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Original Article

Concurrent chemotherapy in advanced head and neck carcinoma – A prospective randomized trial

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Abstract:

Purpose: The aim of this study is to compare two different concurrent chemoradiotherapy regimes – weekly cisplatin and three weekly cisplatin along with standard external beam radiotherapy in advanced head and neck cancer.

Procedures: 90 untreated patients of advanced squamous cell carcinoma of head and neck were randomized into three arms: Arm A (n=30) patients received inj cisplatin 30mg/m^2 weekly along with radiation; Arm B (n=30) patients received inj. cisplatin 100mg/m^2 on a three weekly basis with radiation; Arm C (n=30) received only radiation. Radiotherapy was delivered to a dose of 66 Gy to 70 Gy in conventional fractionation in telecobalt machine.

Findings: Complete response rate is significantly higher in arm B compared to that of arm A and arm C. Major toxicitities include neutropenia, anaemia and mucositis. Grade 3 neutropenia, anaemia and mucositis were found in arm A and arm B. No grade 3 toxicity was found in arm C. There was no grade 4 toxicity in any arm.

Conclusion: We conclude that concurrent chemoradiation produce better response compared to that of radiation only. Toxicities were also increased in concurrent regimes. Out of two concurrent regimes, three weekly regimes showed better response with slightly increased but manageable hematological toxicities. Hence, this regime can be considered as standard of care for advanced head and neck cancer.

Key words: *Advanced head and neck cancer, Concurrent chemo-radiation, weekly versus three weekly cisplatin.*

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Introduction:

Head and neck malignancy is the commonest cancer seen in males of Indian subcontinent, constituting around 25% of the overall cancer burden.[1] Only one third of these patients present with localized disease. The vast majority of them present with loco-regionally advanced disease. When these advanced cases are treated with external beam radiation alone, achievement of cure is difficult. Local failure rate sometimes approaches as high as 50%.[2]

To improve this outcome the addition of chemotherapy (CT) to radiotherapy (RT) has become one of the important developments for the management of loco-regionally advanced head and neck cancers. There are various researchers who investigated different combinations of CT and RT like concurrent chemoradiation (giving chemotherapy along with radiotherapy or CRT), neoadjuvant chemotherapy (the addition of chemotherapy prior to surgery and/or RT), adjuvant chemotherapy (giving chemotherapy after surgery or RT) and sequential therapy (induction chemotherapy followed by concurrent CRT).

Initial trials of neoadjuvant and adjuvant chemotherapy in advanced head and neck cancer showed increased response rate, organ preservation and improved quality of life. But there is no survival benefit.[2]

Concurrent radiotherapy was also evaluated by several trials. In the postoperative settings, randomized trials[3,4] have shown increased response and survival in favor of chemo-radiation. In unresectable disease, a phase III trial showed significantly improved survival with addition of CT.[5] Meta analysis of CT-RT trials[6] showed the benefit of adding CT to loco-regional therapy for non-metastatic disease. These trials did not show any significant survival difference between the use of monotherapy and combination therapy. Cisplatin based regimens were established as the most effective regimens with single agent activity, synergistic interaction and non-overlapping toxicity.

The dose and delivery schedules of cisplatin have ranged from intermittent higher dose [100 mg/m ^{2}] every 3 weeks to low dose [6 mg/m ^{2}] daily administration.[7] In theory, high dose CT acts by eradicating occult micro-metastases where as low dose daily or weekly CT has pure radio sensitizing effect. At present there is insufficient data to suggest which CT schedule is superior in terms of better disease control. Benefit of adding CT to RT comes at the cost of markedly increased acute toxicity, but there is not enough data to compare toxicities of CT schedules. In this background, we have compared the two concurrent CT-RT schedules used for head and neck cancers at our institute along with radiotherapy alone in terms of response as well as toxicities

Methods:

Patient Selection:

From Feb 2010 to Jan 2011, a randomized prospective study was performed with 90 patients who met the following inclusion criteria:

