International Journal of Research in Medical Sciences
Drau HK et al. Int J Res Med Sci. 2017 Nov;5(11):4895-4902
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20174941

Original Research Article

A study of weekly paclitaxel vs weekly cisplatin with concomitant chemoradiation in locally advanced head and neck cancer

Himadri Kumar Drau[1]*, Yumkhaibam Sobita Devi[2], L. Jaichand Singh[2]

[1]Department of Radiotherapy, Regional Cancer Centre, Agartala, Tripura, India
[2]Department of Radiotherapy, Regional institute of Medical Sciences, Imphal, Manipur, India

Received: 29 August 2017
Accepted: 29 September 2017

***Correspondence:**
Dr. Himadri Kumar Drau,
E-mail: drhk.daru@gmail.com

ABSTRACT

Background: The purpose of this study was to compare the role of concomitant chemoradiation using paclitaxel versus cisplatin in locally advanced head and neck cancers.
Methods: 52 patients were randomly assigned to one of the two concomitant chemoradiation arms: arm I (n=26) and arm II (n= 26) who received injection of paclitaxel 40 mg/m2 I/V 1-hour infusion before radiation, repeated weekly for 6 cycles, and cisplatin 30 mg/m2 I/V 1-hour infusion before radiation, repeated weekly for 6 cycles, respectively. The planned radiotherapy dose was 66-70 Gy, 2 Gy/day, 5#/Week in 6-7 weeks.
Results: Response rates were 69.2% and 57.7% in arm I and arm II, respectively. There was no statistically significant difference observed between the study group and the control group (P = 0.85) On median follow up of 7-15 months, Disease free survival was (83.3%) in arm I compared with (73.3%) in arm II but the difference was statistically insignificant. Local toxicities including mucositis, dysphasia and skin reactions were more in the study the haematological toxicity was generally mild. On the contrary, non-hematologic toxicities were severe. Grade IV mucositis occurred in 26.9% in arm I and in 3.8% in arm II (P = 0.003). Moreover, grade IV dermatitis were encountered in 23.1% in arm I (P = 0.00).
Conclusions: Both concomitant chemoradiotherapy regimens were easily given in the outpatient clinic. The regimen based on paclitaxel was more effective; however, the difference was insignificant.

Keywords: Concomitant chemoradiotherapy, Paclitaxel, Locally advanced head and neck cancer

INTRODUCTION

In India the incidence of malignancy of head and neck is exceptionally high as compared to western and other developed countries. It is the most common cancer of males in India and the fifth most common in females.[1] This is attributed to certain habits and risk factors like smoking, oral intake of tobacco, betel nut chewing, pan masala and poor oral hygiene. The lack of awareness and education among the population results in presentation in advanced stages. According to the Indian Council of Medical Research (ICMR) approximately 0.2 to 0.25 million new head and neck cancer patients are diagnosed each year in India.[2]

The treatment of patients with unrespectable, locally advanced head and neck squamous cell carcinoma (HNSCC) remains a challenge. Radiation has been the standard treatment for locally advanced, unrespectable HNSCC. Even the most effective radiotherapy regimens result in local control rates not exceeding 50-70% and disease-free survival rates not more than 30 - 40%. This

circumstance has stimulated the investigation of treatments combining radiotherapy and chemotherapy; the most promising approach being the administration of chemotherapy concurrent with radiation.[3] A number of randomized studies have shown improved results when radiation was combined with concurrent cytotoxic agents compared with radiation alone despite increased toxicity of the combined arm, notably hematological and mucosal toxicities, which limited the ability to deliver full doses of radiation or the chemotherapeutic agents.[4-9] Although most trails of concurrent chemoradiation have used cisplatin in combination with 5-fluorouracil (5-FU), there is at present no evidence that this combination performs better than cisplatin alone. Thus, the optimal drugs, doses and schedules of concurrent chemotherapy and radiotherapy for head and neck cancer are not known.

