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ORIGINAL RESEARCH

Efficacy of Split Course Concomitant Chemoradiation with Cisplatin Plus 5-Fluorouracil in Locally Advanced Head and Neck Cancer

Ashok Singh[1], Deepika Malik[2], Shikha Singh[3], Virendra J. Vyas[4]

[1]Assistant Professor, Department of Radiotherapy, Mahatma Gandhi, Institute of Medical Sciences, Sevagram, India
[2]Assistant Professor, Department of Radiotherapy, Maharishi Markandeshwar Institution of Medical Sciences and Research (MMIMSR), Ambala, India
[3]Assistant Professor, Department of Pathology, Mahatma Gandhi, Institute of Medical Sciences, Sevagram, India
[4]Director Clinical Oncology, Indian Institute of Head and Neck Oncology, Indore, India

ABSTRACT

Background: Use of weekly single agent cisplatin (CDDP) in moderate doses (30-40 mg/m2) is now a standard. Concomitant chemoradiotherapy with cisplatin and 5FU with weekly gaps may offer a benefit with less severe toxicity. Taking a cue from the available data on this approach and our own experience with this regime, we used it for the treatment of Locally Advanced Head and Neck Cancer and present an audit of the same.Objective: To assess the efficacy in terms of overall response of head and neck cancer patients receiving concurrent chemo-radiation.

Materials and Methods: All biopsy proven with head and neck squamous cell carcinoma patients who attended the radiotherapy outpatient department of rural medical college. Study Arm A (Control ARM: CTRT with Cisplatin): Patients were treated with concomitant chemoradiation (CTRT) with weekly Inj. Cisplatin (40 mg/m2 IV) and necessary premedication, adequate hydration along with external beam radiation 2 Gy/Day up to a total dose of 60-70 Gy using standard fractionation. Study Arm B (ARM B: CTRT With Cisplatin Plus 5-Fluorouracil): Patients were treated with concomitant chemoradiation (CTRT) with Inj. Cisplatin (60 mg/m2 IV) on day 1 and Inj. 5-Fluorouracil (5FU) (800 mg/m2 iv) infusion days 1 to5 and with necessary premedication, adequate hydration along with External Beam Radiation 2Gy/5 Days a week, every other week for a total of 6-7 cycles (60-70 Gy in 12-13 weeks)

Results: 26 patients (74.29%) & 6 patients (17.14%) in Control arm have achieved CR and PR whereas in Trial arm it was 23 patients (65.71%) and 5 patients (14.29 %) respectively. (p=0.07). No significant difference could be made out from the results. Treatment duration of control arm was around 7 weeks with a mean of 6.58 weeks and that of trial arm was 13 weeks with a mean of 12.8 weeks. There was a significant difference in the duration of treatment which was very difficult for the trial arm patients to follow the schedule causing frequent incompliance to the treatment. PFS when compared with the duration and stage of the patient no significant difference was observed and due to a shorter duration of follow up median PFS could not be reached.

Conclusion: We conclude saying that regarding the toxicity issue administration of multiagent chemoradiotherapy may not be that much of a harmful treatment modality. Planned treatment gaps do not play a helpful role in treating locally advanced head and neck cancer with respect to the long duration & patient compliance. Conventional chemoradiotherapy with weekly Cisplatin is till date the best modality for treating locally advanced head and neck cancer.

Keywords: Split course, Cisplatin, 5 Fluorouracil, concurrent chemoradiotherapy

Corresponding Author: Dr. Ashok Singh, Assistant Professor, Department of Radiotherapy, Mahatma Gandhi, Institute of Medical Sciences, Sevagram, India.

