CHEMORADIO THERAPY FOR ADVANCED HEAD AND NECK CANCER - ANALYSIS OF A PROSPECTIVE, RANDOMIZED TRIAL

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Abstract: *Objective:* To study the efficacy of neo-adjuvant chemotherapy followed by radiotherapy in advanced head and neck cancer. *Study design:* Randomised, prospective study. *Setting:* Tertiary academic referral center. *Patients:* One hundred and eighty patients of advanced head and neck squamous cell carcinoma. *Intervention:* Patients were randomized into two arms. The study arm (CT-RT arm) received 3 cycles of anterior chemotherapy with Inj. Cisplatin 100 mg/m² on D₁ and Inj. 5F.U. 700 mg/m² on D₁-D₃ at an interval of 21 days, followed by external radiation. The control arm (RT arm) received external radiotherapy only. The dose of Radiotherapy was 64 to 68 Gy in conventional fractionation. *Results:* Patients of CT-RT showed better tumour control locally than patients who received only RT. Toxicities were commoner in CT-RT arm but they were manageable. 5 year survival is higher in the CT-RT arm (21% vs 16%; *p* value>0.05). *Conclusion:* Anterior chemotherapy with Cisplatin and 5F.U. is associated with good clinical response which is translated into increased survival along with acceptable toxicities.

Keywords: Head & Neck Cancer, Neo-adjuvant Chemotherapy, Cisplatin and 5F.U.

INTRODUCTION

Head and neck cancer is the commonest malignancy among Indian males [1]. Majority of the patients present as locally advanced disease. Distant metastasis is present at diagnosis rarely. The management of this group of patients remains a challenge with poor locoregional control and limited overall survival. The standard locoregional therapy of head & neck carcinoma remains surgery and postoperative radiotherapy. As surgery is not possible in majority of advanced cases, alternative treatment approaches has to be considered. Various therapeutic modalities are being tried to improve the long term prognosis out of which different radiation fractionation schedule and use of chemotherapy is worth mentioning [2].

In the past there was reluctance to consider chemotherapy as primary modality because of the following reasons: - 1) Disease remains localised till late stage - conventionally loco-regional disease was treated by radiotherapy while chemotherapy was reserved for recurrent and metastatic disease 2) Poor general condition of the patient due to concomitant medical condition and reduced nutritional intake makes chemotherapy difficult. The ability of radiotherapy to cure locally advanced head-neck cancer is limited by the size of the tumour and the accelerated repopulation of the tumour clonogen. The doses required to treat large tumours and to compensate for the accelerated repopulation exceed the limit of toxicity in normal tissue. Efforts to overcome this problem have led to the use of chemotherapy.

Addition of chemotherapy to radiotherapy has shown promising results[3]. But the exact timing and combination are not well defined. Chemotherapy may be added before definitive therapy (surgery or radiotherapy) when it is known as anterior or neo-adjuvant chemotherapy. Concurrent chemotherapy is chemotherapy given at the same time with radiotherapy or it may be added after definitive therapy which is known as adjuvant

chemotherapy. Chemotherapy in neo-adjuvant setting has drawn the attention of investigators because it allows the delivery of maximum amount of drug to a well vascularised tissue and to the best possible host resulting in increased compliance, responsiveness and tolerance to higher doses. Radiation can be given on a reduced tumour volume thereby improving local control. It may also control the micrometastasis at distant sites early in the course of the disease. Theoretically, chemotherapy and radiotherapy could have a synergistic effect. Neoadjuvant chemotherapy followed by radiotherapy has the added advantage of organ preservation without worsening the prognosis. Varieties of drugs have been used in various settings in clinical trials and increasingly in clinical practice during the last decade. Trials with single agent drug have limited response. So combination chemotherapy is used nowadays.

Combination chemotherapy with Cisplatin and 5-F.U has been shown to be very effective with a high response rate[4]. In this perspective we started this study to assess the impact of chemotherapy given anteriorly to radiation therapy on the locoregional control and survival of the advanced disease. The primary objective of this study was to compare the overall survival between the treatment arms. The secondary objectives include the comparison of disease free survival; determine the local control and the incidence of major and minor complications.

MATERIAL AND METHODS

Patients

Eligibility criteria:

- 1) The study was limited to histology proved squamous cell carcinoma of head and neck who presented to our OPD between 01-08-1998 and 31-07-1999
- 2) Patients having locally advanced disease (Stage III and IV)

- 3) Karnofsky Performance Status (KPS) >70
- 4) Age between 18-70 years
- 5) Informed signed consent by the patient
- 6) Laboratory values as follows:-
 - a) Hb.> 10gm %, Absolute polymorphic nuclear cell count>1800 cells/cmm, Platelets>100000/cmm
 - b) Serum creatinine<1.5mg/dl
 - c) Bilirubin less than 2 mg/dl.