- Age between 18 year and 70 year
- Patients of histology proved squamous cell carcinoma of head and neck
- Stage III or IV disease
- Previously untreated
- Performance status: Eastern Co operative Oncology Group 0-2
- Haematological parameters within normal range like hemoglobin > 11mg/dl; absolute neutrophil count > 1900/dl, platelet count > 100000/dl,
- Serum bilirubin < 2 mg/dl; liver enzymes within 1.5 times of normal limits,
- Serum creatinine < 1.5 mg/dl
- Signed informed consent

Patients were excluded from the study if they had already received some form of anticancer therapy, presence of metastatic disease, participation in a clinical trial in the last 30 days and if they had any uncontrolled systemic illness like diabetes, tuberculosis and hypertension.

Patient Evaluation:

All the patients have undergone detailed history taking, thorough physical examination, complete blood count, liver function test, kidney function test, chest skiagram and USG abdomen as baseline evaluation.

Treatment Protocol:

The patients after pretreatment evaluation were randomized into three arms by sequential randomization according to their attendance in our OPD:

- Arm A (n=30) patients received inj cisplatin 30mg/m^2 weekly on days 1, 8, 15, 22, 29, 36, 43 along with radiation.
- Arm B (n=30) patients received inj. cisplatin 100mg/m^2 on a three weekly basis on days 1, 22, 43 with radiation.
- Arm C (n=30) received radiation alone.

Radiotherapy was delivered to a dose of 66 Gy to 70 Gy in conventional fractionation with spinal cord sparing after 44 Gy. Radiation was given by telecobalt machine with conventional planning. The portals were mostly lateral parallel opposed fields.

The primary endpoints of the study were disease response and toxicity profile.

Patients were monitored weekly during radiotherapy for toxicity and nutritional support.

Follow up:

After completion of therapy, follow up was done monthly to evaluate response and toxicities. Response was assessed by local examination, indirect laryngoscopy and direct laryngoscopy (where indicated) 4 weeks after completion of radiotherapy.

Toxicity was recorded according to Radiation Therapy Oncology Group Acute Radiation Morbidity Criteria. Acute toxicity was defined as those occurring within 90 days and late toxicity as those occurring after 90 days. Tumor response was evaluated by Response Evaluation Criteria in Solid Tumor (Complete Response, Partial Response, Stable Disease and Progressive Disease).

Quality control:

Initial staging, randomization and response evaluation were done in a joint clinic with oncologists and otorhinolaryngologists. All radiotherapy records including data concerning external beam fields, dose of radiation to tumor and normal tissue particularly spinal cord were reviewed by radiation oncologist and physicist independently. All chemotherapy records including dose and schedule were also reviewed carefully.

Statistical analysis:

All significance tests were done using Student's unpaired t test and Fisher's exact test and statistical significance was accepted for a calculated p-value less than 0.05. Statistical analysis was done according to intend to treat basis.

Results:

Demography: The characteristics of the three arms are summarized in Table I. All the baseline profiles in three arms were comparable. One patient of arm C and one in arm A refused to continue due to personal reasons; but they were included during statistical analysis.

Table-I
Demography

Charecteristics	Arm A (n=30)	Arm B (n=30)	Arm C (n=30)
Age (in years)			
Median	51	52	52
Range	32-70	31-69	26-68
Gender			
Male	28	27	27
Female	2	3	3
Performance Status (ECOG)			
0	14	16	16
1	8	9	18
2	8	5	6
Site			
Larynx & Laryngopharynx	18	16	16
Oral cavity & oropharynx	10	11	10
Nasopharynx	2	3	4
Stage			
III	16	17	19
IV	14	13	11
Histology			
Well differentiated	11	13	15
Moderately differentiated	10	8	8
Poorly differentiated	9	9	7

Treatment Compliance:

In arm A, one out of 30 patients did not complete the treatment regime and one in arm C also dropped out due to personal reasons. [Table II] In arm A, 188 cycles of chemotherapy (90%) could be administered out of 210 possible cycles. The reasons of non compliances were hematological toxicity (12 cycles), mucositis (6 cycles) and patient's unwillingness (4 cycles). In arm B, 85 cycles (94%) was given out of 90 cycles. Hematological toxicity (3 cycles) and mucositis (2 cycles) were the causes for non compliance. Treatment interruption was less in arm C. The average delay in completing radiation was 2.3 days in arm C whereas in arm A and arm B these were 4.6 days and 5.2 days.