INTRODUCTION

Among all diseases, cancer has become a big threat to human beings globally. Human beings have had cancer throughout the recorded history.[1]

Radiotherapy (RT) is the standard of care in nonsurgical management of squamous cell cancer (SCC) of the locally advanced head and neck region. This approach is largely based on the updated results of the meta-analysis of the MACH-NC collaborative group, which demonstrated an absolute survival gain of 6.5% at 5 years with concurrent chemo-radiation (CT-RT).[2] Use of weekly single agent cisplatin (CDDP) in moderate doses (30-40 mg/m2) is now a standard.[3] We are using the same concomitant chemotherapy schedule at our department with promising results and with similar toxicity profile. The toxicity profile for 5-Fluorouracil (5-FU) and cisplatin combination therapy is similar to that for cisplatin therapy alone with conventional radiotherapy. Concomitant chemoradiotherapy with cisplatin and 5FU with weekly gaps may offer a benefit with less severe toxicity. Taking a cue from the available data on this approach and our own experience with this regime, we used it for the treatment of Locally Advanced Head and Neck Cancer and present an audit of the same.

MATERIALS & METHODS

Study design

Previously untreated patients, with histological proven SCC of Head and Neck (excluding naso-pharynx and para-nasal sinuses), in stages III and IV, M0 were treated with this protocol. Surgery was not a part of their planned treatment. Inclusion criteria were age upto 70 years, Karnofsky performance status (KPS) >70, normal routine biochemical examination of blood. All eligible patients were informed about the treatment protocol and consent was obtained. The patients were treated on an outpatient department of radiotherapy in a rural medical college that primarily caters population from the rural belt of Vidharbha region of Maharashtra.

Radiotherapy

All patients were planned with a thermoplastic head immobilization device or custom-made plaster immobilization devices and treated on a Theatron Phoenix telecobalt unit. A parallel opposed field was used in all the patients. However, missing tissue compensation was not done. In the 1st phase 44 Gy/22- fractions/5 days per week was delivered to the primary and draining lymph node regions by the above technique at mid plane. In the 2nd phase, an off-cord field reduction was carried out to exclude the spinal cord and include the primary tumour and nodal sites with a 2-3 cm margin to a total planned dose of 70 Gy (at 2 Gy/fraction, 5 fractions per week). Two arms were planned with control arm consisting of continuous radiotherapy upto 7 weeks and the trial arm consisted of alternate week radiotherapy upto 13 weeks.

Chemotherapy

The control arm consisted of weekly doses of concurrent CDDP at 40 mg/m2 infused over two hours, preceded by intravenous hydration a day before and on the day of chemotherapy antiemetics and mannitol diuresis followed by chemotherapy and further hydration, as an inpatient procedure. Similarly in trial arm chemotherapy was administered alternate weekly with radiotherapy but with CDDP on day 1 and 5Fu (500 mg/m2) from day 1 to day 5. Chemotherapy administration was postponed if the total leukocyte count was less than 3000

mm3, platelet less than 90,000 mm3, haemoglobin less than 9 gm% and serum creatinine more than 1.6 mg% till recovery was observed. No dose modifications were made.

Evaluation during and following treatment

During treatment patients were reviewed weekly for toxicities induced with radiation and chemotherapy. After treatment completion, patients were reviewed monthly for the first six months, then two-monthly thereafter. Response were assessed using the Response assessment Criteria in Solid Tumors (RECIST) version 1.14. Acute and Late Toxicities were assessed using the WHO Common Terminology Criteria for Adverse Events (CTCAE) version 5.05.

Statistical analysis

The data was analyzed in terms of locoregional response and grade of acute and late toxicities in both the arms. Prolongation of Treatment Time in both the arms were compared. Progression Free Survival at the end of 1 year in both the arms were compared. Survival curves were computed using the Kaplan- Meier method. All P values were two-sided and considered significant at <0.05.

