Conventional Radiation Therapy with Chemo Boost in Locally Advanced Squamous Cell Carcinoma of Head and Neck

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ABSTRACT

Introduction: Combining chemotherapy with radiation to improve tumor control and organ preservation rates have been the subject of intensive investigation in various cancers during the last several decades. Cytotoxic agents have been given before (induction or neoadjuvant chemotherapy), after (adjuvant chemotherapy), or concurrently with radiation. Study aimed to evaluate the efficacy and acute radiation toxicities by using concomitant chemo boost schedule in the treatment of squamous cell carcinoma of Head and Neck region' in Locally advanced diseases.

Material and Methods: 28 patients with squamous cell carcinoma of Head and Neck region' in Locally advanced diseases were randomly assigned to radiation therapy by Conventional 200 cGy / # /35# / 7 weeks or chemotherapy added at last two weeks (Days 26 - 35) 10 days.

Results: The overall local control rate with concomitant boost schedule in our study is 79%. This is 17% higher than that of conventional fractionation schedule (62%). The incidence of Grade 1 and 2 mucositis is 43% (control 38%). No patient had Grade 3 or 4 mucositis requiring parenteral nutrition or treatment interruptions.

Conclusion: Concomitant chemo boost schedule offers the prospect of an improvement in the therapeutic ratio in clinical radiotherapy.

Keywords: Chemoradiation, Concomitant Boost, Toxicity, Efficacy

INTRODUCTION

Major advances have occurred in the treatment modalities for Head and Neck cancers over the past 50 years. Development in surgical oncology has improved in ablative and reconstruction surgical techniques and skill as well as anesthesia and supportive care. These have resulted in major cancer surgery with relative safety and better functional outcome.[1] Progress in radiation oncology was initially linked to technological developments in the planning and delivery of precise treatment, but the past 20 years treatment has been influenced by applications or Biological concepts in Radiobiology. The major clinical application of the Principle of radiation Biology has been in the design and testing of novel fraction in strategies for radiotherapy, which could be predicted to yield an improved therapeutic ratio fir tumor eradications versus late normal tissue injury.[2] Medical oncology research has focused primarily on new drug development with the hope that agents would be found with greater and more selective activity against specific form of cancer and/or non-overlapping toxicity with other active agents. Mechanisms by which commonly used Chemotherapy drugs can increase the cytotoxicity of Radiotherapy, including cell cycle synchronization, selective eradication of hypoxic cells, activity against cells in the S phase of the cell cycle, inhibition of tumor cell repopulation between fractions of radiotherapy.[3,4] French investigators compared standard fractionation radiotherapy with the same Radiotherapy to 70Gy. Finally a comparison of hyperfractionated Radiotherapy (1.2 Gy twice daily to a total dose of 75Gy) with same Radiotherapy schedule plus cisplatin. It is worth noting that in all these trials, toxicity with Chemoradiotherapy was increased compared with the radiotherapy alone. However long term complications were not increased. Thus while organ preservation was not a primary goal of these studies, most of the surviving patients were cured without surgery.[5,6]

Study aimed to evaluate the efficacy and acute radiation toxicities by using concomitant chemo boost schedule in the treatment of squamous cell carcinoma of Head and Neck region' in Locally advanced diseases.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Radiotherapy at Madras Medical College in patients with squamous cell carcinoma of Head and Neck region' in Locally advanced diseases.

Inclusion criteria: Squamous all carcinoma from mucosal site head and neck, State III, IV, Zubrod performance status score < 2, absolute Granulocyte count >1500 dls/ml, platelet count >1,00,000 cells/ml, serum bilirubin <1.5 mg/dl, serum creatinine <1.5 m/dl, blood Hb not less than 10 gm%.

Exclusion Criteria: Nasopharyngeal primary tumors, distant Metastasis, prior history of cancer, diabetes mellitus and Hypertension.

Pretreatment evaluation

i. History and clinical examination.

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ii. Assessment of general condition - Karnofsky performance status is followed.
iii. Staging: The Union Internationale Contre de Cancer (VICC) TNM staging is followed.
iv. Tumour Board: All patients were initially seen in a combined modality Head and neck tumour board.
v. Dental evaluation: Dental evaluation of appropriate cases by a dentist, is done prior to treatment. Dental extraction is to be done at least 14 days prior to RT.

Routine blood investigations were done including hemogram and blood chemistry. Mirror examinations included Indirect laryngoscopy or Direct laryngoscopy with biopsy. Blood VDRL and Human immunodeficiency virus tests were done in appropriate cases. Plain x-ray chest PA view and soft tissue neck AP and lateral views were taken. Barium swallow neck AP and lateral views in appropriate cases and CT/MRI in selected cases, were done.

