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Original Research Paper

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CONCOMITANT BOOST RADIATION THERAPY IN LOCO-REGIONALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMAS

Dr. Prem Kumar Devdoss MD DM Associate Professor ,Department of Medical Oncology, Government Stanley medical college,Chennai.

Dr. Naveen Ravel* MD DM Professor , Department of Medical Oncology, Government Stanley medical college,Chennai. * Corresponding Author

ABSTRACT

AIM: To investigate the feasibility of combining concomitant boost accelerated radiation regimen (ACB) with weekly mono-chemotherapy using Cisplatin and to access its local response and acute toxicity patterns in patients with advanced locoregional head and neck squamous cell carcinoma (HNSCC).

MATERIALS AND METHODS: It was a prospective study, 24 patients met the eligibility criteria of the protocol and were recruited. Eligibility criteria include:

Patients with adequate bone marrow function, Creatinine clearance >50 ml/min determined by 24-hr collection or nomogram, No symptomatic coronary artery disease (angina) or myocardial infarction within the last 6 months and Patients with a history of non-melanoma skin cancer, or other previous malignancies from which the patient has remained continually disease free for ≥ 3 years are eligible.

Ineligibility Criteria

Histology other than squamous cell carcinoma, Evidence of metastases (below the clavicle or distant) by clinical or radiographic examinations, Prior chemotherapy for any reason or radiotherapy to the head and neck region, Initial surgical treatment excluding diagnostic biopsy of the primary site or neck disease, Patients with simultaneous primaries, Pregnant women because of the embryotoxic effects if chemotherapy and associated Co-morbid conditions like, DM,HT, IHD, etc.

RESULTS: Overall response to therapy was recorded in all patients (100%). This included a complete response in 19 patients (79.2%) and partial response in 5 patients (20.8%). Of the 5 patients with residual disease (partial response), 3 patients (12.4%) had residual disease at the primary site, 1(4.2%) patient had residual disease at the nodal site and 1(4.2%) patient had residual at the primary and nodal site.

A significant observation was the association between the grade of squamous cell carcinoma and complete response with 33% of grade-I, 60% of grade-II, and 70% of grade-III carcinomas showing complete response ($p<0.01$). Site-wise 100% of laryngeal cancers, 66.7% of hypopharyngeal cancers and 81.25% of oropharyngeal cancers showed complete response (p=NS). 100% of T2 tumors, 100% of T3 tumors, and 61.5% of T4a tumors showed complete response (p=NS). Nodal response demonstrate 100% complete response among patients with N0, N1 and N2a lesions, while N2c lesions showed 28.5% complete response respectively (p=NS).

CONCLUSION: This data shows that it is feasible to combine ACB and weekly mono-chemotherapy using cisplatin with manageable, although substantial, toxicity. The compliance to therapy is high, and the loco-regional response achieved compared favourably with ACB alone or other concurrent chemoradiation regiments using standard or altered fractionation regiments tested by the Institute. It also compares well with the available literature. An extended Phase - II trial, and a new Phase – III trial comparing ACB plus cisplatin against standard radiation plus cisplatin is being planned at the institute to determine whether the use of ACB in the concurrent chemoradiation setting further improves outcome.

KEYWORDS : Cisplatin, squamous cell carcinoma, oropharyngeal cancers and hypopharyngeal cancer.

INTRODUCTION

Cancer of the head and neck has been one of the foremost problems among Indian Oncologists over the past several decades, in fact, ever since tobacco was first introduced to the subcontinent by the Spanish, and smoking and tobacco chewing, along with betel nut, became a popular habit with the locals. This habit o chewing betel-nut and tobacco in the form of a quid steadily caught on, not only among the tribals, but also with the higher social strata, so that today, in some states like Gujarat, Madhya pradesh and rural Maharashtra, more than 50% of the population imbibes tobacco in one form or another. To compound the problem, 70-80% of the cases coming for treatment are stages III and IV of the disease, where management is difficult and prognosis poor.

