

Site	Complete response	Partial response
Oral cavity	2	2
Oropharynx	11	4
Larynx	3	4
Hypo pharynx	2	2

The only haematological toxicity encountered during the study was anaemia. The total number of patients in the paclitaxel arm experienced anaemia was more compared to cisplatin group [28 patients in Paclitaxel group compared to 24 in Cisplatin group]. One patient in the paclitaxel group had experienced grade 3 anaemia. None of the patients had neutropenia or thrombocytopenia.

Table 4: Site wise response paclitaxel arm.

Site	Complete response	Partial response
Oral cavity	2	2
Oropharynx	13	2
Larynx	3	4
Hypo pharynx	3	2

DISCUSSION

For all patients with locally advanced head and neck cancers, the option of concurrent chemo radiation should be considered seriously in order to preserve organ function. By avoiding surgery in appropriate cases the functional morbidity associated with loss of organ can be avoided. The general consensus drawn from various western data is concurrent chemo radiation with a total radiation dose of 66 to 70 Gy in conventional fractionation along with single agent chemotherapy using Cisplatin 100 mg/m^2 D1, D22 and D43 is an acceptable standard regimen. But head and neck cancers constitute a heterogeneous entity with variations in incidence, histology, and tumour grade and tumour biology. The molecular pathogenesis behind these variations is not yet unwinded. In such a scenario how far a single schedule of chemo radiation can become optimal for all heterogeneous head and neck cancer varieties is a question that remains unanswered.

While incorporating chemotherapy along with radiation, the question is whether sequential chemo radiotherapy or concurrent chemo radiotherapy is superior. The MACH – NC (meta- analysis of chemotherapy in head and neck) study pooled data from randomised studies during 1965 to 1993 and compared loco regional therapy and loco regional therapy plus chemotherapy.[1] Individual data from more than 10000 patients in 63 trials were included in the study. The overall survival of patients in the control arm was 32 % at 5 years. The trials including only nasopharyngeal carcinoma were not included. The absolute benefit from chemotherapy was 4% resulting in increase in survival from 32 % to 36% at 5 years.

There is significant interaction between the chemotherapy timing in relation to radiation (p=0.01). There were eight trials including 1854 patients which used adjuvant chemotherapy. The absolute benefit obtained from chemotherapy at 5 years was 1% (p=0.74). Similarly the benefit obtained from induction chemotherapy which was used in 31 trials including 5269 patients was 2% (p=0.10). The greatest benefit was obtained when chemotherapy was used concurrently with radiation. There were 26 trials including 3727 patients and the absolute benefit at 5 years was 8% (P=0.0001).

This high dose cisplatin is associated with high grade acute and late toxicities. Hence people started using weekly cisplatin compared to three weekly cisplatin. A study by Akihiro Homo et al including 53 patients with locally advanced squamous cell carcinoma used weekly cisplatin 40 mg/ square metre on 7 weeks along with radiation which comprised of 70 Gy in 35 fractions.[2] The overall survival rate was 93.7% and disease free survival was 88%. The toxicity was manageable in all patients except one patient who died of sepsis. This study showed that weekly cisplatin is a feasible alternative with less toxicity without compromising the results. Also the patients can be monitored frequently and dose adjustments can be made if required.

The Basket University experience in weekly cisplatin concurrent with radiation was presented in conjunction with 2011 ASCO annual meeting. A retrospective analysis of 53 eligible patients showed that there is no significant difference in median overall survival in weekly cisplatin and three weekly cisplatin groups. The loco regional control and distant relapses were also similar in both groups. The conclusion of the study was concurrent chemo radiotherapy with weekly cisplatin is as effective as three weekly cisplatin with very high bolus dose.[3]

A study conducted by Tejpal Gupta et al at Tata Memorial Hospital, Mumbai included 264 patients with locally advanced squamous cell carcinomas. All patients received radiotherapy 66-70 Gy using conventional fractionation along with weekly cisplatin 30 mg/ square metre. The study was conducted during 1996-2004. Two third of patients (65%) received planned cisplatin dose. The 5 year loco regional control was 46%. The incidence of grade 3 mucositis was 29%. The conclusion drawn from the study was weekly cisplatin has moderate efficacy with acceptable toxicity with the potential to become an optimal chemotherapeutic regimen especially in a limited resource setting.[4] Some of the other Indian studies using weekly Cisplatin is given in Table 5.[5,6]

Table 5: Previous Indian studies using cisplatin.