Patients were randomly assigned to radiation therapy by Conventional 200 cGy / # /35# / 7 weeks or chemotherapy added at the last two weeks (Days 26 - 35) 10 days.

Treatment schedule

A. Radiation Therapy

70 cy/200 cy/#/35# in 7 weeks. (shrinking field technique). Initial: 50 cy both Gross clinically evident diseases and subclinical files of disease extension. (Draining lymphatics of the neck and supraclavicular fossa). Final: 20 Cy to clinically evident disease only, (these boost field had a 1-1.5cm margin around this disease.

B. Chemotherapy

Delivered concurrently with radiation therapy as a boost. Inj. Cisplatin (CDDP) 10 mg/sq.m infused over 30 minutes to 1 hour daily in the last 10 days of Radiation Therapy. (Half an hour before) (Days 26-35).

RESULTS

30 patients were included in this study, 2 patients were excluded after incomplete treatment. Among 28 patients, 26 were male and 2 were female patients. The median age of the patients is 55 years (range 40-70) (table-1). There were 11 patients less than 55 years (39%) and 17 patients for more than 55 years (61%). Except for 1 patient, other patients were habituated to any one of the following; smoking, alcohol or chewing tobacco. As per the Karanofsky performance status system, the score was 90-100 in 65% of patients; and 35% of patients scored 60-90. 18% of patients had a positive family history of malignancies-head and neck cancers, solid tumours or hematological malignancies. The most common symptom of presentation was dysphagia (68%) followed by odynophagia (46%), change of voice (29%). 14% of patients had referred otalgia: 68% of patients presented with complaints of swelling in the neck and 17% presented with ulcers. The median time elapsed between the onset of symptoms and the established diagnosis was 4 months (range 1-7 months). 6 patients tumor in the oropharynx, 9 patients had a tumor in the oral cavity, 6 patients had a tumor in supraglottis, 3 patients had a tumor in the larynx and 4 had tumors in the hypopharynx (figure-1). The gross tumour morphology is classified into 3 clinical varieties, as proliferative tumours in 21 patients, ulcerative tumours in 4 patients or infiltrative tumours in 3 patients. Tumor response was evaluated 6 weeks after completion of treatment. In our study, the complete response rate is 79% (22 out of 28 cases) and partial response 21% (table-2). The local control rates are better than those of conventional fractionation schedules (62%) alone. Concomitant Chemo boost schedule produced an improvement in the local control rate by 17% over conventional radiation alone (Concomitant Chemo Boost).

Age Group (Yrs)	T_2N,	T_3N_0 T_3N,T_4N_1	Total
40-50	5	2	7
50-60	10	4	14
60-70	4	3	7
Total	19	9	28

Table-1: Distribution of Age group with Tumours

Variables		Complete response
Gender	Male	50%
	Female	50%
Age	40-50 years	80%
	> 50 years	20%
Grade	Poorly	83%
	Well	75%
T	2-4	81%
	>4	79%
N		79%
ST	III	81%
	IVa	75%

Table-2: Tumour response evaluation

Category	Concomitant Boost - CR (n=28)		Historical control cohort (n=47)	
T2 N1	13/16	81%	14/19	74%
T3 No T3 N1 T4, N2	9/12	75%	15/28	54%
Oropharynx	12/15	80%	20/30	67%
Larynx supraglottis	10/13	77%	9/17	53%
Well differentiated	12/16	75%	16/27	59%
Poorly differentiated	10/12	83%	13/20	65%
Overall	22/28	79%	29/47	62%

Table-3: Response of Radiation therapy after 6 weeks

Reactions	Concomitant Boost - CR (n=28)		Control (n=47)	
Patchy mucositis	12	43%	18	38%
Confluent mucositis	0	0%	2	4%
Odynophagia/ Dysphagia	10	36%	11	23%
Hoarseness of voice	9	32%	12	25%
Skin reactions RTOG grade I	13	46%	23	49%
Dry mouth RTOG Grade I	12	43%	18	38%
Loss of taste RTOG Grade I	5	18%	10	21%
Weight loss >10%	1	4%	5	11%