The problems we face in head and neck cancers, in developing countries are;

1) The large number of cancer patients in relation to the population; >20.6 per 1,00,000 among males and >10 per 1,00,000 females (Age adjusted rates) as per the National Cancer Registry Program of India (1998), annually.
2) Poor economic conditions of the people.
3) Lack of education. 4) Ignorance and superstition.
4) Delay in diagnosis and seeking treatment, leading to advanced disease.
5) Lack of adequate treatment centres, especially for the poor, particularly radiation Oncology centres.

Main lacunae is between the time of diagnosis and treatment, as patients are invariably guided by quacks and well-meaning relatives to try local remedies and avoid surgery, and it is only when the tumour increases that they end up at cancer treatment centres.

The Treatment of head and neck cancer is complex and difficult, both technically and physically. Tumours in each site in the head and neck region (oropharynx, larynx, hypopharynx and oral cavity) have the same squamous tissue and biologic features, but their clinical presentation and responses to therapy differ according to site. In addition to this level of complexity, there is the inescapable fact that structures of the head and neck control essential, continuously operational functions; speech, swallowing, eating and breathing. Locally advanced presentation adds significantly to the dilemma in choosing the right treatment option, local control being difficult to achieve with the traditional approaches. Local or regional recurrences and distant metastases are frequent and high after surgical treatment of stage II] or IV squamous-cell carcinoma of the head and neck.

MATERIALS & METHODS

It was a prospective study, 24 patients met the eligibility criteria of the protocol and were recruited. **Eligibility criteria** include:

1. Patients with adequate bone marrow function defined as an absolute peripheral granulocyte count (AGC) of ≥2000 cells/mm, platlet count of ≥ 1,00,000 cells/mm, adequate hepatic function with bilrubin≤1.5 mg%, creatinine clearance ≥ 50 ml/min, SGOT or SGPT < 2x the upper limit of normal, and

serum calcium (without intervention).
2. Creatinine clearance >50 ml/min determined by 24-hr collection or nomogram:CrC1male = (140 – age) X (wt. as kg) (Serum Cr mg/dl)X72 CrC1 female = 0.85 x (CrCl male)
3. No symptomatic coronary artery disease (angina) or myocardial infarction within the last 6 months.
4. Patients with a history of non-melanoma skin cancer, or other previous malignancies from which the patient has remained continually disease free for $\geq$ 3 years are eligible.
5. . Informed consent form signed prior to study entry.

INELIGIBILITY CRITERIA
1. Histology other than squamous cell carcinoma.
2. Evidence of metastases (below the clavicle or distant) by clinical or radiographic examinations.
3. Prior chemotherapy for any reason or radiotherapy to the head and neck region.
4. Initial surgical treatment excluding diagnostic biopsy of the primary site or neck disease.
5. Patients with simultaneous primaries.
6. Pregnant women because of the embryotoxic effects if chemotherapy.

PRETREATMENT EVALUATION
1) Complete history and physical examination.
2) Biopsy of primary tumor and/or fine needle aspirate/biopsy of metastatic lymph node.
3) Location, type, and size of all measurable lesions within 2 weeks prior to treatment be recorded and diagrammed prior to treatment.
4) Laboratory studies (within 30days prior to study entry)
4.1 CBC with differential and platelet count
4.2 Serum sodium, potassium, glucose, calcium, serum creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, SGPT or SGOT, and LDH),
4.3 Creatinine clearance.
4.4 Optional : Prothrombin time (PT), Partial thromboplastin time (PTT).
5) Radiographic Studies
5.1. Appropriate radiographic study of tumor: CT Scan
5.2 Chest X-ray or thoracic CT scan (within 8 weeks of study enrolment).
5.3 Abdominal CT if abnormal LFT's are noted.
5) Optional: Panendoscopy
Dental evaluation with management.
Feedinng tubes (either Dobhoff, percutaneous endoscopic gastrostomy [PEG] or percutaneous fluoroscopic gastrostomy [PEG] before treatment began if not naso-gastric intubation.

RADIATION THERAPY:
1.DOSE FRACTIONATION
I.Radiotherapy administered according to the concomitant boost regimen. The initial target volume encompassing Primary tumor and neck nodes should received 1.8 Gy per fraction, five fractions a week to 54 Gy in 30 fraction over 6 week to the primary tumor and upper neck nodes. At 32.4 Gy /18 Fx (i.e.,latter part of week 4) the boost target volume covering gross tumor and clinically/ radiological involved nodes received boost irradiation of 1.5 Gy/Fx as second daily fraction (at least 6h interval) for a total of 12 treatment days.
II.The primary6 treatment fields fields reduced off the spinal cord at 45G
III.Clinically/radiological nodesreceived aminimim dose of 72 Gy 42 fraction in 6 week. All treatment times were documented on the treatment record.