Study	Cisplatin dose (weekly)	CR (%)	PR (%)	No Response (%)
Asif R et al[5]	30 mg/m^2	66.6	26.6	6.6
Maqbool LM et al[6]	40 mg/m^2	57.7	31.1	11.1

CR- complete response; PR- partial response

Since paclitaxel has shown good results in head and neck cancers, there are various studies which explored the possibilities of weekly paclitaxel along with concurrent radiation. Some of the studies which had head to head comparison of weekly cisplatin and weekly paclitaxel are given below in Table 6.[7-9]

Table 6: Previous studies comparing weekly cisplatin and paclitaxel.

Study	Drug		
Jain RK et al[9]	Cisplatin 30 mg/m^2	CR	64%
		PR	36%
	Paclitaxel 20 mg/m^2	CR	73%
		PR	37%
Essa HH et al[7]	Cisplatin 30 mg/m^2	CR	75%
		PR	25%
	Paclitaxel 30 mg/m^2	CR	85.7%
		PR	14.3%
Kanotra SP et al[8]	Cisplatin 40 mg/m^2	CR	52%
		PR	48%
	Paclitaxel 40 mg/m^2	CR	72.7%
		PR	23.3%

The results of our study using paclitaxel 40 mg/m^2 are complete response 70 % and partial response 30 %. These results are comparable to above mentioned Indian studies. But unfortunately the statistical power of this study is not adequate due to small sample sizes. Another observation in the present study is that in patients with oropharyngeal and hypo pharyngeal tumours paclitaxel did better than cisplatin. In oropharynx paclitaxel arm had 86.6% complete response compared to cisplatin which produced only 73.3% complete response. Similarly the complete response rate in hypo pharynx in paclitaxel arm and cisplatin arm is 60% and 50% respectively. This may be due to degree of differentiation associated with these tumours. In the present study except one patient in oral cavity, all the other patients in oral cavity and larynx has well differentiated tumours whereas in oropharynx and hypo pharynx all tumours are moderately to poorly differentiated.

In all of the above mentioned studies the toxicity profile in paclitaxel arm is acceptable and not significantly higher than the cisplatin arm. The present study also confirmed the above finding. In paclitaxel arm the incidence of radiation dermatitis, mucositis, dysphagia and laryngitis are slightly higher compared to cisplatin group. This may be due to higher potentiation of radiation by paclitaxel compared to cisplatin. But none of these toxicities found dose limiting and are manageable according to general guidelines. Cisplatin arm had higher incidence of gastrointestinal toxicity compared to paclitaxel arm. In the present study with weekly

paclitaxel at a dose of 40 mg/m^2 the haematological toxicities are not significant as expected. None of the patients had thrombocytopenia or neutropenia. Only anaemia was significantly higher in paclitaxel arm compared to cisplatin arm. This may be due to haematological toxicity of paclitaxel. Also paclitaxel potentiates the radiation more and the patients had more severe dysphagia and mucositis which decreases the food intake. Hence the higher incidence of anaemia in present study is not purely a haematological toxicity but a multifactorial one.

The weekly paclitaxel dose of 40 mg/m^2 was chosen based on the above mentioned studies which compare weekly paclitaxel and weekly cisplatin concurrent with radiation. Out of the three studies one study uses paclitaxel at a dose of 40 mg/m^2 weekly. The other two studies use doses of 30 mg/m^2 and 20 mg/m^2. Also a previous study by Hoffman et al which compares various doses of paclitaxel recommends a weekly dose of 30 mg/m^2.[10] Hence in the present study we decided to use the maximum dose of weekly paclitaxel among the previous studies.

CONCLUSION

To conclude the weekly paclitaxel concurrent with radiation is a feasible alternative to weekly cisplatin in locally advanced squamous cell carcinomas of head and neck. However the present study involves 60 patients with 30 patients in each arm. Hence the statistical power of the study is not adequate. So a phase III randomised control study involving a large number of patients is recommended to validated the above observation. In the present study the weekly paclitaxel at a dose of 40 mg/m2 is well tolerated with manageable toxicities. Hence another dose escalation study using 50 mg/m2 of weekly paclitaxel is also recommended.

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