Table-4: Radiation induced Acute toxicity

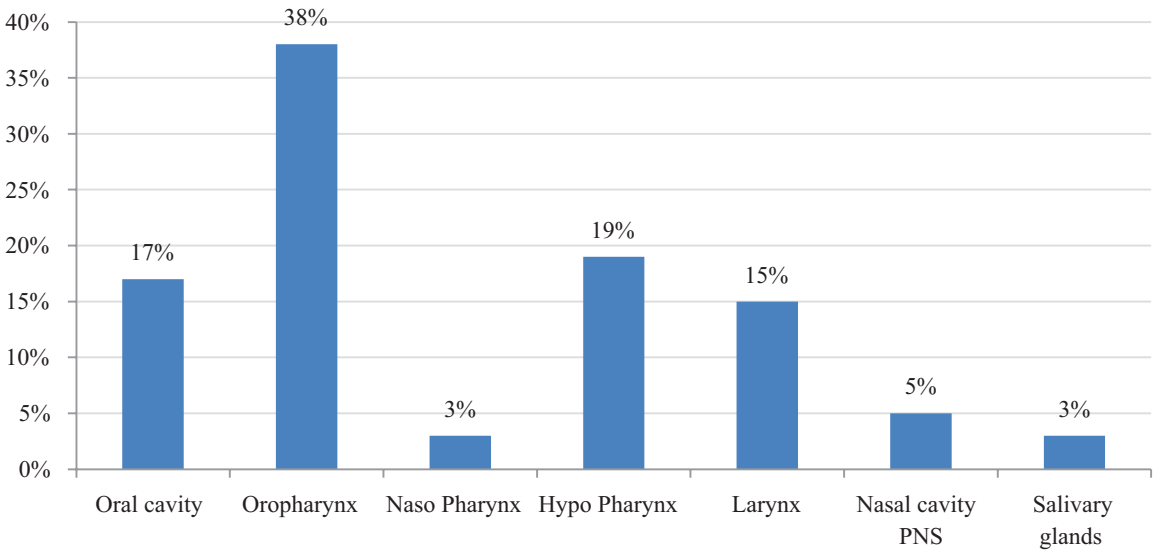

Figure-1: Distribution of site

Stagewise, 13 out of 16 cases (81%) with T2 Nl tumours had a complete response. 9 out of 12 cases (75%) with T3No / T4 N2 had a complete response. The response is better in 'poorly differentiated' tumours with concomitant Chemo boost technique (83% vs 65%) compared to conventional fractionation (table-3).

The primary tumour at the oropharyngeal site had a complete response rate of 80% (12 out of 15 cases) and larynx or supraglottic tumours had a CR of 77% (10 out of 13 cases) with the concomitant Chemo boost schedule. However, the values of response rates do not have a significant p-value. As our sample size was small. A larger trial of this fashion is warranted. Residual nodes are assessed 8 weeks after RT. Among the node positive case (19), 79% of patients (15 out of 19) achieved a complete response, and 21% of patients (4 out of 19) had a partial response. Acute mucositis occurred by the 3rd week of patients in 14% of patients by the end of the boost, in 29% of patients. The grading of acute mucositis is both objective and functional. Persistent mucositis is defined as the mucositis not subsiding by 6 weeks or more. Overall Grade I or II (Patchy) mucositis was observed in 43% of patients. No patients had Grade III or IV confluent acute mucositis, necessitating treatment interruptions. The incidence of Grade I or II mucositis is comparable -43% (12 out of 28 cases) in concomitant boost fractionation) with that of conventional fractionation (38%). Dry mouth or xerostomia is classified as mild, moderate (if some degree of moisture) and severe (complete absence of moisture). Overall 43% of patients had xerostomia. Loss of taste (Ageusia or hypogeusia) occurred in 18% of our patients. Odynophagia (pain on swallowing due to sore throat) and dysphagia are observed in 36% of the cases (table-4). Hoarseness of voice due to arytenoid edema, is seen in 32% of patients. Skin reactions (erythema, pigmentation and dry desquamation) were observed in 46% of patients. The weight loss attributable to mucositis treatment or related odynophagia is monitored. The median weight loss was 4 Kg. (range 2.7 Kg). 16% of cases had weight loss of less than 10% and 4% of cases had weight loss of more than 10%. Patients are reviewed regularly every 4 weeks up to 1 year; every 8 weeks up to 2 years and every 6 months thereafter. Follow up includes clinical examination for local recurrences and metastatic workup. Patients are reviewed in a joint head and neck clinic with indirect laryngoscopy or direct mirror examinations periodically. Xrays and barium swallow neck are routinely done on follow up. CT scans of the head and neck are performed in appropriate cases.