Table-II
Treatment Compliance

	Arm A (n= 30)	Arm B (n=30)	Arm C (n=30)
Drop out	1	0	1
Completed	29	30	29

Response to treatment:

All of the patients who completed the protocol achieved at least partial response. Complete response rate is significantly higher in arm B (76%) compared to that of arm A (67%) and arm C (60%). [Table III]

Table-III

Treatment response at one month after treatment completion

Response	Arm A (n=30)	Arm B (n=30)	Arm C (n=30)
CR	20 (67%)	23 (76%)	18 (60%)
PR	9 (30%)	7 (24%)	11 (37%)
SD	1	0	1

Acute Toxicities:

All 90 patients were considered for toxicity since all of them had received at least one fraction of radiotherapy. The toxicities were more in chemotherapy arms. The dose limiting toxicity was neutropenia. Grade 3 nutropenia was found in arm A (33%) and arm B (43%); difference is not statistically significant. There was no grade 4 toxicity or death in any arm. Among the non hematological toxicities, mucositis was the commonest and found in both chemotherapy arms equally. In radiation only arm, there was no grade 3 nausea, vomiting which was 20% in chemotherapy arms. One in arm A and two in arm B showed raised serum creatinin level at later part of therapy. But during follow up, the level come down to normal. [Table IV]

Table-IV

Acute toxicities

	Arm A (n=30)			Arm B (n=30)			Arm C (n=30)		
Toxicity Grade	1	2	3	1	2	3	1	2	3
Upper G. I.	4	20	6	6	19	5	16	14	0
Lower G. I.	3	6	0	2	7	1	4	0	0
Mucositis	4	16	10	6	12	12	6	19	5
Skin	5	20	5	4	22	4	8	17	5
Anaemia	6	16	8	5	14	11	4	0	0
Neutropinea	6	13	10	4	13	13	1	0	0
Thrombocytopinea	14	7	0	15	8	2	0	0	0
Renal	1	0	0	2	0	0	0	0	0

Late Toxicities:

The median follow up period is 9 months. The follow up period is not long enough to give any definite comment on late toxicity. Laryngeal edema, dry mouth and edema of skin of neck are the late toxicities found equally in all the three arms. All the patients are alive without any serious complication till date. [Table V]

Table-V

Late toxicities

Toxicities	Arm A (n=25)	Arm B (n=26)	Arm C (n=25)
Laryngeal edema	2	1	2
Dryness of mouth	6	5	5
Edema of skin of neck	4	3	3

Discussion:

The dominant pattern of failure for squamous cell carcinoma of head and neck remains loco-regional, although distant metastases are now being increasingly documented. Radiotherapy and chemotherapy given concomitantly in advanced head and neck cancer is a dose-intensive approach that exploits the independent complementary activity of radiotherapy locally and chemotherapy distantly (spatial co-operation) and the enhanced local active (within the radiation field). Hence, radical radiotherapy with concurrent chemotherapy is contemporary standard of care in the management of this loco-regionally advanced cancer.

A variety of chemotherapeutic agents have been used concurrently with RT either as monotherapy or combination therapy in different schedules in the management of advanced head and neck cancer. The various combinations of chemotherapeutic drugs used are based on the response for metastatic and recurrent cancer. Single agent cisplatin;[8-11] fluorouracil;[12,13] methotrexate;[14] bleomycin[15] and mitomycin[16] have been used in combination with radiation therapy in several trials. These trials have shown improved response rates.[8-16] Some of the trials have shown improvement in survival.[9,10,13,14] Several groups have evaluated cisplatin and 5-FU in combination with radiation and shown improved control but at the cost of increased toxicity.[2] MACH-NC, one of the largest meta-analyses, showed survival benefit of 8% from chemoradiation at five years.[4] Although efficacious, this is associated with high acute morbidity necessitating intensive supportive care with attendant resource implications. The meta-analyses also showed that cisplatin is the most impressive of all agents and single agent CT based on platinum is the treatment of choice. [4]