RESULTS

Case accrual was started from January 2014. Last follow up has been taken on August 2015 and analysis of data was done on September 2015. The baseline characteristics of patients and tumours are shown in [Table 1]. Median age of patients in control arm is 60 years whereas 54 years in trial arm with a range 33-68 years in control arm and 30-68 years in control arm respectively which shows a comparable age distribution in both the arms. Male patients were predominant in both the arms. (82.86 % in control arm and 74.29% in trial arm). Patients' performance status was determined by Karnofsky Performance Status (KPS) scale 100. Patients were commonly accrued with KPS 90 [21 patients (60 %) in control arm and 20 patients (58 %) were in trial arm]. Oral cavity was commonest site in Control arm and Trial arm, 14 patients (40%) in Control arm and 28 patients (80%) in Trial arm had disease in Oral cavity whereas next common site was larynx, 12 (34.29%) and 3 (8.57%) patients in Control arm & Trial arm suffered from disease at that site. Other sites were Oropharynx (6 in control arm & 3 in Trial arm) and hypopharynx (3 in Control arm and 1 in trial arm). Well differentiated squamous cell carcinoma (WDSCC) were most common histopathology among the patients of either groups, 17 patients (48.57 %) in control arm and 18 patients (51.43 %) in trial arm. One (2.86%) and Eight (22.86%) patients were having stage III disease in control arm and Trial arm respectively and number of stage IV disease in these two arms were 34 (97.14%) and 27(77.14%).

Treatment compliance

This is shown in [Table 2]. Thirty-four patients in control arm had completed the Treatment. Twenty-seven patients in trial arm completed treatment. EBRT TIME control Arm and EBRT TIME trial Arm Mean doses of radiation (RT) received were 64 Gy and & 68 Gy (p=0.0001). EBRT completion time in control arm and trial arm had mean values of 6.59 and 12.80 weeks respectively.

Acute Morbidity

[Table 3] shows the acute morbidity during treatment. Six patient had died during in trial arm. One patient did not continue the treatment due to treatment related toxicity and rest of the patients in control arm completed treatment. Oropharyngeal Mucositis was observed in both the arms. But at the end of the treatment both the arms had no significant difference (p=0.84). No patients in Control arm and trial arm were complicated with grade 4 radiation

dermatitis at last week of treatment. Grade 2-3 dysphagia was seen in 93% of patients in control arm and 68% of patients in trial arm respectively (p=0.69). Two patients in the trial arm presented with chemotherapy induced febrile neutropenia which was managed with parenteral antibiotics and GCSF. During that period chemotherapy was withheld until neutropenia was recovered.

Table 1: Patient and Disease Characteristics

Characteristics	Particulars	Control Arm	Trial Arm
Age	Mean	55.45	52.44
	SD	± 10.8	± 10.07
	Range	33-68	30-68
Gender	Male	29(82.86%)	26(74.29%)
	Female	6(17.14%)	9(25.71%)
KPS	90	21(60%)	20(57.14%)
	80	14(40%)	15(42.86%)
Subsites	Oral Cavity	14(40%)	28(80%)
	Oropharynx	6(17.14%)	3(8.57%)
	Hypopharynx	3(8.57%)	1(2.86%)
	Larynx	12(34.29%)	3(8.57%)
HPE%	WDSCC	17(48.57%)	18(51.43%)
	MDSCC	15(42.86%)	16(45.71%)
	PDSCC	3(8.57%)	1(2.86%)
Staging	Stage III	1(2.86%)	8(22.86%)
	Stage IV	34(97.14%)	27(77.14%)

Table 2: Treatment Compliance

Particulars		Control Arm	Trial Arm
Compliance	Left treatment	1(2.86%)	8(22.9%)
	Completed Treatment	34(97.14%)	27(77.1%)
Treatment Time	N	35	35
	Mean	6.59	12.8
	Std. Deviation	± 0.89	± 0.8
Dose Delivered	N	35	35
	Mean	64	68.87
	Std. Deviation	± 5.48	± 4.05

Table 3 Acute Morbidity

Acute toxicity	Grade	Control Arm	Trial Arm
Mucositis	Gr0	0(0%)	0(0%)
	Gr1	0(0%)	0(0%)
	Gr2	9(34.29%)	10(28.57%)
	Gr3	21(54.29%)	17(48.57%)
	Gr4	5(14.29%)	2(5.71%)
Dermatitis	Gr0	0(0%)	0(0%)
	Gr1	4(11.43%)	7(20%)
	Gr2	19(54.29%)	23(65.71%)
	Gr3	11(31.43%)	1(2.86%)
	Gr4	0(0%)	0(0%)