With a paradigm shift towards organ preservation, combined modality treatment employing radiation and chemotherapy has taken a more centralized place in the management of head and neck cancers. Most of the cancers (70-80%) of head and neck are diagnosed with locally advanced disease.[10] In the past, the 5-year survival of locoregionally advanced disease was reported to be only 40% and locoregional failure was the predominant cause of recurrence.[11] In addition, almost half of the patients who die from head and neck cancer have locoregional disease as the only site of failure and 90% of patients who develop distant metastasis also have persistent locoregional disease. Thus, the efficacy of any curative approach is measured by its ability to achieve locoregionalcontrol.[12] The traditional method of management of patients with locoregionally advanced disease has been surgery followed by postoperative radiotherapy with chemotherapy reserved for palliative purposes. The 5-year survival rates with these approaches have been poor due to frequent local or regional recurrences.[13] The addition of chemotherapy to these approaches has increased the locoregional control with a marked improvement in survival and organ preservation.[14-16]

In 1987, the Radiation Therapy Oncology Group (RTOG) first reported results from a phase II trial testing radiation and concurrent high dose cisplatin (100 mg/m^2 given every three weeks during radiation therapy). A complete response rate of 71% and a 4-year survival rate of 34% were reported in a cohort of 124 patients.[17] Since then many clinical trials have consistently proved the increased rate of locoregional control and survival with combined chemoradiation.[18-20]

Chemotherapy has been used in various combinations with standard local treatment. This includes induction chemotherapy, concurrent chemotherapy and adjuvant chemotherapy. The rationale behind the combination of chemotherapy with radiotherapy is three-fold. Firstly, concomitant chemoradiotherapy can be used with organ preserving intent, resulting in improved cosmesis and function compared with surgical resection with or without adjuvant treatment. Secondly, chemotherapy can act as a radiosensitizer improving the probability of local control and survival, by aiding the destruction of radio resistant clones. Thirdly, chemotherapy may eradicate distant micrometatasis.[21]

The use of radiosensitizers has reduced the failure rates of radiotherapy alone. The radio sensitivity of a cell is dependent on the phase of cell cycle; cells in the S phase are more radio resistant while cells in the G2-M phase of the cell cycle are most radiosensitive.[22,23]

The most commonly used radiosensitizers (cisplatin, 5-FU, and taxanes) do have inherent cytotoxic activity and can increase damage to normal tissues. Cisplatin is a potent radiosensitizer and the drug most commonly used for chemoradiotherapy in head and neck cancers.[21] Various studies using cisplatin as a single agent in chemoradiotherapy have demonstrated survival rates ranging from 37 to 73%.[20,24]

Taxanes are another group of radiosensitizers which have a unique mechanism of action which leads to the formation of high affinity bonds with microtubules promoting tubulin polymerization and stabilization. Both Paclitaxel and Docetaxel have demonstrated single agent activity in patients with squamous cell carcinoma of head and neck in several trials.[25-28] They act to promote tubulin polymerization and the formation of stable microtubules. The microtubules produced in the presence of taxanes are resistant to disassembly by physiologic stimuli, and cells exposed to these agents exhibit an accumulation of disorganized microtubule arrays. This affects the normal mitotic process and eventually results in cell death. Both drugs are active as single agents in patients with head and neck cancer with response rates ranging from 20% to 40%. They may be combined with other cytotoxic agents, radiotherapy, or both.

Paclitaxel (30 mg/m^2/day on day 1-5 and on day 29-33) given concomitantly with a split-course accelerated radiotherapy (2 x 1.5 Gy/day with a rest period of nine days after 30 days) was feasible in 9 of 12 patients having head and neck cancer with neutropenic fever. The overall response rate was 100%.[29,30]

Another phase I trial studied the simultaneous treatment of continuous 24-hour paclitaxel (75mg/m^2/day) concomitantly with radiotherapy in 24 patients with advanced head and neck cancer. The dose-limiting toxicities were febrile neutropenia and stomatitis. All patients had major responses.[31]

Paclitaxel induces microtubule stabilization, and a cell cycle blockade at the G2 phase to mitosis (G2/M) transition, the most radiosensitive portion of the cell cycle.[32,33] An additional mechanism seems to involve enhanced tissue oxygenation. Recently it was shown that paclitaxel activates c-Jun-terminal-kinase or protein-kinase A, leading to phosphorylation of the antiapoptotic