The primary objective of this prospective study was to assess the efficacy and acute toxicity of two different schedules of cisplatin i.e. concurrent weekly cisplatin-based radical radiotherapy and concurrent three weekly cisplatin-based on radical radiotherapy. Hence, to find out their potential to be an optimal regimen in advanced head and neck cancers. In 3 weekly regime, 76% CR was very promising and it is 67% in weekly cisplatin arm, which is also higher compared to that of radiation only arm. To reveal whether there is any survival benefit, we need a longer follow up.

Acute reactions are markedly increased with chemo-radiation and patients need intensive supportive care for management of pain and maintenance of nutrition. At our institute, we have involved a team of pain and palliative care doctors along with radiation oncologists for the management of toxicity and pain. Dietary counseling is also done periodically.

We compared our two schedules with other studies reported in the literature. In our study, patients treated with 3 weekly regimen showed considerably less grade III toxicity of skin and mucous membrane compared to that of weekly regime. This could be attributed to delivery of CT in longer interval. Similar study also showed that with this approach the severity of systemic toxicity and mucositis was low without affecting the local control.[17] When we compared grade III hematological toxicity, it was 37% for anemia and 43% for nutropenia in our study in 3 weekly arm, 61 % in RTOG [3] and 13% in EORTC [4] study again reflecting the importance of CT delivery in fractionated doses. Eighty three percent of patients completed all 3 cycles of CT in our study in 3 weekly arm, which is comparable with the studies reported in the literature. Some studies[17,18] showed that a substantial fraction of patients could not receive the third planned dose of cisplatin and

suggested that a cumulative dose of 200 mg/m ^{2} might be adequate to yield same beneficial effect.

Very few studies with weekly CT have documented toxicity. Grade III mucositis was 40% in weekly regime and 33% in 3 weekly regimes in our study. Vokes EE *et al*.[19] with 30 mg/m ^{2} reported 14% of grade III toxicity. CT completion [7 cycles] in our study was 64%. Glaser *et al* .[17] reported CT completion in 87% of patients with 35 mg /m ^{2}.

When we compared weekly and 3 weekly schedules of CT, grade III skin, mucous membrane and hematological toxicity were higher in weekly CT. Although statistically not significant, the percentage of patients with significant weight loss was more in weekly CT group suggesting the need for feeding procedure for all patients. Also this group had more number of treatment interruptions. Quite a number of studies have shown those treatment interruptions during RT decreases local control and which is also true for altered fractionation schedule [20,21] but its effect with concurrent CT-RT is not clear.

This trial on head and neck squamous cell carcinoma patients confirms that the use of concurrent cisplatin is safe and concurrent chemoradiation is superior to radiation alone resulting in higher response. It can be recommended as standard of care. Among the two chemoradiation schedules, three weekly cisplatin is less toxic and thus with better compliance than weekly one. Weekly cisplatin can be made more acceptable by reducing the dose and using feeding tubes supplementing nutritional support.

References:

1. GLOBOCAN 2002: Cancer incidence, mortality, and prevalence worldwide. In *Version 2.0 IARC Cancer Base No.5*. Lyon: IARC Press; 2004. .
2. Taylor SG 4 thsub , Murthy AK, Vannetzel JM, Colin P, Dray M, Caldarelli DD, et al . Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. J Clin Oncol 1994; 12: 385 – 95.
3. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004; 350: 1937-44.
4. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al . Postoperative irradiation with or without concomitant CT for locally advanced head and neck cancer. N Engl J Med 2004; 350: 1945 – 52.
5. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoRT in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003; 21: 92-8.
6. Pignon JP, Baujat B, Bourhis J. Individual patient data meta-analyses in head and neck carcinoma: what have we learnt? Cancer Radiother 2005; 9: 31-6.
7. Bernier J, Bentzen SM. Head and Neck cancer management: Which postoperative treatment best serves your patient? ASCO: Educational Book; 2003. 306 – 12.
8. Glickman AS, Slotman G, Doolittle C 3 rdsub , Clark J, Koness J, Coachman N, et al . Concurrent cis-platinum and radiation with or without surgery for advanced head and neck cancer. Int J Radiat Oncol Biol Phys 1994; 30:1043 -50.