Neutropenia	Gr0	35(100%)	27(77.14%)
	Gr1	0(0%)	2(5.71%)
	Gr2	0(0%)	0(0%)
	Gr3	0(0%)	0(0%)
	Gr4	0(0%)	0(0%)
Nausea and Vomiting	Gr0	6(17.14%)	20(57.14%)
	Gr1	18(51.43%)	11(31.43%)
	Gr2	0(0%)	0(0%)
	Gr3	0(0%)	0(0%)
	Gr4	0(0%)	0(0%)

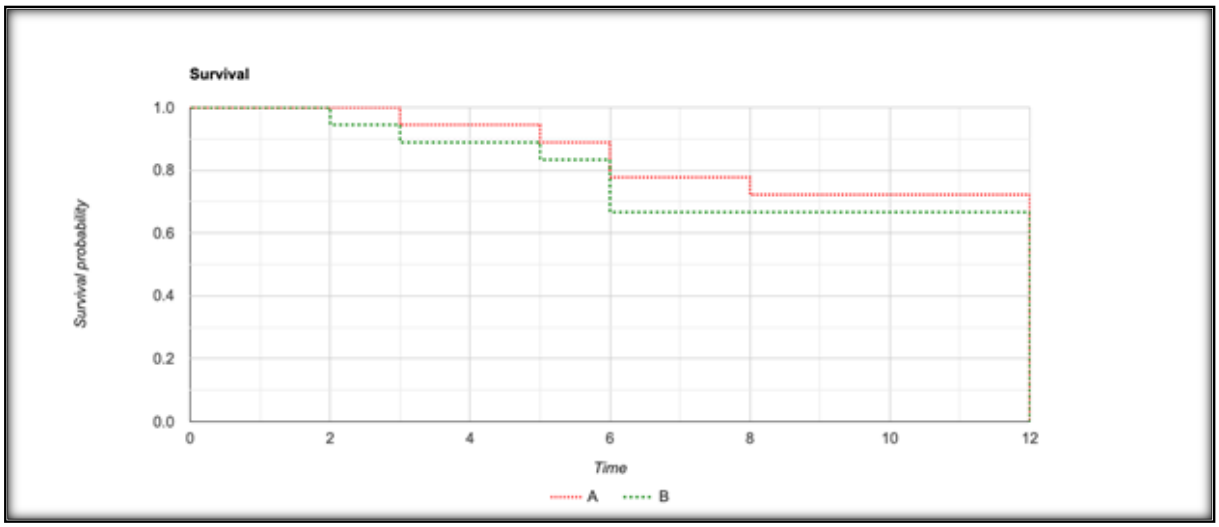

Figure 1: Kaplan Meier curve for END DFS

Response

After one year of follow up 33 patients (94.29 %) in control arm (Single agent CTRT) and 28 patients (80%) in Trial arm (multi agent CTRT) are alive. two patients in Control arm and seven patients in Trial arm have died respectively. Response was assessed using the Response assessment Criteria in Solid Tumors (RECIST) version 1.1. Following abbreviations will be used in this section. CR=Complete response, PR=Partial Response, PD= Progressive Disease, SD = Stable Disease, D=Death, R=Relapse.

After 1 month of treatment, 26 patients (74.29%) & 6 patients (17.14%) in Control arm have achieved CR and PR whereas in Trial arm it was 22 patients (62.86%) and 6 patients (17.14 %) respectively. (p=0.07). After 6 months of completion of treatment 22 (62.86%) &.19 (54.29%) patients in Control arm and Trial arm showed CR, were as in Control arm 5 (14.29%) patients and in Trial arm 3 (8.57%) patients had PR. 2 (5.71%) patients showed PD in control arm and 3 (8.57%) patients showed PD in trial arm. Three patients (8.57%) in control arm and two patients (5.71%) in trial arm had relapsed. Two patients in control arm and one patient in trial arm had stable disease up to 6 months of follow up (p=0.22). On 12 months follow up 22(62.86%) and 18(51.43%) patients in control arm and Trial Arm still show CR. Number of patients with PD are 6 (17.14%) & 3(8.57%) in control arm& trial arm respectively. Four patients (11.43%) and three patients (8.57%) have relapse at the last follow up. (p=0.39).