DISCUSSION

Combining chemotherapy with radiation to improve tumor control and organ preservation rates has been the subject of intensive investigation in various cancers during the last several decades. Cytotoxic agents have been given before (induction or neoadjuvant chemotherapy), after (adjuvant chemotherapy), or concurrently with radiation. This chapter summarizes the rationale and data of these different modes of chemotherapy in combination with radiation treatment for the management of advanced head and neck squamous cell carcinoma (HNSCC). Although a very large number of phase I-II studies have been conducted, to date only a fraction of regimens investigated have undergone proper testing in randomized clinical trials. The results of completed trials in aggregate have begun to change the standard of care for patients with advanced HNSCC, predominantly those with carcinomas of the oropharynx, larynx-hypopharynx, and nasopharynx.

The goals of induction chemotherapy are to reduce the primary tumor and, when present, nodal size (downstaging), thereby increasing the chance of cure with subsequent local therapy and also to eradicate systemic microscopic metastases.[7] Unfortunately, induction chemotherapy may induce accelerated repopulation of tumor clonogen, making the tumor more difficult to control locally by means of radiation therapy.[8] The primary goal of concurrent chemotherapy is mainly to enhance the cytotoxicity of radiation therapy against macroscopic disease.[7] It may also eradicate systemic microscopic disease, although to avoid severe

side effects, the dose of chemotherapy used for concurrent chemoradiation may be too low to yield a demonstrable effect on micrometastases. Adjuvant chemotherapy is used to eradicate microscopic loci presumed to remain after local therapy and to destroy microscopic metastatic deposits.[7]

Adelstein et al.[9] randomized 100 patients to receive conventional radiation therapy (1.8-2 Gy per fraction to 66-72 Gy total dose) with or without concurrent cisplatin and 5-FU. Chemoradiation therapy patients had a significantly higher rate of grade 3-4 neutropenia (38% versus 0%, $p < 0.001$), thrombocytopenia (16% versus 0%, $p< 0.001$), and mucositis (84% versus 26%, $p < 0.001$). A greater percentage of patients treated with chemoradiation therapy lost >10% of body weight (12.5% versus 6.3%, $p<0.001$ and required tube feeding (58% versus 32%, $p<0.001$. In addition, 36% of the patients undergoing chemoradiation therapy required hospitalization for the care of neutropenic fever but no toxic deaths occurred in either arm. In terms of late effects, significantly more second malignancies occurred in the chemoradiation group ($p=0.03$). Nine patients in the chemotherapy arm developed second cancers (including four aerodigestive tract tumors), as opposed to two in the radiotherapy arm (one in the aerodigestive tract). Of these 11 patients, 8 died of second malignancies.

The intergroup study on advanced nasopharyngeal carcinoma (0099)[10] compared the efficacy of radiation (70 Gy in 35-39 fractions) with or without concurrent and subsequent adjuvant chemotherapy (Table 30.3). The stratification variables were tumor stage, nodal stage, performance status, and histology. Chemotherapy consisted of cisplatin in a dose of 100 mg/m 2 given on days 1, 22, and 43 of radiation followed 4 weeks later by three cycles of cisplatin (80 mg/m 2 on day 1) and 5-FU (1 g/m2/day on days 1-4) given 4 weeks apart. In terms of toxicity, the incidence of grade 3-4 leukopenia and vomiting was higher in the combined therapy arm ($p<0.05$). Overall, 63% of patients received three courses of concurrent chemotherapy and 55% received all three cycles of adjuvant chemotherapy. The late treatment toxicities have not been reported in detail.

Data presented earlier clearly show that the addition of chemotherapy to radiation, particularly when given concurrently, increases treatment-induced toxicity, hence compromising the therapeutic index. In addition, acute treatment toxicity also prevents completion of chemotherapy and/or radiation as planned, partially offsetting its therapeutic efficacy. Refinement of radiotherapy technology can reduce the volume of normal tissues exposed to a high radiation dose, thereby reducing morbidity or increasing the compliance to the combined modality therapy. Chemical compounds were having the potential to protect normal tissues from radiation and/or cytotoxic agent-induced damage are being developed and tested.

CONCLUSION

The concomitant chemo boost fractionation schedule emphasizes the major interest of modified radiotherapy regimes, based upon radiobiological concepts. It is clear from this study that concomitant chemo boost schedule in squamous cell carcinoma of the head and neck region is feasible; improves local control rates with acceptable acute and late normal tissue reactions. Concomitant chemo boost schedule offers the prospect of an improvement in the therapeutic ratio in clinical radiotherapy. Since, accelerated treatment is given only during the last 10-12 days of radiotherapy, acute reactions are less, and the post-irradiation functional results are better.

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