9. Crissman JD, Pajak TF, Zarbo RJ, Marcial VA, Al-Sarraf M. Improved response and survival to combined cis-platin and radiation in nonkeratinizing squamous cell carcinomas of the head and neck. An RTOG study of 114 advanced stage tumors. Cancer 1987; 59:1391 – 7.

10. Marcial VA, Pajak TF, Mohiuddin M, Cooper JS , al Sarraf M, Mowry PA, et al . Concommitant cisplatin CT and RT in advanced mucosal squamous cell carcinoma of the head and neck. Long-term results of the Radiation Therapy Oncology Group study 81-17. Cancer 1990; 66:1861 – 8.

11. Koch WM, Lee DJ, Eisele DW, Miller D, Poole M, Cummings CW, et al . ChemoRT for organ preservation in oral and pharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 1995; 121: 974 – 80.

12. Byfield JE, Sharp TR, Frankel SS, Tang SG, Callipari FB. Phase I and II trial of five-day infused 5-fluorouracil and radiation in advanced cancer of the head and neck. J Clin Oncol 1984; 2: 406 – 13.

13. Browman GP, Cripps C, Hodson DI, Eapen L, Sathya J, Levine MN. Placebo-controlled randomized trial of infusional fluorouracil during standard RT in locally advanced head and neck cancer. J Clin Oncol 1994; 12: 2648 – 53.

14. Gupta NK, Pointon RC, Wilkinson PM. A randomized clinical trial to contrast RT and RT and methotrexate given synchronously in head and neck cancer. Clinical Radiology 1987; 38: 575 – 81.

15. Cachin Y, Jortay A, Sancho H, Eschwege F, Madelain M, Desaulty A, et al. Preliminary results of a randomized E.O.R.T.C. study comparing RT and concommitant bleomycin to RT alone in epidermoid carcinomas of the oropharynx. Eur J Cancer 1977; 13: 1389 -95.

16. Haffty BG, Son YH, Papc R. CT as an adjunct to radiation therapy in the treatment of squamous cell carcinoma of the head and neck: Results of the Yale mitomycin C randomized trials. 1996.

17. Glaser MG, Leslie MD, O'Reilly SM, Cheesman AD, Newlands ES. Weekly cisplatinum concomitant with radical RT in the treatment of advanced head and neck cancer. Clin Oncol 1993; 5: 286 – 9.

18. Allal AS, de Pree C, Dulguerov P, Bieri S, Maire D, Kurtz JM. Avoidance of treatment interruption: an unrecognized benefit of accelerated RT in Oropharyngeal carcinoma? Int J Radiat Oncol Biol Phys 1999; 45: 41 – 5.

19. Vokes EE, Kies M, Haraf DJ, Mick R, Moran WJ, Kozloff M, et al . Induction CT followed by concomitant chemoRT for advanced head and neck cancer: Impact on the natural history of the disease. J Clin Oncol 1995; 13: 876-83.

20. Harrison LB, Pfister DG, Fass DE, Armstrong JG, Sessions RB, Shah JP, et al. Concomitant CT-radiation therapy followed by hyperfractionated radiation therapy for advanced unresectable head and neck cancer. Int J Radiat Oncol Biol Phys 1991; 21: 703 – 8.

21. Gasparini G, Pozza F, Recher G, Panizzoni GA, Cristoferi V, Squaquara R, et al . Simultaneous cisplatin and RT in inoperable or locally advanced squamous cell carcinoma of the head and neck. Oncology 1991; 48: 270 – 6.