Exclusion Criteria

- 1) Presence of metastatic disease
- 2) Prior anti-cancer therapy
- 3) Second primary tumour
- 4) Pregnancy

Treatment protocol: Patients who fulfill the above eligibility criteria were included in the study. Staging was done meticulously in a joint clinic by an E.N.T. surgeon and oncologist. Patients were routinely seen by Dental Surgeon for oral hygiene. Then they were randomized into two arms. Study arm (CT-RT arm) patients received three cycles of anterior chemotherapy followed by radiotherapy. Chemotherapy was given with a dose of Inj. Cisplatin 100mg / m² on D₁ and Inj 5 F.U. 700 mg / m² on day 1 to 4. Cycle was repeated on day 22. Two cycles of chemotherapy was given. Radiotherapy was started 7 days after 2nd cycle of chemotherapy. Radiation was delivered by telecobalt machine. The initial treatment volume includes gross disease with a margin of 2 cm, potential sites of tumour extension and regional lymph nodes. Total radiation dose ranges between 64-68 Gy with a daily fraction size of 2 Gy, 5 fraction per week. Field shrinkage was done after 40 Gy to spare the spinal cord. Boost to lymph nodes where necessary was given with an additional dose of 6 Gy. Control arm (RT arm) patients received only radiotherapy in the same dose.

FOLLOW UP

Patients were evaluated after each cycle of chemotherapy for toxicity and response. National Cancer Institute (NCI) common toxicity criteria were followed for toxicity evaluation. For ascertaining response World Health Organization (WHO) criteria was followed. Patients were evaluated weekly during radiotherapy. Toxicity was evaluated as per Radiation Therapy Oncology Group (RTOG) criteria. After completion of primary treatment, patients were seen after 2 weeks, then at monthly intervals for 3 months, then at two monthly interval upto 1 year. After that patients were evaluated every 3 months.

QUALITY CONTROL

All patients were examined and evaluated by ENT specialist at each visit. Radiotherapy records including data concerning external beam fields, doses of radiation to tumour & normal tissue, and other treatment variables were reviewed by a radiation oncologist and physicist independently.

STATISTICAL ANALYSIS

Overall survival was the primary end point for the comparison of the two treatment arms and was calculated from the date of randomization to the date of death or last follow up visit. Death from any cause was considered a failure in this analysis. Disease free survival was also compared in the two groups and was calculated from the date of randomization to the date of first occurrence of disease progression, a second diagnosis of cancer, death from any cause or if none has happened then to the date of last follow up visit.

All patients who could be assessed were included in the intent to treat analysis. The Kaplan-Meier method was used to calculate the survival rates. Log rank tests were used to compare treatments.

RESULTS

Patients characteristics

180 patients were accrued for the study. Patient's characteristics were summarised in Table I. Patients were predominantly males, with a wide age range. The median age for RT arm was 57 years and that for CT-RT arm was 55 years. The primary tumour sites were oropharynx, hypopharynx and larynx, majority being from larynx and hypopharynx. All patients were from stage III & IV with stage III predominating. The two arms were found to be statistically comparable in respect of site, stage of disease, age and sex of patients

Table- I : Patients characteristics

Characteristic	CT-RT ARM (n= 90)	RT ARM (n= 90)
Age range in years	28 - 73	26 - 72
Median age in years	55	57
Sex		
Male	84	86
Female	6	4
KPS		
90-100	33	29
70-80	57	61
Site		
Larynx	39	41
Oropharynx	20	17
Hypopharynx	31	32
Stage		
III	35	39
IV	55	51

RESPONSE TO THERAPY

Tumour response at the end of 6 weeks after radiation was noted. In the RT arm 67 patients (74%) showed complete response (CR) whereas 22 patients (25%) experienced partial response (PR). Only 1 patient failed to achieve CR or PR. In CT+RT arm 69 patients (78%) achieved CR and 19 patients (22%) had PR making together cent per cent response. In analyzing the data it was seen that

response to chemotherapy is generally predictive of response to subsequent radiation. Though Grade II & III radiation toxicity occurred in higher number of patients, it was found to be statistically insignificant (p value <0.05).

TOXICITY

Toxicity of chemotherapy

14 patients did not complete the treatment protocol. Out of the 90 patients in CT-RT arm, all patients received at least one cycle of chemotherapy and hence evaluated for toxicity of chemotherapy. Major toxicities of chemotherapy were vomiting and leucopenia (Table-II). All chemotherapy cycles were administered in full doses as planned. Seven patients received blood transfusion due to grade II hematological toxicity. Four patients had delay of cycle of one week or more.