II. PHYSICAL FACTORS
Megavoltage equipment Cobalt-60 unit to provise appropriate photon energies
1. treatment distance at 80 cm SSD.
2. LocaliationRequirments
1. Slimulationflim of the fiels and the calculation form.
2. portals were simulated.

III. TARGET VOLUME
The primary tumor and known or suspected lymph nodes disease were treated with either lateral- opposed field(or several beam-directed field with a margin) All field start with a 2-3 cm margin around gross primary and nodal disease. A reduction off t he spinal cord to limit its dose to <45 Gy mandatory. There reduced field have a 1-1.5 cm margin around gross disease.

IV. DOSE CALCULATION
1. Complete isodose curves were required .The specification of the target dose is in terms of a dose to a point at or near the center of target volume. the following portal arrangement are specified are specified for photon beams.
1.1 For two opposed coaxial Equally weighted beams : on the central ray at mid separation of beams.
1.2 For arrangement of 2 or more intersecting beams : at the intersection of the central ray of the beams.
1.3 Other or complex treatment arrangement : at thee central of the target (s) area
2. Appropriate wedges were used as needed ato ensure does homopgeneity . The variation within the target volume did not exceed 10% of the target
3. Boost does were specified at eh actual sites(s) of gross Primary and nodal disease.

CONCURRENT CHEMOTHERAPY:
Cisplatin Dose Schedule:Patients received Cisplatin (40 mg/m^2) administered intravenously on days 1, 8, 15 and 22.
Premedication: Ondansetron 16 mg i.v. will be given 30 minutes prior to cisplatin chemotherapy. Patients received vigorous hydration and dieresis. Dose Modifications for day 22 Cisplatin.

RESPONSE CRITERIA FOR MEASURABLE LESIONS
- **Complete Response (CR) –** Complete disappearance of measurable and palpable disease.
- **Partial Response (PR) –** Tumor shrinkage greater than 50% of the product of the perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (excluding regional nodes) or without appearance of new areas of malignant disease within the treated volume.
- **Minor Response (MR) –** Tumor shrinkage greater than 25% but less than 50% of the product of the perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (excluding regional nodes) or without appearance of new areas of malignant disease within the treated volume.
- **No change (NC)** – Up to 25% growth or 25% shrinkage of the product of perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (excluding regional nodes) or without appearance of new areas of malignant disease within the treated volume.
- **Progression (P) –** Growth of tumor greater than 25% of the product of the perpendicular diameters of the two largest dimensions

RESPONSE CRITERIA FOR EVALUABLE, NON-MEASURABLE LESIONS
- **Complete Response (CR)** – Complete disappearance of known disease
- **Partial Response (PR)** – A definite decrease in tumor size. This should be confirmed by at least two investigators evaluating independently, or photographs or x-rays should be submitted for review.
- **Minor Response (MR)** – Not applicable
- **No Change (NC)** – Insufficient regression of lesion to meet criteria above and no new areas of malignant disease.

- **Progression (P)** – An estimated increase in the size of the tumor of greater than 25% or appearance of new areas of malignant disease.

EVALUATION AFTER TREATMENT

- Patients evaluated at 2-week intervals, whenever possible, after completion of treatment and until their acute reactions resolved. They were then seen every three months for 2 years, every 6 months through year 5, and then annually.

RESULTS:

Some significant observations noted were that dysphagia and odynophagia were common troublesome symptoms in patients with oropharynx, while voice change was the troublesome symptom among patients with laryngeal cancer; in hypopharyngeal cancers the troublesome symptoms were swelling, pain and dysphagia, ($p<0.01$). Nasogastric tube feeding was required prior to treatment increasingly with cancers of the hypopharynx and oropharynx ($p<0.05$). Computed tomography helped upstage the disease in 16 (66.67%) patients (p=NS).