Survival

The analysis of survival was conducted in the intention-to-treat population END PFS with the use of the Kaplan Meier method [Figure 1]. In follow up both the arm tends to show similar

Progression Free Survival (PFS) (P: 0.522) (Hazard Ratio 1.266, 95 % CI 0.60– 2.62 in Control arm and Hazard Ratio 0.789, 95 % CI 0.38 – 1.63 in Trial arm). Median PFS did not reach.

DISCUSSION

Optimal results in the treatment of head and neck squamous cell cancer cannot be achieved without careful selection of the treatment modalities for each patient. This is not possible without estimation of the factors that determine the prognosis. Although the TNM staging of tumours remains an important method in outcome estimation and treatment selection, evaluation of new tumour- and patient-related factors that can help to classify patients into precisely defined prognostic subgroups is a priority.[4]

Most randomized clinical trials show the superiority of combined radiotherapy (RT) and chemotherapy to RT alone for the treatment of locally advanced, non-metastatic squamous cell carcinoma of the head and neck (HNC). Platinum-based chemotherapy has been used to treat head and neck cancer for approximately 15 years. In the control arm weekly-cisplatin at 40 mg /m2 when delivered concomitantly with conventional radical RT in locally advanced head and neck cancer is well tolerated with minimal hematologic and nephrological toxicity and can be routinely delivered on an out-patient basis. On the other hand, trial arm Cisplatin at 50 mg/m2 on day1 and 5-Fu at 500 mg/m2 on days 1-5 delivered concomitantly with radiotherapy for 5 days, every other week. Thus, an increased dose of chemotherapy was delivered as compared to the control arm. Dose received in the control arm was 66-70Gy/33-35#. While chemotherapy tolerated in trial arm was maximum up to 6 cycles. Trial arm on the other hand maximum dose received by the patient was 66-70Gy/33-35# with chemotherapy up to 7 cycles. Hospitalization was required in case of trial arm as toxicity during chemotherapy was much higher, 6 patients died because of chemotherapy induced toxicity in trial arm while no deaths were recorded but one patient left the treatment in control arm during treatment.

Oral and pharyngeal mucositis is the most common and clinically significant acute adverse effect of radiotherapy for head and neck cancer. When using conventional fractionation, radiation-induced mucositis usually appears during the second week of radiation and then proceeds from anathema to spotted or confluent pseudomembranous mucositis. Acute mucosal reactions cause pain, and difficulties in swallowing and speaking. Difficulties in eating may lead to a poor nutritional status and weight loss. Mucositis also predisposes to local and systemic infections. Severe mucosal reactions are the predominant cause for interruption of radiotherapy for head and neck cancer, which can result in significant loss of the tumour control probability. In the prospective randomized trial conducted in Tata Memorial center stated acute grade 3 or worse mucositis and dermatitis was seen in 77 (29%) and 92 (35%) patients respectively, essentially in patients receiving doses ≥66 Gy and 6 or more cycles of chemotherapy.[6] Similar mucosal toxicity was found in our trial with minimal difference in both the arms no significance was observed. Other toxicities (hematologic, nausea and vomiting) were mild and self-limiting. Overall, the acute toxicity of this concomitant weekly chemo-radiation regimen though mildly increased did not mandate intensive supportive care.

Merlano et al conducted a trial treatment of advanced squamous cell carcinoma of head and neck with alternating chemotherapy and radiotherapy.[7] The toxicity profile for 5-FU and cisplatin combination therapy is similar to that for cisplatin therapy alone. Prominent mucositis (grade 3 or 4, 40–98%), hematologic toxic effects (grade 3 or 4, ~30–40%), and renal dysfunction (in up to 5% of patients) were noted. Patients need to be prescreened for their ability to tolerate cisplatin (i.e., a normal renal creatinine clearance, good performance status, and younger age).