TABLE - II : Toxicity of chemotherapy

	Grade I	Grade II	Grade III
Gastro-intestinal			
Nausea	60	23	7
Vomiting	36	16	8
Diarrhoea	8	1	0
Haematological			
Hb	12	4	0
W B C	19	3	0
Platelet	4	0	0
Others			
Mucositis	6	1	0
Renal	2	0	0

ACUTE TOXICITY OF RADIOTHERAPY

For radiation toxicity, all 90 patients of RT arm and 88 patients of CT-RT arm were evaluable. Two patients of CT-RT arm did not turn up for radiotherapy. Important toxicities of radiation therapy were skin changes, mucositis, change in voice quality and cough. Nausea and anorexia were also present in the majority (Table-III). Leucopenia was rare. These toxicities were commoner in CT-RT arm. Three patients in this arm required 1 week interruption of radiotherapy due to severe mucositis.

Table- III : Acute toxicity of radiation therapy

	RT arm				CT + RT arm			
	GRI	GR II	GR III	Total	GRI	GR II	GR III	Total
Skin	71	15	4	90	68	17	3	88
Mucous membrane	37	52	1	90	22	61	5	88
Larynx	25	46	13	84	16	58	14	88
Upper G.I	63	21	0	84	59	29	0	88
Leucopenia	1	0	0	1	3	0	0	3

LATE TOXICITY OF RADIOTHERAPY

Late toxicity was observed in skin, subcutaneous tissue, and

mucous membrane changes but the major problem was laryngeal oedema with consequent voice changes and pain in the throat. They were slightly more in CT-RT arm than in RT arm (Table-IV).

Table- IV : Late Toxicity

	RT arm		CT + RT arm	
	Grade I & II	Grade III & IV	Grade I & II	Grade III & IV
Skin	1	0	1	0
Mucous Membrane	4	0	6	0
S.C. Tissue	5	2	6	3
Larynx	18	1	17	3

SURVIVAL

The median duration of follow up was 60 months. There was increased survival in favour of CT-RT arm. But it was not statistically significant. The actuarial overall 5 year survival for the RT and CT-RT arm calculated by Kaplan- Meier method was 16% and 21% respectively (p value >0.05 by log rank test).

DISCUSSION

The benefit of neoadjuvant chemotherapy in the management of locally advanced head & neck cancer is a debatable subject [2,5]. Although improved local, clinical and pathological responses have been consistently reported in the literature, increase in overall survival is controversial [6,7]. Among the various chemotherapeutic agents tested, cisplatin has the highest single agent activity. Generally a combination of cisplatin is used because combination chemotherapy has superior response rate along with acceptable toxicity. Among the various combinations cisplatin and 5-fluorouracil is widely used because of its superior tumoricidal activity and acceptable toxicity profile. Wendt reported increased overall survival and decreased distant metastasis in his study of neoadjuvant chemotherapy followed by external radiation in advanced head and neck cancer patients compared with controls treated with radiation therapy alone [8]. Similar results were produced by al-Saraf when he found decreased incidence of systemic recurrence with neoadjuvant chemotherapy using cisplatin and 5 F.U [3]. But other investigators have found only increased locoregional control but not increased survival in their patients. The Department of Veteran Affairs Laryngeal Cancer Study Group trial demonstrated no significant difference in survival of patients who received induction chemotherapy followed by radiation [9]. Chougley P.B. had summarized that though the beneficial effects of chemotherapy in patients with advanced head and neck carcinoma remains controversial in terms of survival, it had shown some promise in improving locoregional control and quality of life [4].

In this study, anterior chemotherapy with cisplatin and 5 F.U. is associated with good clinical response along with acceptable toxicities. A high clinical response was also observed in the neck among patients with palpable neck nodes suggesting significant downstaging of the disease in these patients at the beginning of radiation. Nausea, vomiting and mucositis were the commonest toxicities both in frequency and severity consistent with prior

reports of neo-adjuvant chemotherapy. Neutropenia is the commonest haematological toxicity observed. All of them were easily managed. Tolerance to radiotherapy was also good. Only 3 patients required interruption of radiotherapy for one week.

In summary the combination of Cisplatin and 5 F.U. as neo-adjuvant therapy is a potentially useful regime in the initial treatment of locally advanced head and neck squamous cell carcinoma. It can result in significant tumour regression. Neo-adjuvant chemotherapy should be given for at least 3 cycles because chemotherapy response continues to increase. Chemotherapy responders respond further to radiation therapy but the response of non-responders is not satisfactory. The present study demonstrates that tolerable doses of chemotherapy can be administered with manageable toxicities and good tumour response. Apart from survival the quality of life (organ preservation) is another important advantage when compared with surgery. To conclude anterior chemotherapy followed by external radiation produces better tumour response, disease control and survival than radiotherapy alone in cases of locally advanced head and neck squamous cell carcinoma

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Fig 1: A clinical survival curve by Kaplan - Meier method

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