The fractionation regimen was according to protocol specification in all patients (100%). The duration of Radiation therapy was ≤ 46 days in 22 patients (91.67%) and was 47-51 days in 2 patients (8.33%). All the patients received 4 cycles of Cisplatin. All patients received therapy as per protocol or acceptable variations for both radiation and chemotherapy.

TABLE 1: DISTRIBUTION OF CASES:

Variables	No of Patients	Percentage
Sex		
Male Female	22 2	91.7 8.3
Age(years)		
Median	55 years	
Range	40 - 65 years	
ECOG Scale		
Ecogl	24	**100.**
HABITS Smoking Tobacco Smoking + alcohol + tobacco	1 4 9	4.2 16.7 37.5
Smoking + alcohol	10	41.7
TUMOR		
T2	2	8.3
T3	9	37.5
T4a	13	54.2
NODE		
N0	4	16.7
N1	11	45.8
N2a	2	8.3
N2c	7	29.2
NODE SIZE		
> 3 cm	19	79.2
< 3 cm	5	20.8
FIXITY		
Mobile	14	58.3
Fixed	10	41.7

Table 2: Distribution of patients based on the stage.

STAGE Grouping	*Corresponding T-N Stage*	*Patients*	
		Total No.	Percentage
III (37.4%)	T2 N1	2	8.3
	T3 N0	2	8.3
	T3 N1	5	20.8
V (62.6%)	T3 N2c	2	8.3
	T4a N0	2	8.3
	T4a N1	4	16.7
	T4a N2a	2	8.3
	T4a N2c	5	20.8

Table 3: Frequencies of cases based on site:

SITE / SUBSITE						
SITE/ SUBSITE						
OROPHARYNX					HYPOPHARYNX	SUPRAGLOTTIS
Tonsile	***Post 1/3 tongue***	Ant 2/3 tongue, with post 1/3 extn.	Soft palate	Vallecula	Pyriform fossa	Epiglottis
1	9	2	2	2	6	2

TUMOR RESPONSE

Overall response to therapy was recorded in all patients (100%). This included a complete response in 19 patients (79.2%) and partial response in 5 patients (20.8%). Of the 5 patients with residual disease (partial response), 3 patients (12.4%) had residual disease at the primary site, 1(4.2%) patient had residual disease at the nodal site and 1(4.2%) patient had residual at the primary and nodal site.

A significant observation was the association between the grade of squamous cell carcinoma and complete response with 33% of grade-I, 60% of grade-II, and 70% of grade-III carcinomas showing complete response ($p<0.01$). Site-wise 100% of laryngeal cancers, 66.7% of hypopharyngeal cancers and 81.25% of oropharyngeal cancers showed complete response (p=NS). 100% of T2 tumors, 100% of T3 tumors, and 61.5% of T4a tumors showed complete response (p=NS). Nodal response demonstrate 100% complete response among patients with N0, N1 and N2a lesions, while N2c lesions showed 28.5% complete response respectively (p=NS).

Conclusion

In conclusion, this data shows that it is feasible to combine ACB and weekly mono-chemotherapy using cisplatin with manageable, although substantial, toxicity. The compliance to therapy is high, and the loco-regional response achieved compared favourably with ACB alone or other concurrent chemoradiation regiments using standard or altered fractionation regiments tested by the Institute. It also compares well with the available literature. An extended Phase - II trial, and a new Phase – III trial comparing ACB plus cisplatin against standard radiation plus cisplatin is being planned at the institute to determine whether the use of ACB in the concurrent chemoradiation setting further improves outcome.

DISCUSSION

The findings that a number of modified radiation fractionation and concurrent chemoradiation regiments are more effective than conventionally fractionated radiation therapy in the treatment of advanced HNSCC generated interest to test the combination of altered fractionation regimes with chemotherapy. In a retrorespective study, for example, Wolden et al compared the data of 50 patients with nasopharyngeal carcinoma who had received concomitant boost radiation with two cycles of concurrent cisplatin (plus cisplatin based adjuvant chemotherapy in most cases) with the data of an earlier cohort of 51 patients matched for prognostic factors who were treated with radiotherapy alone. They showed that the loco-regional control, progression free survival, and overall survival rates were better in the combined treatment group. Of note is that the regimen used was comparable to treatment regiments used by many co-operative groups and this study.