After 1 month of treatment, 26 patients (74.29%) & 6 patients (17.14%) in Control arm have achieved CR and PR whereas in Trial arm it was 23 patients (65.71%) and 5 patients (14.29 %) respectively. (p=0.07). No significant difference could be made out from the results. Similar results were noted in a randomized trial conducted in 1997 a single institutional trial by Taylor et al. When assessed 6 weeks after the end of treatment, 45 patients (63%) had no clinical evidence of disease, whereas 27 (37%) still had some persistent abnormality.[8]

Treatment duration of control arm was around 7 weeks with a mean of 6.58 weeks and that of trial arm was 13 weeks with a mean of 12.8 weeks. There was a significant difference in the duration of treatment which was very difficult for the trial arm patients to follow the schedule causing frequent incompliance to the treatment. Alternate week gaps though helped in reducing the severe toxicity of the regimen, but the overall toxicity at the end was similar to the control arm.

From September 1996 through December 2000, Department of Otorhinolaryngology, Kyorin University School of Medicine, Tokyo, and Department of Otorhinolaryngology, National Defense Medical College, Saitama, Japan carried out a phase II study of concomitant chemoradiotherapy. Of the 40 patients evaluable for response, 20 (50%) achieved complete response (CR) and 12 (30%) partial response with an overall response rate of 80%[9]. Compared with the multiagent concomitant chemoradiotherapy similar response was observed at the end of 12 months. No significant difference was observed in the overall response.

PFS when compared with the duration and stage of the patient no significant difference was observed and due to a shorter duration of follow up median PFS could not be reached. A single institutional trial by Taylor et al. The 5-year progression-free survival was 60% (confidence interval [CI] = 49% to 72%).[9]

The QOL assessment at the end of the treatment displayed toxicity profile regarding pain and swallowing similar results without any significant difference. Though the toxicities were managed effectively and some were self-limiting. Pain and difficulty in swallowing were not the complaints at the end of 12 months of follow up. Late toxicities in both the arms were similar. When compared to the randomized trials no significant inference could be made out. Laryngeal cancer generally presented with subcutaneous neck edema. Oral cancers patients generally presented with trismus and dental complications. In the multi-institutional French trial, GORTEC 94-01, the dental complications were twice as much in combination regimen as compared to the conventional regimen.[10]

One of the most common and distressing adverse effects of head and neck radiotherapy is persistent xerostomia resulting from radiation-induced salivary gland damage. Parotid gland salivary flow is markedly reduced following a cumulative dose of 30 to 50 Gy using conventional fractionation. In the trial arm also, we have found similar results.

CONCLUSION

In summary, successful treatment of head and neck squamous cell cancer often requires a carefully planned combination of different treatment modalities to achieve optimal tumour control at a minimal level of side-effects. At present, advanced tumours appear to be best treated with continuous-course radiotherapy combined with concomitant chemotherapy. In radiotherapy for head and neck cancers, giving the radiotherapy as a continuous treatment whenever feasible, with no gaps, is essential.

The optimal chemoradiotherapy schedules and the most effective chemotherapy agents to be used remain to be determined. Choice of chemo to be given whether single agent or multi agent has not been defined till date, though many trials have stated that, the combination of cisplatin and 5-FU with radiation therapy is highly efficacious. Low dose weekly chemotherapy may be offered but the toxicity profile is much higher. Planned gaps with

concomitant chemoradiation resulted in similar response and progression free survival with similar toxicity profile but with long treatment duration. Patient compliance, severity of the disease, age and performance status should be considered for better response to the treatment. No randomized trial has adequately compared cisplatin with cisplatin and 5-FU chemoradiotherapy.

In our study also significant toxicity difference between the arms was not evident very much. Only in the quality of life issue minimal changes in pain and swallowing scores were observed, but the difference in mean values are not at all alarming. In this very short period of follow up long term data cannot be interpreted from our study but in future with this same patient cohort we will work up on the overall survival data. The treatment duration shows a significant difference in our trial which is the main drawback of the split course treatment regimen.

At last we want to conclude saying that regarding the toxicity issue administration of multiagent chemoradiotherapy may not be that much of a harmful treatment modality. Planned treatment gaps do not play a helpful role in treating locally advanced head and neck cancer with respect to the long duration & patient compliance. Conventional chemoradiotherapy with weekly Cisplatin is till date the best modality for treating locally advanced head and neck cancer.

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