Bcl-2 protein. Phosphorylation of Bcl-2 decreases its binding to the proapoptotic Bax protein, and an increase in the free Bax level promotes apoptosis.[34] This apoptotic effect of paclitaxel is independent of the p53 pathway.[35]

Keeping all this in mind in our setting we planned to compare the role of concomitant chemoradiation using paclitaxel versus cisplatin in advanced head and neck cancers. Cisplatin arm was used as a control arm as cisplatin is one of the most extensively used agents effective in the management of squamous cell carcinoma of head and neck which can be used either as a single agent or combined with a variety of other drugs and has shown improved overall response rate ranging from 23% to 71%.[36] Paclitaxel is a newer active single agent in head and neck cancer, it was used in the study arm in low dose weekly schedule.

METHODS

Between September 2014- August 2016, 52 patients with Locally advanced squamous cell carcinoma of head and neck attending Radiotherapy OPD, Regional Institute of Medical Sciences, Imphal, Manipur, were randomly assigned in this prospective study.

Eligibility criteria

Patients with biopsy proven HNSCC stages III and IV tumors for all sites were eligible except nasopharyngeal cancer. Patients must have been either ineligible for curative resection or have refused surgery and must have had no prior radiotherapy to the head and neck region or chemotherapy.

Patients with obvious metastatic disease on diagnostic imaging were excluded from the study. Additional eligibility criteria included the following: Karnofsky Performance Status (KPS) ≥60%, age between 30 to 70 years, Haemoglobin ≥10gm%, Total leucocyte count ≥4000/mm^3, Platelet count ≥100000/mm^3, serum bilirubin, SGOT, SGPT, serum creatinine within normal limit, no other history of active malignancy and no other serious medical disease. Patients willing to remain on follow up after treatment.

Pretreatment evaluation

Pretreatment evaluation included complete history, physical examination, head and neck examination including mirror and panendoscopic examination, histopathologic examination of the primary tumor or cervical lymph nodes, complete blood count, blood chemistry including liver function tests, and kidney function, computed tomography and or magnetic resonance imaging of the head and neck to define the extent of the disease and metastatic workup including chest x-ray and imaging of liver by ultrasound or computed tomography in all patients.

Bone scan was restricted to those with bone pain or elevated serum alkaline phosphatase. Dental care was applied to each eligible patient before therapy.

Treatment schedule

All patients were treated on cobalt 60 Theratron 780Cteletherapy unit. Patients of both arms received a total dose of 66-70 Gy radiation, 200 cGy/day, 5#/Week in 6-7 weeks. Arm I patients received concurrent dose of paclitaxel 40 mg/m^2 I/V 1-hour infusion with premeditation 4-6 hours before radiation, repeated weekly for 6 cycles. Arm II patients received concurrent dose of cisplatin 30 mg/m^2 I/V 1-hour infusion with full hydration 4-6 hours before radiation, repeated weekly for 6 cycles. During the study, patients were hospitalized and given symptomatic treatment as needed. Patients were reviewed every week and assessed with complete clinical examination including indirect laryngoscopy and in addition, were evaluated for toxicities according to RTOG acute radiation morbidity scoring criteria. Systemic toxicities were graded according to the common toxicity criteria, version 2. Laboratory and clinical toxicities were considered acute if discovered during the first 12 weeks after the initiation of therapy.

Post-treatment evaluation

Six weeks after completion of radiotherapy, response was assessed by clinical examination, endoscopic examination, and CT and/or MRI of head and neck. Early treatment response was evaluated by RECIST (Response Evaluation Criteria for Solid Tumors). Criteria for response were as follows: Complete response (CR): defined as complete regression of all evidence of tumor. Partial response (PR): defined as an estimated decrease in tumor size of 50% or more. Stable disease (SD): defined as < 50% decrease in tumor size or < 25% increase in pretreatment tumor size. Progressive disease (PD): defined as > 25% increase in pretreatment tumor size.

Re-evaluation was done at 3 months interval from 6 months till the end of follow up. Late toxicities of radiation were assessed using RTOG/EORTC criteria for late radiation effects. Late treatment response in terms of Disease free survival, Survival with disease, Overall survival were assessed till the end of follow up. Overall survival was calculated from the date of randomization to the date of death or lost to follow up. Disease free survival was calculated from the date on which complete response was documented until date on which progressive disease was diagnosed.