In comparison with chemoradiation treatment strategies attempted in this institution, this treatment protocol compares favourably. A concurrent chemoradiation study conducted in this institution with conventional radiation and concurrent chemotherapy using Cisplatin (3 cycles) had yielded a complete

response rate at 69% and acute grade-III toxicity rates of 61.6%. Another study that evaluated hyperfractioned radiation therapy and concurrent Cisplatin- 5FU chemotherapy (2 cycles, week 1 and 5) recorded a complete response of 73.1% and acute grade-III toxicity of 62%. Thus with a marginally increased but acceptable level of toxicity the response rate and feasibility achieved in this study is improved by about 6-10%. A study which evaluated altered fractionation radiation therapy alone with accelerated concomitant boost regimen alone for loco-regionally advanced HNSCC at this department resulted in a complete response rate of 60% and acute grade III toxicity of 46.2%.

Table 4: A comparison with studies from our institution

Regimen	RT	Chemo	Response	Toxicity
Chemo-RT (26/30 Pt's) 2003-2004	66Gy **Standard Fx**	**CDDP** D-1,22,43 100mg/m^2	CR : 69.2% PR : 39.8%	Grade III: 61.6% Grade IV: 0
ACB alone (25/30 Pt's) 2002-2003	**7200 cGy Similar to this study**	------	CR : 60% PR : 40%	Grade III: 46.2% Grade IV: 0
HyperFx-RT & Conc' Chemo (26 Pts), 2004	**7200cGY 120cGy/fx, 2Fx/day, 60 fx, 5d/wk, 6 wks**	**CDDP:** 12mg/m^2 **5-FU:** 600mg/m^2 D1-5, Wk 1 & 5	CR: 73.1% PR: 26.9%	Grade III: 63.6% Grade IV: 0
ACB + CDDP (2004-2005)	7200cGy 42 fx, 6 wks	CDDP: **100MG/M^2** D 1, 22	CR: 79.1% PR: 16.7% PD: 4.2%	Grade III: 87.5% Grade IV: 12.5%
PRESENT STUDY **ACB+CDDP (2006-2007)**	**7200cGy 42 fx, 6 wks**	**CDDP: 40mg/m^2 D1, D8, D15 & D22**	**CR: 79.2% PR: 20.8%**	**Grade III: 66.67% Grade IV: 12.5%**

The results of six phase III trials testing the efficacy of such combinations of altered fractionation regiments with concurrent chemotherapy against radiation alone have been reported. The radiation regiments used were accelerated fractionation in three trails, and split-course altered fractionation in two trials.. Collectively, most trials show that combinations of modified fractionation regimens with chemotherapy achieve better local control and, in several trials, improved survival compared with standard or altered fractionation alone. However, the value of altered fractionation in the concurrent chemoradiation setting (i.e, the potential benefit of combining altered fractionations instead of standard fractionation with chemotherapy) has not been tested. Building on the results of RTOG 90-03, which show loco-regional tumor control benefit by concomitant boost regimen, Jose Antonio Medina et al, at the Hospital Clinico Universitario, Malaga, Spain, undertook a phase-II trial to determine the feasibility of delivering four cycles of Cisplatin(40mg/m^2) on days 1, 8, 15 and 22 of ACB in a co-operative group setting. This study shows an estimated 4yr overall survival of 41%. The complete response rates in this study was 66%, and acute grade-4 and grade-3 toxicity rates were 50% and 85% respectively.

This study was based on the, SPANISH trial, but in the setting of a developing country and a Telecobalt treatment facility. All the patients completed the treatment, both radiation therapy and chemotherapy as specified or with very minor variations. The acute toxicity of the treatment was rather severe, as expected. Comparing the acute toxicity with trials conducted by several institutions, however, is rather difficult because of inconsistency in recording and reporting, as cleared pointed out by Trotti and Bentzen. These authors noted that four different recognized grading systems and two descriptive efforts had been used in reporting the results of nine frequently cited trials addressing the combination of radiation and chemopathy HNSCC published within the last decade. Comparison of the results of this study with these other trivals revealed similar incidences of Grade III and Grade IV adverse effects.

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