Analysis of results

All data were categorical and represented as numbers and percentage. Statistical analysis was done using SPSS Version 21. The baseline characteristics and adverse effects of the two treatment arms were compared using

the Chi-square test. P value of < 0.05 was taken as significant.

RESULTS

Patient's characteristics

From September 2014 to August 2016, 52 patients were recruited and randomly assigned into two treatment arms, arm I (study arm) with 26 patients and arm II (control arm) with 26 patients. A total of 52 patients received complete treatment as defined per protocol or with an acceptable variation with respect to overall days of therapy and total dose.

Table 1: Patients characteristics.

Characteristics	Total (%)	Arm I (%)	Arm II (%)	P value
Age				
<60 year	27 (51.9)	12 (46.2)	15 (57.7)	0.405
>60 years	25 (48.1)	14 (53.8)	11 (42.3)	
Sex				
Male	40 (76.9)	19 (73.1)	21 (80.8)	0.510
Female	12 (23.1)	7 (26.9)	5 (19.2)	
Smoking				
Smoker	30 (57.7)	20 (76.9)	10 (38.50)	0.05
Never smoker	22 (42.3)	6 (23.1)	16 (61.5)	
KPS				
90-100%	15 (28.8)	9 (34.6)	6 (23.1)	
80-90%	25 (48.5)	11 (42.3)	12 (53.8)	0.619
70-80%	12 (23.1)	6 (23.1)	6 (123)	
Site				
Oral cavity	22 (42.3)	12 (46.2)	10 (38.5)	
Oropharynx	14 (26.9)	6 (23.1)	8 (30.8)	
Hypopharynx	11 (21.2)	5 (45.5)	6 (23.1)	0.859
Larynx	5 (9.6)	3 (11.5)	2 (7.7)	
T- stage				
T1	8 (15.4)	4 (15.4)	5 (19.2)	
T2	12 (23.1)	6 (23.1)	6 (23.1)	
T3	20 (38.5)	12 (46.2)	7 (26.9)	0.430
T4	12 (23.1)	4 (15.4)	8 (30.8)	
N-stage				
N0	12 (23.1)	6 (23.1)	6 (23.1)	
N1	12 (23.1)	8 (30.8)	4 (15.4)	
N2	18 (34.6)	6 (23.1)	12 (46.2)	0.292
N3	10 (19.2)	6 (23.1)	4 (15.4)	
AJCC staging				
III	18 (34.6)	10 (38.5)	8 (30.8)	0.560
IV	34 (65.4)	16 (61.5)	18 (69.2)	

Table 2: Response.

Response	Arm I (%)	Arm II (%)	P
CR	18(69.2)	15(57.7)	
PR	3(11.5)	4(15.4)	
SD	4(11.5)	4(15.4)	0.859
PD	2(7.7)	3(11.5)	

Table 1 shows the pre-treatment patients characteristics. They were well balanced among the both treatment groups. The age group ranged from 30 to 70 years of which 15 (57.7 %) were < 60 years of age in the control arm and 14 (53.8%) in the study arm were in the age group of more than > 60 years, but the differences were statistically insignificant. Males were predominantly representing 76.9% of the cases,19 male to 7 females in the study arm and 21 to 5 in the control arm (P =0.510). 57.7 % of our patients were smokers. The oral cavity was the most common primary site in the study, accounting for 42.3%. Maximum number of patient in the study arm had T3 status (46.2%) compared to the control arm showing predominance in T4 stage (30.8). Majority of patients presented in N1 nodal status in the study arm (30.8%) whereas in the control arm, majority of patients

presented in N2 nodal status (46.2%). All patients were stage III (34.6 %) and stage IV (65.4 %). The differences were comparable and were statistically insignificant.

Early treatment response

Response assessment was done 6 weeks after the completion of treatment. Complete response was achieved in 69.2% of patient in arm 1 versus 57.7% for arm II. Partial response was achieved in 11.5% versus 15.4% in arm I, II respectively but the difference was statistically insignificant (p=0.859) (Table 2).

Table 3: Acute adverse effect during concomitant chemoradiation.

Early toxicities	Grade	Arm I (%)	Arm II (%)	P value
Anaemia	G1	9 (42.9)	12 (57.1)	
	G2	11 (52.4)	10 (47.6)	0.645
Leucopenia	G1	6 (42.9)	8 (57.1)	
	G2	6 (54.5)	5 (45.5)	0.813
Thrombocytopenia	G1	7 (53.8)	6 (46.2)	
	G2	5 (62.5)	3 (37.5)	0.648
Dermatitis	G1	3 (11.5)	10 (38.5)	
	G2	3 (11.5)	11 (42.3)	
	G3	14 (53.8)	5 (19.2)	0.000
	G4	6 (23.1)	0 (0.0)	
Mucositis	G1	3 (11.5)	11 (42.3)	
	G2	5 (19.20	10 (38.5)	
	G3	11 (42.3)	4 (15.4)	0.003
	G4	7 (26.9)	1 (3.8)	
Dysphagia	G1	8 (30.8)	6 (23.1)	
	G2	10 (38.5	11 (42.3)	0.833
	G3	5 (19.2)	7 (26.9)	
Weight loss	G1	20 (80.0)	19 (73.1)	0.605
	G2	4 (16.0)	4 (15.4)	

Table 4: Late adverse effects seen on follow up.

Late toxicities	Grade	Arm I (%)	Arm II (%)	P value
Xerostomia	G2	16 (61.5)	14 (53.8)	0.792
	G3	5 (19.2)	7 (26.9)	
Neck edema	G1	9 (34.6)	7 (26.9)	0.808
	G2	3 (11.5)	4 (15.4)	
Dysgeusia	G1	15 (57.7)	16 (61.5)	0.931
	G2	5 (19.2)	4 (15.4)	
Myelitis (CNS)	G0	0	0	NS

Toxicity

As regard toxicity, toxicity was higher in the paclitaxel group but it was tolerable and manageable and all patients in both arms could successfully complete the treatment. Table 3 shows the site and grade of acute effects by treatment groups. The most common sites of grade 3/4 or worse acute side effects were the skin and the mucous membranes. Compared to arm II, arm I had significantly increased grade 3 or 4 acute side effects as dermatitis (P=0.000), mucositis (P=0.003). Grade I/II hematological toxicities (anaemia, leucopenia and thrombocytopenia) were seen in both the arm, were comparable. Grade I/II weight loss was seen in both the arms (p =0.605). Grade 3 dysphagia was observed more in the arm II (23.1%) compared to 19.2% in the arm I (P=0.833). Control arm recorded a higher percentage of grade III dysphagia (26.9%) when compared to 19.2% of patients in the study arm but were comparable (P=0.833).

Table 4 highlights the late side effects of the study arm and control arm. The late adverse effects were assessed using RTOG toxicity criteria to evaluate the late effects of normal tissue by concurrent chemoradiation. The patients were followed every 3-monthly beginning 6 months after completion of treatment to access the late adverse effects. Grade 3 xerostomia occurred in both arms but it was statistically not significant. (P=0.792). Other side effects were also comparable. No myelitis was seen in both the arms.

Table 5: Late treatment response.

Type of response	Arm I (%) (n=18)	Arm II (%) (n=15)	P
DFS	15 (83.3)	11 (73.3)	
SWD	11 (42.3)	14 (56)	NS
OS	26 (100)	25 (96.1)	

DFS =disease free survival; SWD= survival with disease; OS= overall survival

Survival

The median follows up was 9 months (ranging from 7-15 months) in arm I versus 11 months (ranging from 7 -12 months) in the arm II. DFS was (83.3%) in arm I compared with (73.3%) in arm II but the difference was statistically insignificant (P=NS) (Table 5).

DISCUSSION

Locally advanced head and neck cancer poses a great challenge for radiation oncologists. The most aggressive non-surgical treatment is the combination of chemotherapy and radiation. however, grade 3 and 4 toxicity also significantly increase along with more intensive schedules.[37,38] This study was intended to compare concomitant chemoradiation using paclitaxel in low dose weekly schedule versus the most widely used agent cisplatin with conventional radiation in advanced head and neck cancers. In our study, no significant difference in efficacy was noted between both arms. This was true for the primary end, response rates and locoregional control, as well as for other end points, disease free survival and overall survival. Although some patients in our study in the paclitaxel arm sustained high local toxicity, mucositis and dermatitis, but it was tolerable and manageable and all the patients could complete the proposed treatment. No dose limiting systemic toxicity was encountered in our study. A 69.2% complete response was achieved with paclitaxel versus 57.7% with cisplatin in patients with advanced HNSCC. This response achieved in our study in the paclitaxel arm is comparable to those achieved with the regimens employed by Hoffmann et al and by Steinberg et al.[30,31]

RK Jain et al reported 73% CR with a lower dose of paclitaxel 20 mg/m^2 versus 64% with cisplatin in patient with HNSCC with the same chemotherapy used in our study.[39] Hoffman et al studied the combination of conventional radiotherapy with weekly 1-hour infusion of paclitaxel in 18 patients with unrespectable HNSCC.[30] Paclitaxel was given at a starting dose of 20 mg/m^2, and subsequent dose escalations of 10 mg/m^2 were applied. Radiation therapy was administered over 6-7 weeks with 200 cGy daily, up to total doses of 60-70 Gy. The maximum tolerated dose of paclitaxel in this setting was 30 mg/m^2/week, with mucositis being dose limiting.

Steinberg et al described a study in which 24 patients with stage III and IV HNSCC were administered radiotherapy (daily fractionation to total doses of 66 to 72 Gy) in combination with paclitaxel given as 24-hour continuous infusions on days 1, 22, and 43.[31] Dose escalations of 75, 90 and 105 mg/m^2 were given. This regimen achieved CR of 72% at the primary site. The maximum-tolerated dose was retrospectively determined to be less than 75 mg/m^2, because more than 50% of the patients developed febrile granulocytopenia at that dose. Significant local toxicities also were reported. Most notable of these were skin toxicity and grade 3 mucositis, necessitating enteral feeding tubes.

Lovey et al examined the use of low-dose paclitaxel concurrently with radiation for patients with locally advanced head and neck cancers.[40] 26 patients were treated with external beam radiotherapy and received concomitantly 2 mg/m^2 paclitaxel three times a week. Beside an acceptable efficacy (RR: 65%, 2-year overall survival 46%) the treatment was well tolerated and resulted in a favorable toxicity profile. This regimen is resource effective and allows successive therapy if necessary, and therefore may serve as an alternative for patients in poor condition with locally advanced head and neck.

Tishler et al reported a study in which 14 patients with stage III and IV HNSCC were treated with paclitaxel administered at a dose of 100 mg/m^2/3weeks), in combination with external beam radiation therapy (daily fractionation to total doses of 60 to 70 Gy).[41] Of these 14 patients, 10 had received prior cisplatin, fluorouracil, and leucovorin. Overall, the concurrent therapy achieved a CR in 13 (92%) of the 14 patients. Three of the 13 went on to develop recurrent disease (one with distant metastasis and two with local/regional disease). The major toxicities included grade 3 and 4 mucositis. Tishler et al reported a higher CR, comparisons of efficacy are difficult to interpret because 67% of those patients with a CR had received prior therapy.[41]

Although no conclusions can be drawn as the optimal regimen based on the present study, both concomitant chemoradiotherapy regimens were easily given in the outpatient clinic. The regimen based on paclitaxel was more effective; however, the difference was not much.

CONCLUSION

Although no conclusions can be drawn as the optimal regimen based on the present study, both concomitant chemoradiotherapy regimens were easily given in the outpatient clinic. The regimen based on paclitaxel was more effective; however, the difference was not much.

ACKNOWLEDGEMENTS

Authors would like to thank Prof. L Jaichand Singh, Head of Department of Radiotherapy, Regional Institute of Medicine Sciences, Manipur, India for allowing publication of the article.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Drau HK, Devi YS, Singh LJ. A study of weekly paclitaxel vs weekly cisplatin with concomitant chemoradiation in locally advanced head and neck cancer. Int J Res Med Sci 2017;5:4895-902.